The NLRP3 inflammasome rs35829419 C>A polymorphism is associated with type 2 diabetes mellitus in Saudi Arabia

Yahia A. Kaabi, MSc, PhD.

ABSTRACT

الأهداف: استقصت هذه الدراسة نسبة وجود الطفرة الجينية rs35829419 C>A الموجودة في مورث NLRP3 في سكان المملكة العربية السعودية من منطقة جازان (جنوب غرب المملكة العربية السعودية) واختبرت ارتباطها المحتمل مع مرض السكري من النوع الثاني.

المنهجية: تضمنت دراسة الحالات والشواهد هذه 546 متطوعًا (271 مريضًا بالسكري من النوع الثاني و 275 أصحاء كمجموعة ضابطة) تم جمع العينات من العيادات الخارجية في مستشفى جامعة جازان ومستشفى الملك فهد المركزي في جازان، بين ديسمبر 2021 ويوليو 2022. تم DNA من جميع العينات وتحديد rs35829419 C>A باستخدام مقايسة التمييز الأليلي TaqMan. تم استخدام تحليل الانحدار اللوجستي لتقييم العلاقة بين الطفرة الجينية rs35829419 C>A ومرض السكري من النوع الثاني.

النتائج: كانت نسب الأنماط الوراثية للطفرة rs35829419 C>A كالتالي: 90.5٪ لـ (CC) و 9.3٪ لـ (CA) و 0.2٪ لـ (AA). كان النمط الوراثي CA هو الاكثر شيوعًا في مجموعة مرضى السكري (12.2٪) مقارنة بالمجموعة الضابطة (6.5٪) وأظهر تحليل الانحدار اللوجستي ارتباطًا ذا دلالة إحصائية بين الطفرة الجينية ومرض السكري من النوع الثاني حسب النمط الوراثي المتنحي (CA مقابل CC؛ [نسبة الأرجحية (OR=1.99؛ فاصل الثقة 95٪ (CI=1.11–3.61)؛ p=0.0270] ، أو السائد (CA+AA مقابل CC)؛ OR=2.05؛ CI=1.16–3.75؛ p=0.019).

الخلاصة: كشفت هذه الدراسة عن نسبة انتشار الطفرة الجينية rs35829419 C>A في مورث NLRP3 في مجتمعنا وأبلغت عن وجود ارتباط بين الأليل A وخطر الإصابة بالسكري من النوع الثاني. تسلط هذه الدراسة الضوء على أهمية هذه الطفرة في فيسيولوجيا مرض السكري.

Objectives: To investigate the frequency of NLRP3 gene rs35829419 C>A single-nucleotide polymorphism (SNP) in a Saudi Arabian population from Jazan (Southwest Saudi Arabia) and test its potential association with type 2 diabetes mellitus (T2DM).

Methods: This case-control study included 546 volunteers (271 patients with T2DM and 275 healthy controls) recruited from outpatient clinics at Jazan University Hospital and King Fahad Central Hospital in Jazan, Saudi Arabia, between December 2021 and July 2022. Genomic DNA was extracted from all samples and genotyped for the NLRP3 rs35829419 C>A SNP using TaqMan technology. The association between the NLRP3 rs35829419 polymorphism and T2DM was examined using logistic regression analysis.

Results: Overall genotype distributions were 90.5% (CC), 9.3% (CA), and 0.2% (AA). The heterozygous CA genotype was more frequent in T2DM group (12.2%) compared to the control group (6.5%) and logistic regression analysis showed a statically significant association with T2DM risk under codominant (CA versus CC; odds ratio [OR]=1.99; 95% confidence interval [CI]= [1.11-3.61]; *p*=0.0270), and dominant (CA+AA versus CC; OR=2.05; CI=[1.16-3.75]; *p*=0.019) models of inheritance.

Conclusion: This study revealed the frequency of NLRP3 rs35829419 C>A polymorphism in our population and showed a direct correlation between having the minor allele for A and having a higher risk of developing T2DM. This study highlights the significance of NLRP3 rs35829419 C>A polymorphism in the pathophysiology of T2DM.

Keywords: type 2 diabetes mellitus, inflammasome, NLRP3 rs35829419 C>A SNP, Saudi Arabia

Saudi Med J 2023; Vol. 44 (8): 745-750
doi: 10.15537/smj.2023.44.8.20230322

From the Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, Jazan University, Jazan, Kingdom of Saudi Arabia.

Received 29th April 2023. Accepted 24th June 2023.

Address correspondence and reprint request to: Dr. Yahia A. Kaabi, Department of Medical Laboratory Technology, College of Applied Medical Sciences, Jazan University, Jazan, Kingdom of Saudi Arabia.
E-mail: ykaabi@jazanu.edu.sa
ORCID ID: https://orcid.org/0000-0001-5418-5782

Over the last 3 decades, type 2 diabetes mellitus (T2DM) has become a critical wellbeing threat affecting most populations worldwide. Saudi Arabia has the highest incidence rate of T2DM, comprising approximately 31.6% of the population.[1] Peripheral insulin resistance and hyperglycemia are the main manifestations of T2DM. Despite the significant role of genetics in T2DM, the precise etiology of the disease remains poorly elucidated. However, in T2DM patients, elevated plasma levels of proinflammatory molecules suggest a central role of inflammation in the pathogenesis of insulin resistance and T2DM.[2] In T2DM, production of reactive oxygen species (ROS), stimulated by high blood glucose and dyslipidemia, may lead to increased oxidative stress and chronic inflammation; the foundation for molecular processes resulting in T2DM and its complications.[3]

Inflammasomes are large multi-protein complexes that are assembled within stimulated immune cells upon sensing danger- or pathogen-associated molecular patterns, leading to the initiation of innate inflammatory response through activation of caspa-1 and pro-interleukin-1 beta (IL-1β).[4] The nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 (NLRP3) is the most frequently studied inflammasome among numerous inflammasome complexes.[5] Activation of the NLRP3 protein by mitochondrial free radicals, ROS or cardiolipin leads to formation of the NLRP3 inflammasome complex, which triggers and regulates the innate immune response.[6] Activation of the NLRP3 inflammasome by glucose and glycolipids in T2DM is closely associated with a chronic inflammatory state that may contribute to insulin resistance.[7,8] The NLRP3 encoded by the NLRP3 gene, (contains 9 exons) found on the long (q) arm of chromosome-1.[9] Mutations in the NLRP3 gene associated with several pathological conditions, where inflammation plays a role such as organ-specific autoimmune diseases and metabolic disorders.[10] Until now, more than 60 single-nucleotide polymorphisms (SNPs) are found in the NLRP3 gene including rs35829419 C>A polymorphism (Q705K). The NLRP3 gene rs35829419 C>A SNP is a gain-of function polymorphism located within exon-3 of the NLRP3 gene, causing overactivity of the NLRP3 inflammasome, overproduction of bioactive interleukin (IL)-1β, and elevated basal proinflammatory phenotype.[9] This SNP has not been directly linked to the T2DM risk factors. However, it has been linked to several autoimmune disorders including systemic lupus erythematosus, type1 diabetes mellitus, and Alzheimer's disease.[11]

Therefore, the goal of this study was to explore the frequency of the NLRP3 gene rs35829419 C>A SNP in a Saudi Arabian population from Jazan, Saudi Arabia, and to test its potential association with T2DM or other anthropometric parameters.

Methods. The current case-control study involved 546 Saudi Arabian volunteers of both genders, ranging in age from 35-98 years. The samples were divided into 2 groups: 271 patients diagnosed with T2DM and 275 healthy non-diabetic individuals who served as controls. Volunteer samples were collected from the blood donation area and outpatient clinics at Jazan University Hospital and King Fahad Central Hospital in Jazan, Saudi Arabia, between December 2021 and July 2022. The inclusion criteria were: i) a Saudi Arabian male or female citizen; ii) ≥35 years old of age; III) with or without T2DM. Participant aged <35 years old, morbidly obese subjects, pregnant women, and patients with other form of diabetes were excluded from this study. Prior to sample collection, each participant signed a written informed consent form. This study adhered to the ethical standards outlined in the Declaration of Helsinki and was approved by the local Research Ethics Committee of Jazan University (REC-43/02/017).

Before blood sample collection, basic demographic information, such as age, gender, weight, and height, were recorded. Body mass index (BMI) was calculated using body weight (kg) and heights (m) according the formula; BMI=kg/m^2. Serum was tested for plasma glucose after an overnight fast using a colorimetric glucose oxidase-based technique. Plasma levels of glycated hemoglobin A1c (HbA1c) were measured using a turbidimetric immunoassay. The diagnosis of T2DM was established based on fasting plasma glucose (FPG) levels of ≥126 mg/dL or HbA1c readings of ≥6.5%.

Each participant donated 5 mL of venous blood, which was drawn using the aseptic phlebotomy technique in an ethylenediaminetetraacetic acid-containing tube. Approximately 200 µL of whole blood was then used for genomic DNA isolation in a final elution buffer volume of 200 µL using the GeneJET gDNA purification kit (Thermo Fisher Scientific, Waltham, MA, USA). Immediately after DNA extraction, Thermofisher NanoDrop spectrophotometer was used to measure the amount of DNA found in each sample. The DNA concentration range was from 20-30 ng/µL. The A260/

Disclosure. Author has no conflict of interests, and the work was not supported or funded by any drug company.

A280 ratio for each sample was also calculated to assess the purity of the extracted DNA; all samples had a ratio between 1.8-2.0. All DNA samples were then used directly for subsequent polymerase chain reaction (PCR) genotyping or stored frozen at -20°C.

All DNA samples were genotyped for the NLRP3 rs35829419 C>A polymorphism in an ABI 7300 real-time polymerase chain reaction (RT-PCR) thermal cycler (Applied Biosystems) using TaqMan SNP Genotyping assay (ID: C_25648615_10; Thermo Fisher Applied Biosystems, Foster City, CA, USA). The reagents for this allelic discrimination assay included TaqMan primers and allele-specific probes labeled with fluorescein amidites and victoria fluorescent dyes for the detection of A and C alleles. The primers and probes were designed specifically for this assay to enable discrimination between the 2 alleles. Polymerase chain reaction was carried out in a 96-well plate in a total volume of 25 µL. Initially, 1.25 ul of the 20x TaqMan SNP genotyping assay reagent was mixed with 12.5 µL of the 2x TaqMan genotyping master mix and placed in each well. Next, 10 ng of the sample DNA diluted in 11.25 µL of water was added to the designated wells and mixed by gentle tapping. The 96-well plate was then briefly centrifuged to bring all the samples to the bottom of the tubes and transferred to a thermal cycler for RT-PCR. The PCR protocol for DNA amplification and polymorphism detection were comprised of 3 steps: I) pre-PCR read (30 seconds reading of baseline fluorescence at 60°C); II) DNA amplification (10 minutes of initial denaturation at 94°C, then 40 cycles of 15 seconds DNA denaturation at 92°C, and one minute extension step at 60°C); III) post-PCR read (30 seconds reading of final fluorescence at 60°C).

For allelic discrimination, Sequence Detection System, version 3.0 software (Applied Biosystems, Foster City, CA, USA) was used to collect and analyze the data and assign allele calls for each sample.

Statistical analysis. GraphPad Prism 9 software (GraphPad Software, Inc., San Diego, CA, USA) was used. Continuous data were expressed as mean±standard deviation (SD) and were compared using Student's t-test. Categorical data (such as gender and genotype) are presented as frequencies and percentages and compared using the Chi-square (χ^2) test. Using a Chi-square test, Hardy-Weinberg equilibrium (HWE) analysis was carried out on the healthy control group to determine whether the NLRP3 rs35829419 C>A polymorphism frequencies were within equilibrium. Binary logistic regression analysis was used to assess the relationship between the NLRP3 rs35829419 C>A SNP and the risk of developing T2DM by calculating the odds ratios (ORs) at a 95% confidence interval (CI). All tests were 2-sided, and a *p*-value of <0.05 was considered significant.

Results. Table 1 summarizes the demographic baseline characteristics and blood glucose measurements of T2DM patients and healthy controls. No significant differences based on gender or age were found between the 2 groups ($p>0.05$). However, other demographic variables (weight, height, and BMI) showed significant differences ($p<0.05$). Furthermore, T2DM patients exhibited significantly greater levels of FPG ($p<0.0001$) and glycated hemoglobin ($p<0.0001$) than the control group.

Genotypes distribution and allelic frequencies of for the NLRP3 rs35829419 C>A polymorphism in both diabetic and control groups are shown in Table 2. The frequency of the NLRP3 rs35829419 homozygous CC genotype was slightly higher in the healthy controls (93.5%) than in the T2DM group (87.4%). By contrast, the CA genotype was more frequent in the T2DM group (12.2%) than in the control group (6.5%). The AA genotype was extremely rare in our sample population; only one AA genotype was detected in the diabetic group, and no AA genotype was found among the controls. Allelic distribution also showed a higher frequency of the minor A allele in the T2DM group (6.5%) than in the control group (3.3%). The observed genotype frequencies in the control group were consistent with HWE ($p=0.575$). Logistic regression analysis revealed a statistically significant association between the NLRP3 rs35829419 C>A SNP and T2DM risk under codominant (CA versus CC; OR=1.99; 95% CI= [1.11-3.61]; $p=0.0270$), and dominant (CA+AA versus CC; OR=2.05; 95% CI= [1.16-3.75]; $p=0.019$) models of inheritance. This association was also demonstrated at the allelic level (A

Table 1 - Comparison of the demographic variables between type 2 diabetes mellitus patients and healthy control group.

Variables	T2DM (n=271)	Control (n=275)	*P*-values
Gender (male/female)	128/143	124/151	0.616
Age (years)	56.2±11.9	55.8±13.6	0.512
Weight (kg)	74.4±12.9	70.6±12.6	<0.0001
Height (cm)	161.8±8.6	163.3±7.3	0.015
BMI (kg/m^2)	28.4±4.6	26.6±4.9	<0.0001
FPG (mmol/L)	13.4±5.6	5.7±1.0	<0.0001
HbA1c (%)	8.9±1.6	5.8±0.8	<0.0001

Values are presented as means ± standard deviations (SD). T2DM: type 2 diabetes mellitus, BMI: body mass index, FPG: fasting plasma glucose, HbA1c: glycosylated hemoglobin

versus C; OR=2.04; 95% CI= [1.15-3.70]; *p*=0.016).

To assess the effect of the NLRP3 rs35829419 C>A SNP on the basic parameters of the study groups, data were recalculated based on the NLRP3 rs35829419 polymorphism variants and assessed for significant differences between the means (Table 3). Based on our observations, we found that T2DM patients carrying the heterozygous CA genotype exhibited significantly higher weight and BMI compared to those with the CC genotype. No other statistically significant differences were observed.

Discussion. In Saudi Arabia, T2DM is a common disorder and major health concern. Understanding the genetic background of T2DM will facilitate efficient disease control. Although the exact single genetic defect causing T2DM has not yet been reported, genome-wide association studies revealed hundreds of altered gene loci that may contribute to the development of T2DM.[12] This study investigated the frequency of the NLRP3 rs35829419 C>A (Q705K) SNP in Saudi Arabia and its association with the risk of T2DM. Initially, results showed that the polymorphic A allele is a minor allele and was found in approximately 9.5% of the total study population. Different geographical regions showed different frequencies of this SNP, with the highest being reported in Europeans (11%) and the lowest in Japanese (2.2%), but not reported in some populations such as Chinese or African-Americans.[13]

This study found a higher frequency of the minor A allele in T2DM group than controls. Logistic regression analysis revealed a statistically significant association between NLRP3 rs35829419 C>A (Q705K) polymorphism and T2DM in our population. This previously unrevealed finding that emphasized the significance of the NLRP3 inflammasome and innate immunity in the development of T2DM. There is a growing body of research has demonstrated the fundamental connection between diabetes and the NLRP3 inflammasome. Initially, it has been found that the level of the NLRP3 inflammasome is an important indicator for metabolic threat that may lead to the development of T2DM.[14] This was further confirmed by the phenotype of improved glucose tolerance and insulin sensitivity in NLRP3 gene knockout mice, that protected the mice from developing diabetes and obesity.[15] Activation of the NLRP3 inflammasome causes a chronic low-grade systemic inflammation, which is a major contributor to insulin resistance, T2DM incidence, and its complications.[14] In patients

Table 2 - Allele change (frequency) of the nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 rs35829419 single-nucleotide polymorphism among type 2 diabetes mellitus and control group.

SNP	Total (n=546)	T2DM (n=271)	Control (n=275)	HWE's *p*-value	OR (95% CI)	*P*-values*
CC	494 (90.5)	237 (87.4)	257 (93.5)	0.575	1.00	-
CA	51 (9.3)	33 (12.2)	18 (6.5)		1.99 (1.11-3.61)	0.027
AA	1 (0.2)	1 (0.4)	0 (0.0)		NA	NA
CA+AA	52 (9.5)	34 (12.5)	18 (6.5)		2.05 (1.16-3.75)	0.019
C	1039 (95.1)	507 (93.5)	532 (96.7)		1.00	-
A	53 (4.9)	35 (6.5)	18 (3.3)		2.04 (1.15-3.70)	0.016

Values are presented as numbers and precentages (%). *Fisher exact test. SNP: single-nucleotide polymorphism, T2DM: type 2 diabetes mellitus, HWE: Hardy-Weinberg equilibrium, OR: odds ratio, CI: confidence interval, NA: not available

Table 3 - Basic characteristics of studied groups by nucleotide-binding oligomerization domain-like receptor pyrin domain-containing 3 rs35829419 genotype.

Variables	T2DM			Control		
	CC	CA	*P*-values	CC	CA	*P*-values
Age (years)	56.4±11.6	59.2±13.9	0.192	56.2±13.9	54.7±9.6	0.329
Weight (kg)	73.5±11.8	78.2±9.9	0.032	70.6±11.1	66.9±15.6	0.188
Height (cm)	161.9±8.4	162.5±7.7	0.711	163.5±7.0	162.9±10.3	0.874
BMI (kg/m^2)	28.1±4.2	29.7±4.2	0.031	26.8±4.3	26.0±4.3	0.677
FPG (mmol/L)	11.9±4.7	10.9±3.9	0.287	5.7±1.0	5.7±0.8	0.977
HbA1c (%)	8.9±1.8	8.5±1.4	0.179	5.9±0.5	5.3±0.4	0.191

Values are presented as means ± standard deviations (SD). T2DM: type 2 diabetes mellitus, BMI: body mass index, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin

with diabetes, high blood glucose can activate the NLRP3 inflammasome via the ATP/P2X purinergic receptor 4 pathway.[7] Additionally, glucose increases the expression of the thioredoxin interaction protein cofactor necessary for NLRP3 inflammasome activation.[7] The NLRP3 rs35829419 C>A (Q705K) polymorphism is a gain-of-function mutation associated with increased inflammasome activity and increased basal systemic inflammatory state 15 which in turn may contribute to T2DM.[16] Other SNPs found in NLRP3 gene, such as rs10754558 and rs4612666, have also been associated with T2DM risk.[17] Apart from T2DM incidence, activation of the NLRP3 inflammasome has been linked to the development of the diabetes complications. The NLRP3 rs35829419 C>A polymorphism in particular has been linked to increased risk of T2DM complications such as macrovascular complications.[18] Moreover, an inhibitory herbal medicine to the NLRP3 inflammasome has been found to improve diabetic peripheral neuropathy.[19] In another study, activation of the NFLRP3 inflammasome has been linked to diabetic retinopathy.[20]

This study reported higher body weights and mass indices in diabetic patients carrying the minor A allele of the NLRP3 rs35829419 C>A polymorphism than in controls. This finding also suggests a possible role for this polymorphism in the regulation of fat metabolism and obesity, which by itself is associated with low-grade systemic inflammation and T2DM risk.[21] Although there is no direct evidence of a connection between the NLRP3 gain-of-function polymorphism rs35829419 C>A and obesity, some studies have shown that activation of the NLRP3 inflammasome may contribute to adipocytes dysfunction and development of obesity.[22] On the other hand, altered adipose tissue microenvironment in obesity can lead to NLFRP3 activation and initiation of systemic inflammation.[23]

Study limitations. Owing to the scarcity of the studied genetic polymorphism in our population, the relatively small sample size is a major limiting factor that may have affected the statistical power of the study. Moreover, all patients were recruited from only one geographic area in Saudi Arabia (Jazan) with a genetically homogenous population, which may not reflect the entire Saudi Arabian population. Therefore, other studies with larger sample sizes recruited from different regions of Saudi Arabia are required to confirm the findings of this study.

In conclusion, this study aimed to examine the frequency of the NLRP3 rs35829419 C>A polymorphism in a Saudi Arabian population and to test its possible association with T2DM. Here, we report that the minor A allele of the NLRP3 rs35829419 C>A SNP was associated with an increased risk of T2DM in our population. Additionally, T2DM patients carrying the minor A allele exhibited a significant increase in BMI compared to controls. This study highlights the importance of NLRP3 rs35829419 C>A polymorphism in the pathogenesis of T2DM. Further studies are required to investigate the implications of this polymorphism at cellular and molecular levels to elucidate the exact mechanism by which this SNP correlate to the incidence of diabetes mellites or maybe other diseases in Saudi Arabia.

Acknowledgment. *The author gratefully acknowledge Editage for English language editing.*

References

1. Al Mansour MA. The prevalence and risk factors of type 2 diabetes mellitus (T2DM) in a semi-urban Saudi population. *Int J Environ Res Public Health* 2019; 17: 7.
2. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, et al. The role of inflammation in diabetes: current concepts and future perspectives. *Eur Cardiol* 2019; 14: 50-59.
3. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci* 2020; 21: 6275.
4. Zheng D, Liwinski T, Elinav E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. *Cell Discov* 2020; 6: 36.
5. Xu J, Núñez G. The NLRP3 inflammasome: activation and regulation. *Trends Biochem Sci* 2023; 48: 331-344.
6. Kelley N, Jeltema D, Duan Y, He Y. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. *Int J Mol Sci* 2019; 20: 3328.
7. Lu S, Li Y, Qian Z, Zhao T, Feng Z, Weng X, et al. Role of the inflammasome in insulin resistance and type 2 diabetes mellitus. *Front Immunol* 2023; 14: 1052756.
8. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. *Int J Mol Sci* 2020; 21: 1835.
9. Lu F, Chen H, Hong Y, Lin Y, Liu L, Wei N, et al. A gain-of-function NLRP3 3'-UTR polymorphism causes miR-146a-mediated suppression of NLRP3 expression and confers protection against sepsis progression. *Sci Rep* 2021; 11: 13300.
10. Wang Z, Zhang S, Xiao Y, Zhang W, Wu S, Qin T, et al. NLRP3 inflammasome and inflammatory diseases. *Oxid Med Cell Longev* 2020; 2020: 4063562.
11. Zhang Q, Fan HW, Zhang JZ, Wang YM, Xing HJ. NLRP3 rs35829419 polymorphism is associated with increased susceptibility to multiple diseases in humans. *Genet Mol Res* 2015; 14: 13968-13980.
12. 12. Cirillo E, Kutmon M, Gonzalez Hernandez M, Hooimeijer T, Adriaens ME, Eijssen LMT, et al. From SNPs to pathways: biological interpretation of type 2 diabetes (T2DM) genome wide association study (GWAS) results. *PLoS One* 2018; 13: e0193515.

13. SNPedia. [Updated 2022: Accessed 2023 Feb 18]. Available from: https://www.snpedia.com/index.php/Rs35829419%5
14. Gora IM, Ciechanowska A, Ladyzynski P. NLRP3 inflammasome at the interface of inflammation, endothelial dysfunction, and type 2 diabetes. ***Cells*** 2021; 10: 314.
15. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. ***Nat Immunol*** 2010; 11: 136-140.
16. Cordero MD, Alcocer-Gómez E, Ryffel B. Gain of function mutation and inflammasome driven diseases in human and mouse models. ***J Autoimmun*** 2018; 91: 13-22.
17. Liwei Bai MC, Qianqian Zhai, Di Wang, Jie Hai, Sumei Jin, Qinggui Zhang. Association of two common SNPs in NLRP3 with risk of type 2 diabetes mellitus and their interaction with environmental factors. ***Int J Clin Exp Pathol*** 2016; 9: 10499-10506.
18. Menini S, Iacobini C, Vitale M, Pugliese G. The inflammasome in chronic complications of diabetes and related metabolic disorders. ***Cells*** 2020; 9: 1812.
19. Sun Q, Wang C, Yan B, Shi X, Shi Y, Qu L, et al. Jinmaitong ameliorates diabetic peripheral neuropathy through suppressing TXNIP/NLRP3 inflammasome activation in the streptozotocin-induced diabetic rat model. ***Diabetes Metab Syndr Obes*** 2019; 12: 2145-2155.
20. Kuo CY, Maran JJ, Jamieson EG, Rupenthal ID, Murphy R, Mugisho OO. Characterization of NLRP3 inflammasome activation in the onset of diabetic retinopathy. ***Int J Mol Sci*** 2022; 23: 14471.
21. Lee J. Adipose tissue macrophages in the development of obesity-induced inflammation, insulin resistance, and type 2 diabetes. ***Arch Pharm Res*** 2013; 36: 208-222.
22. Javaid HMA, Ko E, Joo EJ, Kwon SH, Park JH, Shin S, et al. TNFα-induced NLRP3 inflammasome mediates adipocyte dysfunction and activates macrophages through adipocyte-derived lipocalin 2. ***Metabolism*** 2023; 142: 155527.
23. Wani K, AlHarthi H, Alghamdi A, Sabico S, Al-Daghri NM. Role of NLRP3 inflammasome activation in obesity-mediated metabolic disorders. ***Int J Environ Res Public Health*** 2021; 18: 511.