Iran Red Crescent Med J. 2018 November; 20(11):e65871. doi: 10.5812/ircmj.65871.

Published online 2018 October 22. **Research Article**

The Association of C-Reactive Protein (CRP) Gene Polymorphism (+1059 G>C) With Type 2 Diabetes Mellitus in the Northwestern Population of Iran

Ziba Jalili [1] and Habib Onsori [2, *]

[1]Department of Genetics, Tabriz Branch, Islamic Azad University, Tabriz, Iran
[2]Department of Cellular and Molecular Biology, Marand Branch, Islamic Azad University, Marand, Iran

[*]*Corresponding author*: Ph.D., Department of Cellular and Molecular Biology, Marand Branch, Islamic Azad University, Marand, Iran. Email: onsoribiomol@marandiau.ac.ir

Received 2018 January 09; **Revised** 2018 February 10; **Accepted** 2018 April 03.

Abstract

Background: C-reactive protein (CRP) is an acute-phase protein that serves as an early biomarker for inflammation. It has been associated with an increased risk of Type 2 Diabetes Mellitus (T2DM).
Objectives: This research investigated the association of +1059 G>C (rs1800947) polymorphism in the *CRP* gene with T2DM in the northwestern population of Iran.
Methods: In this case-control study, genomic DNA was extracted from human subjects, involving 77 unrelated T2DM patients and 80 unrelated non-diabetic volunteers of a northwestern population of Iran. The *CRP* gene was analyzed by genotyping for +1059 G>C (rs1800947), allele-specific polymerase chain reaction (AS-PCR).
Results: There were 24 (15.3%) CC genotypes, 126 (80.2%) CG genotypes, and seven (4.5%) GG genotypes. There was a significant relationship between the CG genotype of *CRP* +1059 G>C gene polymorphism and T2DM (P value = 0.037, 95% CI, OR = 2.385).
Conclusions: The CRP was associated with T2DM in this population. The frequency of the C allele was high in the northwestern population of Iran. The CG genotype almost doubled the risk of T2DM, which has not been reported in Iran previously. However, the primary finding of this study needs subsequent validation studies.

Keywords: C-Reactive Protein, Gene, Polymorphism, Genotype, Type 2 Diabetes Mellitus

1. Background

Insulin resistance and decreased insulin secretion are the basic features of T2DM (1-4). Changes in glucose metabolism are the primitive cause of T2DM (5). Physiological functions are facilitated by plasma levels of glucose up to 100 mg/dL in mammalian species (6). Overall, diabetes can be categorized into two types, as follows: Type 1 diabetes, in which people have problems producing insulin due to the destruction of the cell that produces this hormone (lack of insulin), and T2DM, which includes almost 90% of all diabetes cases, worldwide, and is caused by insufficient production of insulin or by a malfunction of this hormone or its receptor (resistance to insulin) (7, 8). In April 2016, the International Diabetes Federation (IDF), reported that 415 million people had diabetes, worldwide, which is predicted to increase to 642 million (http://www.diabetesatlas.org) by 2040. There were about 4.5 million cases of diabetes in Iran in 2014, and 38 079 people were reported to have died from the disease that year (9).

Furthermore, T2DM is a complex metabolic and endocrine disorder, which results from the interaction between several genetic and environmental factors. These factors lead to a complex and progressive disease that occurs in varying degrees of insulin resistance (10). It has been proposed that increased adipokines, inflammatory cytokines, non-esterified fatty acids, mitochondrial dysfunction, lipotoxicity, glucotoxicity, and amyloid formation for β-cell dysfunction are responsible for insulin resistance. Furthermore, T2DM has a strong genetic component, yet, only a few genes have been identified so far (11). Evidence shows that metabolic and inflammatory factors associated with diabetes, such as high glucose, modified lipoproteins, adipokines, and free fatty acids, may give rise to CRP production by smooth muscle cells, endothelial cells, macrophages, and monocytes (12-18). In recent epidemiologic studies, it has been shown that CRP level is a predictor of diabetes mellitus (19, 20).

As an acute phase reactant, CRP is preoccupied in acute and chronic inflammation (21). Inflammation or tissue injury and infection rapidly stimulate CRP production. While hepatocytes synthesize CRP, several trans-acting cytokines, such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-1 and 6 (IL-1, 6) control its expression (22). The +1059 G>C (rs1800947) polymorphism is located in exon 2 of the *CRP* gene. This SNP does not change the protein structure at the amino acid level; thus, it is a silent SNP (CTG→CTC; Leu→Leu at codon 184). The protein levels of *CRP*, as reported previously, are affected by this SNP, which contributes to Coronary Artery Disease (CAD) progression and T2DM (23).

2. Objectives

Since CRP with T2DM in the population of Northwestern Iran has noticeably received insufficient attention so far, this research aimed at investigating the association of +1059 G>C polymorphism with T2DM in this population.

3. Methods

3.1. Study Subjects

In this case-control study, 77 T2DM patients and 80 control subjects were recruited from health care centers and Taleghani hospital (Tabriz, Iran) between April 2016 and October 2016. All participating subjects were unrelated Iranians and originated from different parts of the northwest of the country. The cases (21 males and 56 females, mean age of 50.43 $\pm$ 15.93 years and BMI = 27.72 $\pm$ 2.50) were diagnosed as having T2DM and confirmed by the World Health Organization (WHO), 1997, criteria (24). Criteria for case (T2DM) selection were the use of hypoglycemic medication or Fasting Plasma Glucose (FPG) $\geq$ 7.0 mmol/L and FPG $\geq$ 11.1 mmol/L after a two-hour Oral Glucose Tolerance Test (OGTT). Controls (30 males and 50 females, mean age of 49.39 $\pm$ 13.18 years and BMI of 25.75 $\pm$ 3.26) were individuals, who had no known history of T2DM, not taking antidiabetic medications, and had FPG < 6.1 mM/L and FPG < 11.0 mmol/L after two-hour OGTT. Following the principles of medical ethics, this study was approved by the Ethics Committee of Tabriz University of Medical Sciences. After informing the participants about the aims of this research, the researchers took their written informed consent and then obtained blood samples. For all participants, data were collected based on gender and age (y), and the Body Mass Index (BMI), as weight in kg/height^2 in m^2, was calculated.

3.2. Genomic DNA Extraction and Molecular Genotyping

All of the molecular experiments in this study were carried out at the laboratory of research molecular biology, Marand branch, Islamic Azad University. From 1 mL of EDTA anti-coagulated peripheral blood leucocytes of all the subjects, genomic DNA was extracted by the Rapid Genomic DNA Extraction (RGDE) method (25). For analyzing the mentioned polymorphism, allele-specific PCR (AS-PCR) method used. The primers used in the PCR were: 5'- CATTTGTACAAGCTGGGAGT-3' as a constant forward primer, 5'- ATGGTGTTAATCTCATCTGGTGGG-3', as a specific reverse for allele C, and 5'- ATGGTGTTAATCTCATCTGGTGGC-3', as a specific reverse for allele G. The PCR reactions were carried out in 15 μL of reaction mixture as a final volume containing 7.5 μl of 2X Master mix (from BIORON company, containing 1 unit Taq DNA polymerase, 0.1 mM of each dNTPs, 2.5 mM $MgCl_2$, 0.01% Tween 20, 65 mM Tris- HCl and 16 mM $(NH_4)2SO_4$), 5 pmoles of each primer, and about 1 μg of genomic DNA on a gradient thermocycler (LabCycler/SensoQuest, Germany). The conditions for touchdown PCR were as follows: 95°C, three minutes, (94°C, 45 seconds; 69 to 63°C, with 1°C decrease in each cycle, 45 seconds; 72°C, 45 seconds) 6 cycles, (94°C, 45 seconds; 63°C, 45 seconds; 72°C, 45 seconds) 30 cycles, 72°C, 7 minutes. The amplified fragments (237 bp) were detected on 2% agarose gel stained with DNA safe stain (Cinnagen, Iran). In order to determine the fragment size, a 50-bp ladder (Cinnagen, Iran, Cat. No. PR901633) was used. To reduce the genotyping error, genotyping was repeated in 10% to 15% of the samples and positive controls were used for both the alleles, Figure 1.

3.3. Statistical Analysis

All the statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). The clinical characteristics of the subjects via Mean $\pm$ SD and the P value for calculating the significance of the differences in the two groups were examined by the *t*-test. Also, the disease outcome was examined by the logistic regression analyses with the results were presented as OR (95% confidence interval). Chi-square (χ^2) analysis was performed for disease association in the groups.

4. Results

Clinical and baseline characteristics of cases and controls have been summarized in Table 1. There was a significant difference in age (P value = 0.00) and BMI (P value = 0.00) between the two groups of patients and healthy controls (P value = 0.00, and BMI P value = 0.00). However,

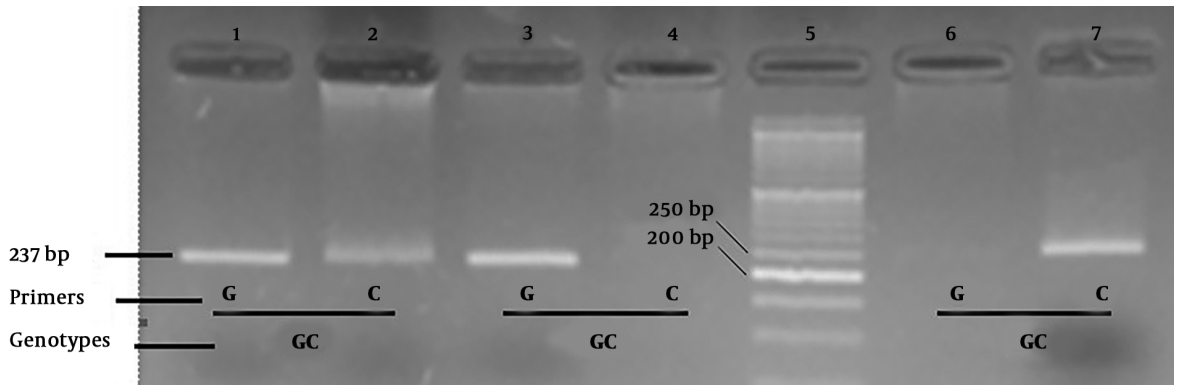

Figure 1. AS-PCR based genotypes for *CRP* +1059 G>C (rs1800947). Lanes 1 and 2 contain the PCR product with heterozygote (GC) genotype, lanes 3 and 4 contain the G allele with homozygote (GG) genotype, lane 5 contains the 50 bp DNA ladder and lanes 6 and 7 contain C allele homozygote (CC) genotype.

there was no significant difference between T2DM patients and healthy controls in terms of gender.

Allele and genotype frequencies of *CRP* +1059 G>C (rs1800947) for each group are shown in Table 2, individually. Table 2 also shows the genotype and allelic distribution of +1059 G>C polymorphism for *CRP* gene between the cases and controls. The allele frequencies for C and G in the control groups were 0.57 and 0.43, and in T2DM patients, the frequencies for C and G alleles were 0.54 and 0.46, respectively. The genotype frequencies for CC, CG, and GG in the controls were 0.103, 0.87, and 0.025, and the T2DM subjects had genotype frequencies of 0.02, 0.737, and 0.062 for CC, CG, and GG, respectively (Table 2).

There was a significant difference between the genotype frequencies among diabetics and controls. An important finding of this analysis was a significant correlation between the *CRP* gene polymorphism and family history of the disease. No such correlation was previously found for this gene, at least in the Iranian population. The genotype frequencies showed a meaningful distinction in comparison to controls (P value = 0.037, OR = 2.385 for CG genotype). The G allele appears to pose a higher risk to T2DM than to controls. According to Table 2, the odds ratio of the C allele in cases to controls was equal to 0.91, showing that allele C frequency in cases was 9% less than that in controls. The odds ratio of the G allele in cases to controls was 1.02. In other words, G allele frequency was 1.02% higher than that in the control group, and the odds ratios of the C allele to the G allele was 0.89. This implies that the group with higher C allele frequency than G allele frequency was afflicted with type 2 diabetes 11% (1 - 0.89 × 100) less than the group with higher G allele frequency. Considering the significant relationship between this disease and the CG genotype, as shown in Table 2, it can be concluded that this disease is caused by the G allele.

5. Discussion

The present study addressed the possible correlation of the *CRP* +1059 G>C (rs1800947) gene polymorphism with susceptibility to T2DM, as well as the relationship between BMI, age, gender, and T2DM in a sample of the Iranian population. The study indicated a high frequency for C allele in the northwestern population of Iran (55.4%), while in studies conducted on other world populations, the G allele was reported to be of high frequency (90.0% to 96.3%) (23, 26).

The results showed a significant difference between the +1059 G>C polymorphism in genotype CG and G allele in the patient and control groups (OR = 2.385 at 95% CI). There are a number of studies about the correlation of CRP +1059 G>C polymorphism with T2DM. In addition, the results of available association studies have conflicting results. Also, several studies have been unsuccessful to report a correlation between the +1059 G>C polymorphism with either Coronary Artery Disease (CAD), T2DM (27) and Acute Coronary Artery (ACA) (28). The results of a study conducted between T2DM and control groups in a Turkish population showed a high level of CRP for the patient group, however, there wasn't any association between +1059 G>C (rs1800947) polymorphism and CRP levels or T2DM (29). In another study on the Chinese population, results showed that there is an association between individuals with GG/GC genotypes and higher CRP levels. Also, in a comparison between cases with CAD or Myocardial Infarction (MI) and control group, CRP levels were high in CAD and MI cases. However, there was no significant association between CAD and +1059 G>C polymorphism (30). On the other hand, a study on an Egyptian population showed that CRP levels are high in carriers of CC and GC genotypes in both individuals with Acute Myocardial Infarction (AMI) and controls, yet there wasn't any associa-

Table 1. Characteristics of the Subjects Included in This Study

Characteristics	Type 2 Diabetics, N = 77	Controls, N = 80	P Value	OR (95% CI)
Age, y	50.42 ± 15.93	39.49 ± 13.18	0.00	0.962
Gender			0.173	
Male	21	30		
Female	56	50		
BMI, Kg/m^2	27.72 ± 2.50	25.75 ± 3.26	0.00	0.843

Abbreviations: BMI, body mass index, OR, odds ratio.

Table 2. Comparison of Genotypic, Allelic Distribution and Genotypic Percentage of *CRP* +1059 G>C (rs1800947) Gene Among the Subjects with T2DM and Healthy Controls

CRP+1059 G>C (rs1800947)	Type 2 Diabetics	Healthy Controls	OR (95%CI)	P Value	χ^2	Nominal	number	Percentage Value
Genotype numbers								
CC	8	16		0.094	2.79	0.134	24	15.3
CG	67	59	2.385	0.037	4.355	0.167	126	80.2
GG	2	5		0.268	1.229	0.088	7	4.5
Total	77	80					157	100
Allele Frequency								
C	0.54 (83)	0.57 (91)		0.111				
G	0.46 (69)	0.43 (69)		0.111				

tion between the genotypes and the risk of AMI (31). Therefore, there is an association between higher CRP levels and alleles in most studies yet not with the disease. In addition, significant differences exist between T2DM and controls regarding of age and BMI, yet there were not any significant differences between T2DM patients and healthy controls regarding gender.

Diabetes is the most common endocrine metabolic disorder, which can reduce life expectancy by one-third (32). Diabetes has affected over 415 million people around the world, and this number will rise by 2040 (9). Poorly controlled diabetes may result in retinopathy, nephropathy, and neuropathy. Most studies have reported the association of T2DM with inflammatory markers. Previously, some studies have reported the association of inflammatory markers, such as interleukin 6 (IL6), adiponectin, and CRP with T2DM (33). In a study on the population of Rotterdam, an association between higher EN-RAGE levels and an increased risk of incident pre-diabetes was revealed, and there was an association between higher IL13 levels and a decreased risk of pre-diabetes, incident T2DM. However, higher IL17 levels were associated with a decreased risk of T2DM incidence. Also, the findings of this study are in line with previous studies, in which the associations between high CRP levels and the increased risk of T2DM were revealed (34). As cross-sectional studies conducted on Chinese population revealed, there is a positive relationship between CRP and prediabetes, such as hyperglycemia and metabolic syndrome on the one hand and prevalent diabetes on the other (35). In addition, recent studies found that the risk of T2DM increases when baseline plasma CRP levels are elevated (15, 20).

Some other studies showed the accumulation of subcutaneous fat to be galore in Chinese women when compared to men. This can explain the strong relationship between CRP and glycemia (5). However, the two cohort studies conducted on Mexican (36) and German populations (37) showed a positive relationship between CRP and T2DM in women rather than men; the two other studies conducted on a Japanese population did not find any significant differences between men and women in this regard (19). A recent study revealed a positive relationship between CRP and increased risk of undiagnosed diabetes rather than the incidence of diabetes, implying that CRP is not or cannot be a causal factor in diabetes yet a marker of hyperglycemia in the pathway (38). There is little information about the role of IL6R polymorphisms in T2DM risk. Qi et al. revealed that the rs2229238 IL6 polymorphism might interact with C-Reactive Protein (CRP) in women and predict diabetes risk. Conversely, the same researchers, investigating this SNP in European Caucasian women, found no significant risk of T2DM (39). In a study with an Iranian sample, Galavi et al. investigated rs2229238 and rs4845625 interleukin 6 receptor gene poly-

morphisms and found a significant association between rs22229238 and rs4845625 polymorphisms and T2DM (18). In this study, the researchers found that there was a significant difference in the CRP +1059 G>C (rs1800947) polymorphism between the T2DM patients and control group and the frequency of CG genotype was significantly higher. However, the current study had several limitations. First, this study was limited to an Iranian population. Second, the sample size was relatively small. Thus, the authors suggest that more carefully constructed replications with different populations are necessary to validate and further expand the finding.

5.1. Conclusions

In conclusion, the current results indicated a significant association between *CRP* +1059 G>C (rs1800947) gene polymorphism and T2DM.

Acknowledgments

The authors thank all patients and volunteers for their participation in the study.

References

1. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. *Diabetes Res Clin Pract*. 2004;**66 Suppl 1**:S37–43. doi: 10.1016/j.diabres.2003.11.024. [PubMed: 15563978].
2. Kahn CR, Vicent D, Doria A. Genetics of non-insulin-dependent (type-II) diabetes mellitus. *Annu Rev Med*. 1996;**47**:509–31. doi: 10.1146/annurev.med.47.1.509. [PubMed: 8712800].
3. Lehtovirta M, Kaprio J, Forsblom C, Eriksson J, Tuomilehto J, Groop L. Insulin sensitivity and insulin secretion in monozygotic and dizygotic twins. *Diabetologia*. 2000;**43**(3):285–93. doi: 10.1007/s001250050046. [PubMed: 10768089].
4. Florez JC, Hirschhorn J, Altshuler D. The inherited basis of diabetes mellitus: Implications for the genetic analysis of complex traits. *Annu Rev Genomics Hum Genet*. 2003;**4**:257–91. doi: 10.1146/annurev.genom.4.070802.110436. [PubMed: 14527304].
5. Jerneld B, Algvere P. Relationship of duration and onset of diabetes to prevalence of diabetic retinopathy. *Am J Ophthalmol*. 1986;**102**(4):431–7. [PubMed: 3766657].
6. Henriksen EJ, Diamond-Stanic MK, Marchionne EM. Oxidative stress and the etiology of insulin resistance and type 2 diabetes. *Free Radic Biol Med*. 2011;**51**(5):993–9. doi: 10.1016/j.freeradbiomed.2010.12.005. [PubMed: 21163347]. [PubMed Central: PMC3071882].
7. Saravani R, Esmaeeli E, Kordi Tamendani M, Narooie Nejad M. Oxytocin receptor gene polymorphisms in patients with diabetes. *Gene, Cell and Tissue*. 2015;**2**(2). e60171. doi: 10.17795/gct-27904.
8. de Almeida-Pititto B, Dias ML, de Moraes AC, Ferreira SR, Franco DR, Eliaschewitz FG. Type 2 diabetes in Brazil: Epidemiology and management. *Diabetes Metab Syndr Obes*. 2015;**8**:17–28. doi: 10.2147/DMSO.S72542. [PubMed: 25609989]. [PubMed Central: PMC4298341].
9. International Diabetes Federation. *International diabetes federation Middle East and North Africa*. 2015. Available from: http://www.idf.org/membership/mena/iran.
10. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: Principles of pathogenesis and therapy. *Lancet*. 2005;**365**(9467):1333–46. doi: 10.1016/S0140-6736(05)61032-X. [PubMed: 15823385].
11. Dedoussis GV, Kaliora AC, Panagiotakos DB. Genes, diet and type 2 diabetes mellitus: A review. *Rev Diabet Stud*. 2007;**4**(1):13–24. doi: 10.1900/RDS.2007.4.13. [PubMed: 17565412]. [PubMed Central: PMC1892523].
12. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, et al. The relation of markers of inflammation to the development of glucose disorders in the elderly: The cardiovascular health study. *Diabetes*. 2001;**50**(10):2384–9. [PubMed: 11574423].
13. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;**286**(3):327–34. [PubMed: 11466099].
14. Festa A, D'Agostino R Jr, Tracy RP, Haffner SM; Insulin Resistance Atherosclerosis Study. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of type 2 diabetes: The insulin resistance atherosclerosis study. *Diabetes*. 2002;**51**(4):1131–7. [PubMed: 11916936].
15. Spranger J, Kroke A, Mohlig M, Hoffmann K, Bergmann MM, Ristow M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: Results of the prospective population-based European prospective investigation into cancer and nutrition (EPIC)-potsdam study. *Diabetes*. 2003;**52**(3):812–7. [PubMed: 12606524].
16. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol*. 2011;**11**(2):98–107. doi: 10.1038/nri2925. [PubMed: 21233852].
17. Qi L, Rifai N, Hu FB. Interleukin-6 receptor gene, plasma C-reactive protein, and diabetes risk in women. *Diabetes*. 2009;**58**(1):275–8. doi: 10.2337/db08-0968. [PubMed: 18852330]. [PubMed Central: PMC2606885].
18. Galavi HR, Saravani R, Alamdari AR, Ranjbar N, Damani E, Nakhzari Khodakhier T. Evaluating the effect of the rs2229238 and the rs4845625 interleukin 6 receptor gene polymorphisms on body mass index and the risk of type 2 diabetes in an Iranian study population. *Int J High Risk Behav Addict*. 2016;**5**(4). e33289. doi: 10.5812/ijhrba.33289.
19. Doi Y, Kiyohara Y, Kubo M, Ninomiya T, Wakugawa Y, Yonemoto K, et al. Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: The Hisayama Study. *Diabetes Care*. 2005;**28**(10):2497–500. [PubMed: 16186286].
20. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;**53**(3):693–700. [PubMed: 14988254].
21. Kushner I. The phenomenon of the acute phase response. *Ann N Y Acad Sci*. 1982;**389**(1 C-Reactive Pr):39–48. doi: 10.1111/j.1749-6632.1982.tb22124.x.
22. de Ferranti S, Rifai N. C-reactive protein and cardiovascular disease: A review of risk prediction and interventions. *Clin Chim Acta*. 2002;**317**(1-2):1–15. [PubMed: 11814453].
23. Kaur R, Matharoo K, Sharma R, Bhanwer AJ. C-reactive protein + 1059 G>C polymorphism in type 2 diabetes and coronary artery disease patients. *Meta Gene*. 2013;**1**:82–92. doi: 10.1016/j.mgene.2013.10.012. [PubMed: 25606378]. [PubMed Central: PMC4205026].
24. Expert Committee on the D, Classification of Diabetes M. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2003;**26 Suppl 1**:S5–20. [PubMed: 12502614].
25. Saremi MA, Saremi M, Tavallaei M. Rapid genomic DNA extraction (RGDE). *Forensic Sci Int: Genet Supplement Series*. 2008;**1**(1):63–5. doi: 10.1016/j.fsigss.2007.12.001.
26. Pasalic D, Marinkovic N, Grskovic B, Ferencak G, Bernat R, Stavljenic-Rukavina A. C-reactive protein gene polymorphisms affect plasma CRP and homocysteine concentrations in subjects with and without angiographically confirmed coronary artery disease. *Mol Biol Rep*. 2009;**36**(4):775–80. doi: 10.1007/s11033-008-9244-1. [PubMed: 18401567].

27. Grammer TB, Marz W, Renner W, Bohm BO, Hoffmann MM. C-reactive protein genotypes associated with circulating C-reactive protein but not with angiographic coronary artery disease: The LURIC study. *Eur Heart J*. 2009;**30**(2):170–82. doi: 10.1093/eurheartj/ehn191. [PubMed: 18499652].
28. Duran GG, Fansa I, Duran N, Jened K, Onlen C, Miraloglu M, et al. The relationship between acute coronary artery diseases with c-reactive protein+1059 G/C and angiotensin-converting enzyme I/D gene polymorphisms. *Int J Clin Exp Med*. 2016;**9**:20126–36.
29. Yavuz DG, Yüksel M, Özben B, Sancak S, Deyneli O, Akalın S. C-reactive protein 1059G/C gene polymorphism in type 2 diabetic patients. *Turk J Endocrinol Metab*. 2010;**14**(4):85–8.
30. Dai DF, Chiang FT, Lin JL, Huang LY, Chen CL, Chang CJ, et al. Human C-reactive protein (CRP) gene 1059 G>C polymorphism is associated with plasma CRP concentration in patients receiving coronary angiography. *J Formos Med Assoc*. 2007;**106**(5):347–54. doi: 10.1016/S0929-6646(09)60319-3. [PubMed: 17561469].
31. Ghattas MH, Abo-Elmatty DM, El-Eraki AZ. C-reactive protein 1059G/C gene polymorphism, C-reactive protein levels and acute myocardial infarction. *J Cardiovasc Med (Hagerstown)*. 2012;**13**(11):716–9. doi: 10.2459/JCM.0b013e3283577170. [PubMed: 22828776].
32. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;**27**(5):1047–53. [PubMed: 15111519].
33. Wang X, Bao W, Liu J, Ouyang YY, Wang D, Rong S, et al. Inflammatory markers and risk of type 2 diabetes: A systematic review and meta-analysis. *Diabetes Care*. 2013;**36**(1):166–75. doi: 10.2337/dc12-0702. [PubMed: 23264288]. [PubMed Central: PMC3526249].
34. Brahimaj A, Ligthart S, Ghanbari M, Ikram MA, Hofman A, Franco OH, et al. Novel inflammatory markers for incident pre-diabetes and type 2 diabetes: The rotterdam study. *Eur J Epidemiol*. 2017;**32**(3):217–26. doi: 10.1007/s10654-017-0236-0. [PubMed: 28258520]. [PubMed Central: PMC5380703].
35. Yang T, Chu CH, Hsieh PC, Hsu CH, Chou YC, Yang SH, et al. C-reactive protein concentration as a significant correlate for metabolic syndrome: A Chinese population-based study. *Endocrine*. 2013;**43**(2):351–9. doi: 10.1007/s12020-012-9743-7. [PubMed: 22810425].
36. Han TS, Sattar N, Williams K, Gonzalez-Villalpando C, Lean ME, Haffner SM. Prospective study of C-reactive protein in relation to the development of diabetes and metabolic syndrome in the Mexico City diabetes study. *Diabetes Care*. 2002;**25**(11):2016–21. [PubMed: 12401749].
37. Thorand B, Baumert J, Kolb H, Meisinger C, Chambless L, Koenig W, et al. Sex differences in the prediction of type 2 diabetes by inflammatory markers: Results from the MONICA/KORA Augsburg case-cohort study, 1984-2002. *Diabetes Care*. 2007;**30**(4):854–60. doi: 10.2337/dc06-1693. [PubMed: 17392546].
38. Pan A, Wang Y, Yuan JM, Koh WP. High-sensitive C-reactive protein and risk of incident type 2 diabetes: A case-control study nested within the Singapore Chinese health study. *BMC Endocr Disord*. 2017;**17**(1):8. doi: 10.1186/s12902-017-0159-5. [PubMed: 28178951]. [PubMed Central: PMC5299777].
39. Qi L, Rifai N, Hu FB. Interleukin-6 receptor gene variations, plasma interleukin-6 levels, and type 2 diabetes in U.S. women. *Diabetes*. 2007;**56**(12):3075–81. doi: 10.2337/db07-0505. [PubMed: 17898129].