ORIGINAL ARTICLE

Adiponectin Gene Polymorphisms as Potential Biomarker for Development of Type 2 Diabetes Mellitus in Kumaon Region Population

Sanjeev Kumar Shukla[1], Seema Gupta[2], Vivekanand Satyawali[3]

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a worldwide health problem caused by resistance to insulin action. Polymorphism of adiponectin gene was found to be implicated in the pathogenesis of T2DM in numerous populations. Adiponectin is secreted by fat cells and is linked with insulin resistance. **Methodology:** The study included fifty patients with T2DM and fifty healthy individuals served as a control group to assess the association of adiponectin gene (*ADIPOQ*). The genotyping studies were performed by polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) methods. **Results:** Mean levels of various anthropometric and biochemical parameters were significantly higher in T2DM than healthy controls. The levels of circulatory adiponectin were found significantly lower in T2DM as compared to healthy controls and Serum leptin levels were moderately higher in the diabetic than those in the nondiabetic. There was no significant association of CC and CG genotypes with T2DM patients. C and G allele frequencies of the *rs266729* were also not significantly associated with T2DM cases as compared to healthy controls. It was observed that significant impact on circulatory adiponectin levels for *rs266729* polymorphism with GG genotype having very low circulatory adiponectin level. There was no significant association of CC, CG genotype and C, G allele frequencies of *rs266729* in with T2DM cases as compared to healthy controls. **Conclusion:** The *rs266729* > G SNP of adiponectin gene is a risk factor for the development of T2DM in Kumaon population.

KEY WORDS: Adiponectin, Diabetes, Disease, Health, Human.

Introduction

Diabetes mellitus is a major global public health problem that has a significant impact on public health and social and economic development worldwide. Although the incidence has begun to decline in some countries, the prevalence of diabetes has increased in most other developed and developing countries over the past decades[1–3]. In India, 77 million adults currently have diabetes and this number is expected to nearly double to 134 million until 2045[4].

Diabetes is a leading cause of chronic disease and is becoming a global health problem of epidemic proportions. T2DM is the most common form of diabetes, accounting for 90% of the diabetic population[5]. T2DM and its complications are a huge burden for both patients and healthcare systems. This phenotype makes vessels more susceptible to diabetes and its complications[6]. Adipocytokines are cytokines secreted by adipose tissue. These include adiponectin and leptin, among others[7]. Adiponectin primarily modulates glucose regulation and fatty acid catabolism[8]. Although adiponectin is produced in adipose tissue, it reduces adiposity, and circulating adiponectin levels are inversely related to body fat percentage in adults, for which there are

Access this article online

Quick Response Code:

Website: www.jmsh.ac.in

Doi: 10.46347/jmsh.v9i3.23.162

[1]Multidisciplinary Research Unit, Government Medical College, Haldwani, Nainital, Uttarakhand, India, [2]Department of Biochemistry, Government Medical College, Haldwani, Nainital, Uttarakhand, India, [3]Department of Medicine, Government Medical College, Haldwani, Nainital, Uttarakhand, India

Address for correspondence:
Sanjeev Kumar Shukla, Multidisciplinary Research Unit, Government Medical College, Haldwani, Nainital, Uttarakhand, India.
E-mail: sanjeevcloning@gmail.com

significantly increases after weight loss[9]. Adiponectin protects against obesity, type 2 diabetes and atherosclerosis. The adiponectin gene is located on human chromosome 3q27[10], a region that has been identified as a susceptibility locus for metabolic syndrome and type 2 diabetes[11].

Low adiponectin is considered an independent risk factor for the development of T2DM, dyslipidemia, and cardiovascular disease[12]. Adipokine is known to play a central role in obesity, insulin resistance, and diabetes. Its expression is also found in mononuclear leukocytes, macrophages, intestinal epithelium, astrocytes, skeletal muscle cells, spleen and bone marrow cells, and its levels are increased in obesity and diabetes[13]. Leptin is a key hormone that regulates energy intake. and costs in the control of appetite and glucose metabolism[14]. It is mainly secreted by adipocytes, and circulating levels of leptin are directly proportional to the total amount of fat in the body[15]. Deficiency of Leptin resistance leads to uncontrolled food consumption, obesity and diabetes. It can also cause atherosclerosis, hypertension and coronary artery disease[16].

Adiponectin, together with leptin, has been shown to completely reverse insulin resistance in mice[17]. Indus has a unique body structure characterized by increased abdominal fat deposition despite a correspondingly low body mass index[18]. Adiponectin and leptin levels are correlated in type 2 diabetes and obesity[19]. The discovery of early biochemical changes associated with this stage of the disease is important in identifying individuals at risk of developing DM and who may benefit from the intervention programs described above[20].Adiponectin belongs to the peptide hormones , which are secreted by fat cells collectively as adipocytokines[21]. Serum adiponectin levels and possibly the risk of developing insulin resistance and subsequent disease outcomes may also be influenced by single nucleotide polymorphisms (SNPs) in *ADIPOQ*, the gene that encodes the protein adiponectin[22]. In this study, with this background, one of the goals is to investigate the genetic association of *ADIPOQ* gene variants with type 2 diabetes and other clinical and anthropometric studies.

Methodology

Patients with type 2 diabetes mellitus

It contained fifty patients with T2DM randomly selected from the tertiary care referral hospital, Medicine Out Patient Department in Dr. Susheela Tiwari Government Hospital, Haldwani, Nainital, Uttarakhand. Inclusion criteria for cases was, age $\geq$ 20 years of both genders diagnosed with T2DM, Patients who were diagnosed by specialist physicians as having T2DM, fasting glucose level was > 126 mg/dl (7.0 mmol/l) with symptoms of T2DM. Patients were excluded from this study, pregnant woman, diagnosed with T1DM, under insulin treatment and treated with antihyperlipidaemic medicines.

Healthy Controls

The control group contained fifty apparently healthy individuals. Inclusion criteria for control was, age $\geq$ 20 years of both genders. They were selected randomly from relatives of patients and other volunteers. They were free from symptoms and signs of any chronic diseases such as DM, cardiac diseases, heart diseases, hypertension, renal diseases or others. All cases completed detailed questionnaire included the essential information, i.e., age, sex, family history, medicine history and any other relevant information. Weight, height and BMI were measured for all participants and the BMI values were calculated.

Biochemical measurements

Biochemical measurements including fasting: blood sugar (FBS), total cholesterol, triglycerides, HDLc, LDLc and VLDLc were achieved by spectrophotometric techniques with the use of enzymatic procedures.

Collection of Blood Samples

Fasting blood samples were collected from subjects' antecubital median vein after an overnight fast using disposable plastic syringes while observing all aseptic precautions. To avoid hemolysis, the blood was immediately transferred to a dry, clean plastic tube with gentle pressure. Blood was collected in EDTA vial (Levram Lifesciences Silvassa, India) from both groups (Healthy Control and T2DM patients) for molecular research studies. The research was done in the Multidisciplinary Research Unit (DHR-ICMR, New Delhi), Government Medical College, Haldwani, Nainital, Uttarakhand, India

Genomic DNA Extraction

Genomic DNA was isolated from human blood samples by using genomic DNA extraction kit (GeneJET Genomic DNA Purification Kit, Thermo Fisher

Scientific, USA) as per the manufacturer's instructions using centrifuged (Eppendorf 5424R, Germany). After extraction, DNA samples (working) was stored at 4°C for 7 days before spectrophotometric (analysis and then stored in a freezer at −20°C (Vestfrost, Denmark). DNA concentration and purity were measured by ultraviolet (UV) spectrophotometry using an Eppendorf Biospectrophotometer (Eppendorf, Hamburg, Germany) using 1 μL of each sample. The spectra were recorded wavelength range of 220–830 nm.

DNA Integrity and Agarose gel electrophoresis

DNA was analyzed by agarose gel electrophoresis (Bio-Rad Mini Gel Electrophoresis Unit, USA) using 0.8% agarose gel (Ameresco USA). Electrophoresis was performed using 10X TBE Buffer (Tris-borate-EDTA) (Thermo Scientific, USA) buffer containing 1 μg/ml of Ethidium Bromide (EtBr) (VWR Amresco Life Science, USA) and a constant voltage of 100 V for 50 min using PowerPac Universal (Bio-Rad Laboratories, USA). The DNA bands were visualized and images were acquired using Gel Doc XR+ Imaging system (Bio-Rad Laboratories, USA).

Polymerase Chain Reaction

Oligonucleotide primers were synthesized (Eurofins Genomics India Pvt. Ltd., Kerala, India), Oligonucleotide the forward primer, 5'-ACTTGCCCTGCCTCTGTCTG-3'and the reverse primer, 5'-CCTGGAGAACTGGAAGCTG-3' (Khan et. al., 2017). The primers for the PCR were as follow by PCR master mixture was prepared. Reactions were performed in a 25 μl volume containing 12.5 μl of the DreamTaq PCR master mix (2x) Thermo Fisher Scientific, USA (containing DreamTaq DNA polymerase, 2X DreamTaq buffer, 0.4 mM of each dNTP and 4 mM of $MgCl_2$), 0.5 μl each of 10 ng/μl forward and reverse primers (Eurofins Genomics India Pvt Ltd, Kerala, India), 11 μl of nuclease free water (Thermo Fisher Scientific, USA) and 0.5 μl of positive controls or nuclease free water for no template controls (NTC) per 25 μl of reaction mix in 0.2 ml flat cap PCR tubes (Axygen Scientific, USA). PCR reaction conditions, after an initial step of 5 min at 94°C, followed by 35 cycles of 30s at 94°C, 30s at 58°C, 30s at 72 °C, and a final extension step at 72°C for 7 min using the program temp control Thermal cycler System (Applied Biosystems ProFlex PCR System, USA). PCR products were verified on 2% agarose gel (VWR Amresco Life Science, USA) containing 10μg/ml EtBr and visualized by using Gel Doc XR+ Imaging system. The PCR products were digested with 10U of HhaI enzyme (Thermo Scientific, USA), at 37°C for overnight using Bacteriological Incubator (MAC, India). The restriction fragments of PCR products were separated on a 2.5% agarose gel. 50bp DNA ladder (Thermo Scientific, USA) was included in each run.

Results

Anthropometric and Clinical Characteristics

A total of 100 subjects were enrolled in this case-control group (50 T2DM subjects and 50 healthy controls). Age and sex were consistent between cases and controls ($p>0.05$). The biochemical profiles of both groups are shown in Table 1. Similarly, biochemical parameters such as blood glucose, HbA1c and SCr were also significantly increased in T2DM cases compared with healthy controls ($p<0.001$). In addition, a significant increase in triglyceride and her VLDL levels was observed in T2DM cases compared with healthy controls ($p = 0.012$ and $p = 0.009$, respectively). The levels of circulatory adiponectin were significantly lower in T2DM as compared to healthy controls ($p=0.02$), shown in Serum leptin levels were moderately higher in the diabetic than those in the nondiabetic.

Genotypes and Alleles Distribution

An amplification product of a 250bp fragment of the *ADIPOQ rs266729* gene (Figure 1) was detected for wild-type CC homozygotes (without the *HhaI* restriction site). For the homozygous GG mutant (presence of *HhaI* restriction site), 138 bp and 112 bp fragments were detected. The heterozygous CG contained three fragments of 250 bp, 138 bp and 112 bp (Figure 2). The genotype and allele frequencies of the *ADIPOQ* gene polymorphisms in the *rs266729* promoter region in T2DM patients and healthy controls are shown in Table 2. The frequencies of CC, CG and GG genotypes of *rs266729* were 60%, 32% and 8% in T2DM cases and 60%, 34% and 6% in healthy controls, respectively. The allele frequencies of C and G were 76%, 24% in T2DM and 77%, 23% in healthy controls. We also analyzed the predominant genotype (CC vs. CG+GG) and found no significant difference between T2DM cases and healthy controls. Similarly, the recessive genotype (CG+CC vs GG) showed no significant difference among T2DMs.

Table 1: Clinical and anthropometric parameters of T2DM cases and control groups

Parameters	Case (n=50)	Control (n=50)	P-value
AGE (years)	48.31±10.88	48.03±11.83	0.83
Gender (M/F)	32/18	29/21	0.28
BMI (kg/m2)	24.96±4.68	24.73±4.74	0.67
WC (cm)	95.13±7.32	96.57±8.58	0.34
WHR	0.99±0.06	0.95±0.06	<0.001*
SBP (mmHg)	140.75±26.65	114.45±7.52	<0.001*
DBP (mmHg)	82.39±15.67	70.21±8.69	<0.001*
FBS (mg/dl)	160.57±48.82	93.83±11.47	<0.001*
PPBS (mg/dl)	246.33±78.14	127.29±24.41	<0.001*
HbA1c (%)	8.01±2.09	5.30±0.72	<0.001*
Total Cholesterol (mg/dl)	166.82±46.22	157.73±46.27	0.09
Triglyceride (mg/dl)	167.80±58.81	148.35±68.36	0.009*
HDL (mg/dl)	37.39±10.48	38.91±11.34	0.34
LDL (mg/dl)	95.47±34.82	91.15±47.11	0.37
VLDL (mg/dl)	33.63±13.26	29.67±13.72	0.012*
Serum Creatinine (mg/dl)	2.27±1.39	0.91±0.25	<0.001*
Adiponectin (μg/ml)	1.89±0.92	2.22±1.68	0.02*
Leptin (μg/ml)	2.29±0.92	1.82±1.68	0.02*

Values are expressed as Mean ± Standard Deviation*Significant considered as P<0.05.
FBS: Fasting Blood Sugar, PPBS: Post-Prandial Blood Sugar, HbA1c: Glycated Haemoglobin, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Sugar, BMI: Body Mass Index, WC: Waist Circumference, TC: Total Cholesterol, TG: Triglyceride, HDL: High Density Lipoprotein, LDL: Low-Density Lipoprotein, VLDL: Very Low-Density Lipoprotein

Table 2: The genotypes and allele distribution of adiponectin *rs266729* gene polymorphism in case (T2DM) and control groups

rs266729 Polymorphism	Case N (%)	Control N (%)	P-value
Co dominant			
CC	30 (60.0)	30 (60)	-
CG	16 (32)	17 (34)	0.81
GG	4 (8)	3 (6)	0.21
Dominant			
CC	30 (60.0)	30 (60)	-
CG+GG	20 (40.0)	20 (40)	0.49

Discussion

SNP *rs266729* showing adiponectin levels and other biochemical parameters in patients from the T2DM population. Serum adiponectin levels were significantly lower in T2DM compared to healthy controls. Serum adiponectin levels in T2DM patients were lower than in healthy controls, and hypoadiponectinemia was strongly associated with T2DM, insulin resistance, obesity, and other metabolic diseases[23,24]. However, adiponectin in the *ADIPOQ* gene transcript is negatively correlated with systole and diastole. Adiponectin has a protective function against the development of hypertension independent of body fat distribution[25]. The *ADIPOQ* SNP, *rs266729*, is associated with prediabetic risk in univariate and multivariate models, further highlighting its interim role[26]. Serum adiponectin is involved in the pathogenesis of prediabetes, making it a potential genetic marker for prediabetes in this area. It remains possible to prevent the progression of prediabetes to T2DM[27,28]. The total concentrations of serum adiponectin while in human plasma, adiponectin

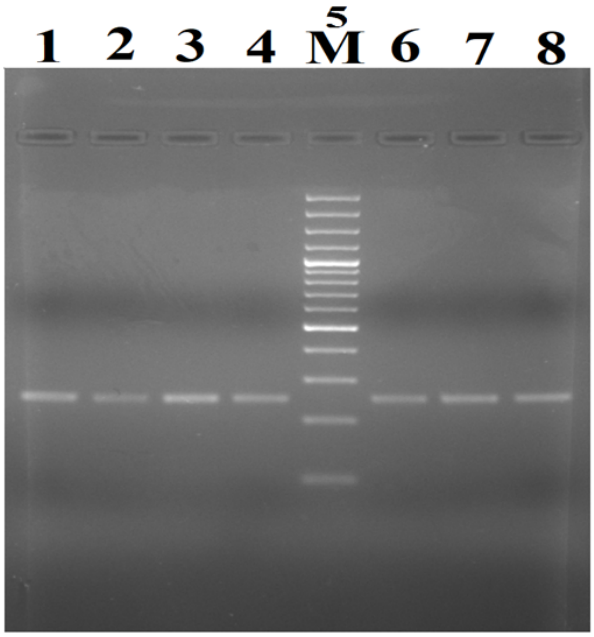

Figure 1: Agarose gel electrophoresis (2% agarose gel) showing fragment of 250 base pair PCR product detect in Adiponectin gene variant *rs266729* (-11377C/G); Lane 5: 100 bp DNA ladder; Lane 1 to Lane 8: 250 bp PCR product

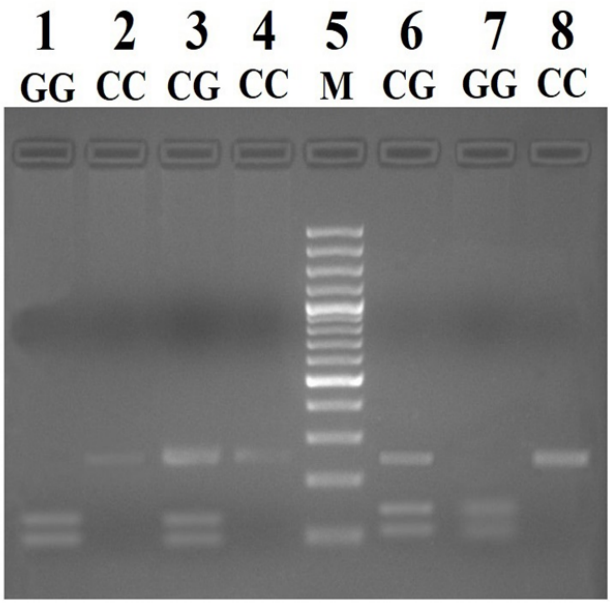

Figure 2: Genotypingresult for adiponectin geneSNP *rs266729*.Lane 5: 100 bp DNA ladder; GG genotype: 138/112bp, CC genotype: 250bp and CG genotype: 250/138/112bp

circulates in trimeric, hexameric and oligomeric forms which might be responsible for adiponectin insulin sensitizing effects[29]. This may be associated with a decreased adverse effect on health because higher waist circumference and central obesity was identified as a higher risk for cardiovascular diseases[30] and metabolic syndrome[31].Therefore, the adiponectin gene alteration is one of the risk factors for developing T2DM and ethnicity is a source of variability in the effects of gene alteration. The gene environment many genetic factors, including the adiponectin gene, influence the occurrence of T2DM.[32] Adiponectin gene is located in a region which is identified as a susceptibility locus for metabolic syndrome and T2DM. Adiponectin stages have been substantially located to be lower while as leptin and resistin is determined to be greater amongst T2DM instances than controls. These records indicate a possible function for the TG/GG genotype in reducing serum adiponectin ranges and in the risk of T2DM. Plasma adiponectin in topics with TG and GG genotypes in the T2DM crew used to be extensively lower than for these with the TT genotype[33]. Adiponectin is an adipokine with receptors expressed in the liver, muscle and endothelium of blood vessels. It has an insulin-sensitizing property and a necessary role in glucose and lipid metabolism[34]. Increasing ranges of plasma adiponectin result in a sensitizing impact on insulin motion and adiponectin concentrations limit in sufferers with T2DM, obesity and cardiovascular diseases[35]. The waist circumference, which is an index of stomach obesity and visceral fats deposition used to be extensively higher in the T2DM crew than in the control group. Therefore, elevated blood glucose ranges in T2DM may additionally be due to impaired insulin action with diminished adiponectin stage is positively related to HDLC stages and might also be protecting in opposition to cardiovascular diseases. The serum adiponectin level has a sizeable high-quality relationship with in nondiabetic topics but not in diabetic patients.

The adiponectin-coding gene is positioned on chromosome 3q27.3, a genomic area recognized as a susceptibility locus for T2DM[36]. So many genetic and environmental elements might also be implicated to recapitulate the influence of the allele. The G allele of SNP in adiponectin gene has an affiliation with obesity, insulin resistance and T2D in quite a few populations[37]. In weight problems the mRNA expression of adiponectin in adipocyte is lowered and low serum adiponectin ranges are associated to

excessive incidence of T2DM. The low adiponectin degree may additionally beautify the formation of small dense LDL particles, which are most damaging in vessels and normal in insulin resistance. It is feasible that adiponectin can also have a direct position on HDL catabolism. It has been stated that adiponectin deficiency may additionally impair the HDL synthesis in the liver[38]. The current case manipulates learn about has some strengths, boundaries and this is the first North Indian find out about that presents the statistics on the genetic affiliation between *ADIPOQ* variations and susceptibility closer to weight problems and metabolic syndrome risk. The find out about gathered the enough information related to the food regimen patterns and life-style behaviors which may want to act as attainable confounding elements in the sickness improvement and similarly worried in figuring out the gene-environment interactions. Some lookup businesses additionally determined comparable frequencies of CC, CG and GG genotype as properly C and G allele[39].

Conclusion

These differences had been impartial of age, gender, BMI and WC of the subjects. There had been no great association of CC, CG genotype and CG allele frequencies of the *rs266729* with T2DM cases as compared to wholesome controls. However, it was once located that GG genotype of *rs266729* has massive have an effect on circulatory adiponectin stages in T2DM cases. Further research is needed to entirely inspect the different polymorphisms of the adiponectin gene in T2DM, mechanisms underlying T2DM, identification of new biological molecules for newer therapeutic retailers for the management of T2DM and discover the outcomes of gene interactions, environmental elements and person genetic background and by the support of Doctor, Medical officer, NGO and community wise local health officer people should be aware of the risks of T2DM.

Acknowledgment

I appreciate the supporting staff of Multidisciplinary Research Unit and who contributed to this research work. I am thankful to Medicine Department and supporting staff for given patient's information and blood samples for this study. I acknowledge to Central lab of Dr. Susheela Tiwari Government Hospital, Haldwani for collection of control samples. I am highly grateful to Department of Health and Research, Ministry of Health & Family Welfare, New Delhi, India for funding of this research and also appreciative to Principal, Government Medical College, Haldwani, Nainital, Uttarakhand for given research place for this work in Multidisciplinary Research Unit laboratory.

Funding

I am highly grateful to Department of Health and Research, Ministry of Health & Family Welfare, New Delhi, India for supporting fund.

Conflict of Interest

None of the authors of this paper have a financial or personal relationship with other people or organization that could inappropriately influence or bias the content of the paper.

References

1. Howlader M, Sultana MI, Akter F, Hossain MM. Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. Heliyon. 2021;7(8):e07851. Available from: https://doi.org/10.1016/j.heliyon.2021.e07851.
2. Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et al. Prevalence and Ethnic Pattern of Diabetes and Prediabetes in China in 2013. JAMA. 2017;317(24):2515. Available from: https://doi.org/10.1001/jama.2017.7596.
3. Dwyer-Lindgren L, Mackenbach JP, Van Lenthe FJ, Flaxman AD, Mokdad AH. Diagnosed and Undiagnosed Diabetes Prevalence by County in the U.S., 1999–2012. Diabetes Care. 2016;39(9):1556–1562. Available from: https://doi.org/10.2337/dc16-0678.
4. International Diabetes Federation (ed) IDF Diabetes Atlas, International Diabetes Federation, Brussels, Belgium. 2021.
5. Wong YH, Wong SH, Wong XT, Yap QY, Yip KY, Wong LZ, et al. Genetic associated complications of type 2 diabetes mellitus. Panminerva Medica. 2022;64(2):274–288. Available from: https://doi.org/10.23736/S0031-0808.21.04285-3.
6. Bhat MA, Bhat SA, Ahmed SB, Qureshi W, Majid S, Ali A, et al. Biochemical profile and genetic polymorphism of MTHFRC677T in risk of type 2 diabetes mellitus. International Journal of Diabetes and Endocrinology. 2017;2(2):19–25. Available from: http://dx.doi.org/10.11648/j.ijde.20170202.13.
7. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in Obesity and Type 2 Diabetes: Close Association with Insulin Resistance and Hyperinsulinemia. The Journal of Clinical Endocrinology & Metabolism. 2001;86(5):1930–1935. Available from: https://doi.org/10.1210/jcem.86.5.7463.

8. Cui M, Gao Y, Zhao Y, Pang H, Chen L, Wang Z, et al. Association between Adiponectin Gene Polymorphism and Environmental Risk Factors of Type 2 Diabetes Mellitus among the Chinese Population in Hohhot. BioMed Research International. 2020;2020:1–9. Available from: https://doi.org/10.1155/2020/6383906.
9. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Reprint of "Paradoxical Decrease of an Adipose-Specific Protein, Adiponectin, in Obesity". Biochemical and Biophysical Research Communications. 2012;425(3):560–564. Available from: https://doi.org/10.1006/bbrc.1999.0255.
10. Dai MH, Xia T, Zhang GD, Chen XD, Gan L, Feng SQ, et al. Cloning, expression and chromosome localization of porcine adiponectin and adiponectin receptors genes. Domestic Animal Endocrinology. 2006;30(2):117–125. Available from: https://doi.org/10.1016/j.domaniend.2005.06.006.
11. Ghadge AA, Harke SM, Khadke SP, Diwan AG, Pankaj M, Kulkarni OP, et al. Circulatory adipocytokines and lipid profile variations in type-2 diabetic subjects: Desirable side-effects of antidiabetic drugs. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2014;8(4):230–232. Available from: https://doi.org/10.1016/j.dsx.2014.09.010.
12. Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC, et al. Circulating Concentrations of the Adipocyte Protein Adiponectin Are Decreased in Parallel With Reduced Insulin Sensitivity During the Progression to Type 2 Diabetes in Rhesus Monkeys. Diabetes. 2001;50(5):1126–1133. Available from: https://doi.org/10.2337/diabetes.50.5.1126.
13. Park KGG, Park KS, Kim MJJ, Kim HSJ, Suh YSS, Ahn JD, et al. Relationship between serum adiponectin and leptin concentrations and body fat distribution. Diabetes Research and Clinical Practice. 2004;63(2):135–142. Available from: https://doi.org/10.1016/j.diabres.2003.09.010.
14. Chong AY, Lupsa BC, Cochran EK, Gorden P. Efficacy of leptin therapy in the different forms of human lipodystrophy. Diabetologia. 2010;53(1):27–35. Available from: https://doi.org/10.1007/s00125-009-1502-9.
15. Bains V, Kaur H, Badaruddoza. Association study of the single-nucleotide polymorphisms −3971G/A and +276G/T in the adiponectin gene with type 2 diabetes in a North Indian Punjabi population. Annals of Human Genetics. 2020;84(3):235–248. Available from: https://doi.org/10.1111/ahg.12366.
16. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, et al. Role of leptin in the neuroendocrine response to fasting. Nature. 1996;382(6588):250–252. Available from: https://doi.org/10.1038/382250a0.
17. Bilir BE, Güldiken S, Tunçbilek N, Demir AM, Polat A, Bilir BE. The effects of fat distribution and some adipokines on insulin resistance. Endokrynologia Polska. 2016;67:277–282. Available from: https://doi.org/10.5603/ep.a2016.0023.
18. Chandalia M, Lin P, Seenivasan T, Livingston EH, Snell PG, Grundy SM, et al. Insulin Resistance and Body Fat Distribution in South Asian Men Compared to Caucasian Men. PLoS ONE. 2007;2(8):e812. Available from: https://doi.org/10.1371/journal.pone.0000812.
19. Tang YHH, Wang YHH, Chen CCC, Chan CJJ, Tsai FJJ, Chen SYC. Genetic and Functional Effects of Adiponectin in Type 2 Diabetes Mellitus Development. International Journal of Molecular Sciences. 2022;23(21):13544. Available from: https://doi.org/10.3390/ijms232113544.
20. Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: A high-risk state for diabetes development. Lancet. 2012;379:2279–2290. Available from: https://doi.org/10.1016/s0140-6736(12)60283-9.
21. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa JI, et al. Paradoxical Decrease of an Adipose-Specific Protein, Adiponectin, in Obesity. Biochemical and Biophysical Research Communications. 2012;425(3):560–564. Available from: https://doi.org/10.1016/j.bbrc.2012.08.024.
22. Alfaqih MA, Al-Hawamdeh A, Amarin ZO, Khader YS, Mhedat K, Allouh MZ. Single Nucleotide Polymorphism in the ADIPOQ Gene Modifies Adiponectin Levels and Glycemic Control in Type Two Diabetes Mellitus Patients. BioMed Research International. 2022;27:6632442. Available from: https://doi.org/10.1155/2022/6632442.
23. Andersson DP, Laurencikiene J, Acosta JR, Rydén M, Arner P. Circulating and Adipose Levels of Adipokines Associated With Insulin Sensitivity in Nonobese Subjects With Type 2 Diabetes. The Journal of Clinical Endocrinology & Metabolism. 2016;101(10):3765–3771. Available from: https://doi.org/10.1210/jc.2016-1883.
24. Gouliopoulos N, Siasos G, Bouratzis N, Oikonomou E, Kollia C, Konsola T, et al. Polymorphism analysis of ADIPOQ gene in Greek patients with diabetic retinopathy. Ophthalmic Genetics. 2022;43(3):326–331. Available from: https://doi.org/10.1080/13816810.2021.2015787.
25. Baden MY, Yamada Y, Takahi Y, Obata Y, Saisho K, Tamba S, et al. Association of adiponectin with blood pressure in healthy people. Clinical Endocrinology. 2013;78(2):226–231. Available from: https://doi.org/10.1111/j.1365-2265.2012.04370.x.
26. Peri-okonny PA, Ayers C, Maalouf N, Das SR, De Lemos JA, Berry JD, et al. Adiponectin protects against incident hypertension independent of body fat distribution: observations from the Dallas Heart Study. Diabetes/Metabolism Research and Reviews. 2017;33(2):2840. Available from: https://doi.org/10.1002/dmrr.2840.
27. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, et al. The Effect of Thiazolidinediones on Plasma Adiponectin Levels in

Normal, Obese, and Type 2 Diabetic Subjects. Diabetes. 2002;51(10):2968–2974. Available from: https://doi.org/10.2337/diabetes.51.10.2968.
28. Al-Nbaheen MS. Effect of Genetic Variations in the ADIPOQ Gene on Susceptibility to Type 2 Diabetes Mellitus. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2022;Volume 15:2753–2761. Available from: https://doi.org/10.2147/dmso.s377057.
29. Ruan X, Jin J, Hua LJ, Liu Y, Wang J, Liu S. The prevalence of metabolic syndrome in Chinese postmenopausal women and the optimum body composition indices to predict it. Menopause. 2010;17(3):566–570. Available from: https://doi.org/10.1097/gme.0b013e3181c8f4e1.
30. Gonzalez D, Nazmi A, Victora CG. Childhood poverty and abdominal obesity in adulthood: a systematic review. Cadernos de Saude Publica. 2017;25:427–467. Available from: https://doi.org/10.1590/s0102-311x2009001500008.
31. Comuzzie AG, Funahashi T, Sonnenberg G, Martin LJ, Jacob HJ, Black AEK, et al. The Genetic Basis of Plasma Variation in Adiponectin, a Global Endophenotype for Obesity and the Metabolic Syndrome. The Journal of Clinical Endocrinology & Metabolism. 2001;86(9):4321–4325. Available from: https://doi.org/10.1210/jcem.86.9.7878.
32. Shukla SK, Singh G, Ahmad S, Pant P. Infections, genetic and environmental factors in pathogenesis of autoimmune thyroid diseases. Microbial Pathogenesis. 2018;116:279–288. Available from: https://doi.org/10.1016/j.micpath.2018.01.004.
33. Yang H, Ye E, Si G, Chen L, Cai L, Ye C, et al. Adiponectin Gene Polymorphism rs2241766 T/G Is Associated with Response to Pioglitazone Treatment in Type 2 Diabetic Patients from Southern China. PLoS ONE. 2014;9(11):e112480. Available from: https://doi.org/10.1371/journal.pone.0112480.
34. Madhu SV, Mishra BK, Mannar V, Aslam M, Banerjee B, Agrawal V. TCF7L2 gene associated postprandial triglyceride dysmetabolism- a novel mechanism for diabetes risk among Asian Indians. Frontiers in Endocrinology. 2022;13. Available from: https://doi.org/10.3389/fendo.2022.973718.
35. Yokoyama H, Emoto M, Mori K, Araki T, Teramura M, Koyama H, et al. Plasma Adiponectin Level Is Associated with Insulin-Stimulated Nonoxidative Glucose Disposal. The Journal of Clinical Endocrinology & Metabolism. 2006;91(1):290–294. Available from: https://doi.org/10.1210/jc.2004-2549.
36. Ghoshal K, Chatterjee T, Chowdhury S, Sengupta S, Bhattacharyya M. Adiponectin Genetic Variant and Expression Coupled with Lipid Peroxidation Reveal New Signatures in Diabetic Dyslipidemia. Biochemical Genetics. 2021;59(3):781–798. Available from: https://doi.org/10.1007/s10528-021-10030-5.
37. Mantovani A, Zusi C, Csermely A, Salvagno GL, Colecchia A, Lippi G, et al. Association between lower plasma adiponectin levels and higher liver stiffness in type 2 diabetic individuals with nonalcoholic fatty liver disease: an observational cross-sectional study. Hormones. 2022;21(3):477–486. Available from: https://doi.org/10.1007/s42000-022-00387-6.
38. Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Current Opinion in Lipidology. 2007;18(3):263–270. Available from: https://doi.org/10.1097/mol.0b013e32814a645f.
39. Alkhateeb A, Al-Azzam S, Zyadine R, Abuarqoub D. Genetic association of adiponectin with type 2 diabetes in Jordanian Arab population. Gene. 2013;512(1):61–63. Available from: https://doi.org/10.1016/j.gene.2012.09.095.

How to cite this article: Shukla SK, Gupta S, Satyawali V. Adiponectin Gene Polymorphisms as Potential Biomarker for Development of Type 2 Diabetes Mellitus in Kumaon Region Population. J Med Sci Health 2023; 9(3):316-323

Date of submission: 05.05.2023
Date of review: 03.06.2023
Date of acceptance: 02.09.2023
Date of publication: 30.12.2023