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EVALUATION OF CLINICAL SIGNIFICANCE OF SIRT-1 GENE SINGLE NUCLEOTIDE POLYMORPHIMS WITH TYPE2 DIABETES MELLITUS AND ITS COMPLICATION IN NORTH WESTERN RAJASTHAN: A CROSS SECTIONAL STUDY

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Abstract

Introduction: The environmental and genetic factors are involved in the pathogenesis of T2DM. Genetic polymorphisms that have impacts on important proteins which participate in glucose metabolism and insulin secretion may also affect susceptibility to T2DM. SIRT1 gene have been shown to play pivotal roles in the regulation of ageing, longevity and in the pathogenesis of age-related metabolic diseases, such as type 2 diabetes mellitus. The aim of the current study was to investigate possible correlations between genetic variation in the SIRT1 gene and related clinical traits of T2DM.

Material and Methods: This was a cross sectional study conducted in Department of Medicine, S.P. Medical College, Bikaner on 60 previously diagnosed type 2 diabetes mellitus patients (study group) and compare them with 30 healthy subjects (control group). All subjects were evaluated by detail history and clinical examination as per Performa. Laboratory investigation CBC, RFT, LFT, fasting and two hours post prandial blood glucose, HbA1c and Lipid profile were done in all subjects. Fundus.examination, urine microalbuminuria and clinical examination for touch sensation with 10gm monofilament, vibration sense by biothesiometer and ankle reflex was done in all cases to find Diabetic complications.

Result: The mean age of diabetic subjects was 53.33±11.56 years and that of non-diabetic 56.6±11.27. We found significant association of single nucleotide polymorphisms (SNPs) with diabetes. SIRT1 rs10509291 polymorphism was positive in 70% cases of diabetes and 40% control subjects, SIRT1 rs3758391 polymorphism was positive in 33.33% of diabetes and 13.33% control subjects (p-value 0.0065 and 0.043 respectively). We observed that odds ratio was more than one for age, BMI, total

cholesterol, triglycerides, VLDL, HbA1c and calorie intake but statistical significance (p-value<0.05) was found only with triglycerides, VLDL, and calorie intake. SIRT1 rs10509291 and SIRT1 rs3758391 gene polymorphism was associated with nephropathy (p-0.035 and 0.025 respectively), SIRT1 rs10509291 gene polymorphism with presence of retinopathy (p<0.0003) and SIRT1 rs3758391 gene polymorphism with neuropathy (p<0.0253).

Conclusion: We observed a statistically significant single nucleotide polymorphisms of SIRT1 rs10509291 and SIRT1 rs3758391 with type 2 diabetes mellitus and diabetic nephropathy. We also observed a statistically significant single nucleotide polymorphisms of SIRT1 rs10509291 with diabetic retinopathy and single nucleotide polymorphism of SIRT1 rs3758391 with diabetic neuropathy. Further large scale, multinational, multicentric studies are required to document significance of SIRT1 polymorphism so as to develop therapeutic target for prevention of diabetes and its complications.

Key words: T2DM, SIRT-I, Nucleotide Polymorphism, SIRT1 rs10509291 and SIRT1 rs3758391.

INTRODUCTION

Epidemiological transitions in India in the 21st century have led to non-communicable diseases becoming a major public health problem of growing magnitude. Environmental and genetic factors are involved in the pathogenesis of T2DM. The majority of genes involved play a role in β-cell function. Genetic polymorphisms that have impacts on important proteins which participate in glucose metabolism and insulin secretion may also affect susceptibility to T2DM. Genome-wide association studies (GWASs), the candidate gene approach, and linkage analysis have identified various genes that contribute to T2DM susceptibility. The development of genetic risk scores using combined analysis of loci has significantly contributed to predicting the incidence of T2DM, Therefore, it is possible to facilitate early diagnosis and determine preventive strategies to reduce the incidence of the disease.[1]

Sirtuins, the silent information regulator-2 (Sir2) family, is a member of NAD-dependent deacetylases. The expressions of sirtuin families have been observed in the ageing, and SIRT1 has been shown to mediate a protective role of calorie restriction (CR) in the progression of the ageing.[2] The beneficial effects of calorie restriction involve the function of SIRT1, which is induced by calorie restriction in various tissues. Large clinical studies indicate that hyperglycaemia is a major contributing factor to the pathogenesis of diabetic vascular complications[3]. There is an urgent need to identify new therapeutic target molecules or cellular processes that underlie the pathogenesis of diabetic nephropathy to establish an additional therapeutic option, independent of glycaemic control and RAS inhibition[4].Therefore the current study was planned to investigate possible correlations between genetic variation in the SIRT1 gene and related clinical traits of T2DM.

MATERIAL AND METHODS

This cross-sectional study was conducted in the De-

partment of Medicine, S.P. Medical College, Bikaner on 60 previously diagnosed cases of type 2 diabetes mellitus patients selected randomly (study group) and 30 healthy subjects (control group). Ethics committee approval was taken before start of the study, all participating subjects were explained about the study and informed consent was taken. Inclusion Criteria for Cases: 1. Previously diagnosed type 2 diabetes mellitus as per ADA 2022 guideline[5] for diabetes. 2.Subjects who had given informed consent for this study. Inclusion criteria for Controls:1. Subjects who had given informed consent for this study. 2.Healthy subjects not suffering from any chronic illness or autoimmune illness like CKD, CLD, CLL, Sjogren syndrome, Rheumatoid arthritis etc. Exclusion Criteria for Cases and Controls: 1. Subjects (case or control) suffering from any acute illness at the time of enrolment for the study or during past one month. 2. Subjects who had not given informed consent for genetic study.

All subjects were evaluated by detail history and clinical examination as per performa including demographic and behaviour variables, anthropometric parameters and Calorie intake (calculated by 24hr dietary recall method). Laboratory investigation CBC, RFT, LFT, fasting (FBS) and two hours post prandial blood glucose (PPBS), HbA1c and Lipid profile were done in all subjects. Fundus examination was done in all cases for presence of Diabetic Retinopathy and classified according to Early treatment diabetic retinopathy study (ETDRS). Urine for microalbuminuria (30-300mg/24 hr) was done in all cases for presence of Diabetic Nephropathy.History of numbness, paraesthesia, tingling sensation followed by clinical examination for touch sensation with 10gm monofilament, vibration sense by biothesiometer and ankle reflex was done in all cases to find Diabetic Neuropathy.

For genetic analysis following Primer were used: (Gtex portal)

- SIRT-1 rs10509291 Sequence (5'-3')

rs10509291- F TTCCAACTACGCTATCAATCT

R CAGATAGAAGCCAAGGGTGT

- SIRTI gene rs3758391 Sequence (5'-3')

rs3758391- F–GTCACGCAGGTAATTGATGCAG

R – GGCTTAGTGGAAAGCCCTTC

Genetic study was conducted at our Multi-Disciplinary Research Unit laboratory, Bikaner.

STATISTICAL ANALYSIS: Statistical analysis was done using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Chi-square test was done for qualitative variables and Student t-test was used for quantitative variables. Multivariate Linear Regression Analysis was done to predict correlation of SIRT1 rs10509291 and SIRTI rs3758391 polymorphism with various variables. $p<0.05$ was considered as statistically significant.

RESULTS

This cross-sectional study was conducted on 60 previously diagnosed cases of type 2 diabetes mellitus patients (study group) selected randomly and 30 healthy subjects (control group) to evaluate association and clinical significance of SIRT-1 gene single nucleotide polymorphism with Type-2 Diabetes

Mellitus and its complications. All cases and controls were well matched for age (p=0.2196) and gender (p=0.5485) as shown in table-1. Majority of the cases were from urban residence (86.67%) and belonging to middle socioeconomical status (90%).

Table-1: Age and Gender distribution in Study and control groups.

S.N	Variables		Diabetic	Non-diabetic	p
1	Age	31-40 years	8 (13.33 %)	0 (0.00%)	0.2196
		41-50 years	20 (33.33%)	12 (40.00%)	
		51-60 years	18 (30.00%)	10 (33.33%)	
		≥61 years	14 (23.33%)	8 (26.67%)	
		Mean±SD	53.33±11.56	56.6±11.27	
2	Gen-	Male	46.67%	40.00%	
		Female	53.33%	60.00%	

We found significant association of single nucleotide polymorphisms (SNPs) with diabetes. SIRT1 rs10509291 and SIRT1 rs3758391 polymorphism were positive in 70% and 33.33% respectively in study group as compare to 40% and 13.33% respectively in control group (p<0.006 and p<0.043 respectively) (Figure-1).

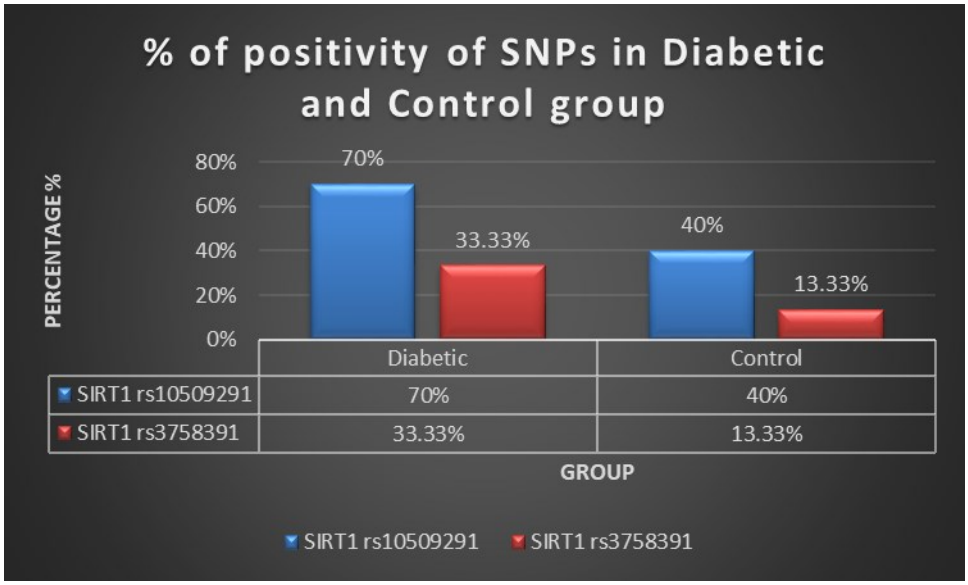

Figure-1: Bar diagram showing significant association of single nucleotide polymorphisms (SNPs) with diabetes.

Table-2: Mean Age, BMI and Calorie intake of diabetic and nondiabetic with positive and negative SNPs.

	SNP	Diabetic (N=60)		p	Non-Diabetic (N=30)		p	Total (N=90)		p
		Positive	Negative		Positive	Negative		Positive	Negative	
		Mean±SD	Mean±SD		Mean±SD	Mean±SD		Mean±SD	Mean±SD	
Age	SIRT1 rs10509291	55.76±11.75	47.67±9.07	0.012*	63.50±11.52	52.00±8.65	0.004*	57.48±12.04	49.83±9.01	0.001*
	SIRT1 rs3758391	58.50±10.12	52.25±10.08	0.032*	64.00±6.93	55.46±7.47	0.001*	59.92±10.47	53.52±10.68	0.006*
BMI	SIRT1 rs10509291	29.74±4.29	24.78±6.71	0.033*	28.73±6.07	23.52±5.87	0.026*	29.96±4.69	23.15±6.76	0.043*
	SIRT1 rs3758391	31.27±4.78	26.43±4.49	0.001*	28.33±6.94	21.34±6.41	0.003*	30.62±5.23	25.00±5.31	0.021*
Calorie Intake	SIRT1 rs10509291	2985.7±334.2	2473.3±523.2	<0.001*	2900±288.1	2274.4±238.1	<0.001*	2966.7±323.9	2373.9±413.1	<0.0001*
	SIRT1 rs3758391	3160±330.1	2668±430.9	<0.001*	2830±265.6	2477.7±202.6	0.007*	3105±339.1	2593.1±427.3	<0.0001*

Table-2 shows clinical correlation of single nucleotide polymorphisms (SIRT1 rs10509291 and SIRT1 rs3758391) with different variables. We found that the mean age of subjects having SIRT1 rs10509291 gene polymorphism and SIRT1 rs3758391 gene polymorphism was significantly high as compare to subjects having negative expression of both gene loci ($p< 0.001$ and $p<0.006$ respectively). The mean BMI was also high in subjects expressing SIRT1 rs10509291 gene polymorphism and SIRT1 rs3758391 gene polymorphism ($p<0.043$ and $p<0.021$). The mean calorie intake of subjects having SIRT1 rs10509291 gene polymorphism and SIRT1 rs3758391 gene polymorphism was more as compare to subjects having negative expression of both gene loci ($p< 0.0001$).

Table-3: Overall Corelation of gene polymorphisms with various laboratory parameters.

Parameter	SIRT1 rs10509291			SIRT1 rs3758391		
	Positive (n=54)	Negative (N=36)	p	Positive (n=24)	Negative (N=66)	p
RBS	178.48±85.35	127.17±71.69	.003794	150.33±78.04	160.73±86.01	.604984
FBS	149.78±72.50	121.11±46.59	.038684	139.58±50.12	137.85±69.56	.911155
HbA1c	8.57±2.33	6.97±2.43	.002403	8.34±1.77	7.78±2.69	.344805
TC	191.59±47.79	169.06±48.67	.032262	207.42±39.94	173.55±49.31	.003302*
TG	157.63±46.11	153.83±54.41	.722795	175.42±29.02	149.09±53.36	.024327*
HDL	51.93±12.24	57.79±15.44	.048072	53.36±12.50	54.60±14.36	.70907
LDL	99.28±30.97	83.08±43.14	.041011	101.75±19.62	89.54±41.17	.167299
VLDL	30.59±8.76	29.50±8.46	.558241	28.52±4.59	30.75±9.63	.278569

Table-3 shows overall corelation of gene polymorphisms with various laboratory parameters. We found significant association of SIRT1 rs10509291 gene polymorphisms with random blood sugar, fasting blood sugar, HbA1c, total cholesterol, HDL and LDL but not with triglyceride and VLDL (Figure-2) while significant association of SIRT1 rs3758391 gene polymorphisms was observed with total cholesterol and triglyceride but not with other parameters (Figure-3). On comparative analysis for association of SIRT1 rs10509291 and SIRT1 rs3758391 gene polymorphisms with various laboratory parameters in Study group (Diabetics; DM) and Control (Non-Diabetics; Non-DM), we found significant association of SIRT1 rs10509291 with random blood sugar, fasting blood sugar, HbA1c, total cholesterol , LDL and age but not with HDL, triglyceride and VLDL in study group while SIRT1 rs3758391 gene polymorphisms was found to be significantly associated with random blood sugar, fasting blood sugar, HbA1c, HDL and age but not with total cholesterol, triglyceride, LDL and VLDL in study group (Table-4).

Figure-2: Showing Association of SIRT1 rs10509291 gene polymorphisms with various Laboratory Parameters in Diabetics and Non-Diabetics

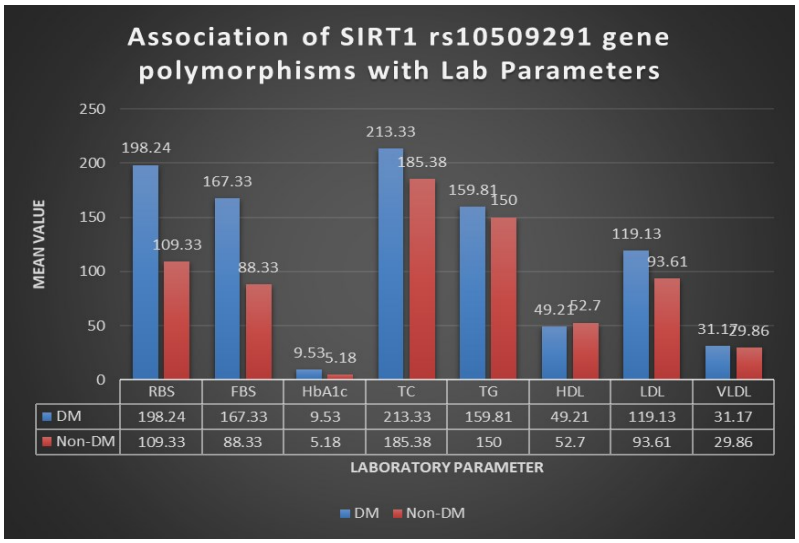

Figure-3: Showing Association of SIRT1 rs3758391 gene polymorphisms with various Laboratory Parameters in Diabetics and Non-Diabetics

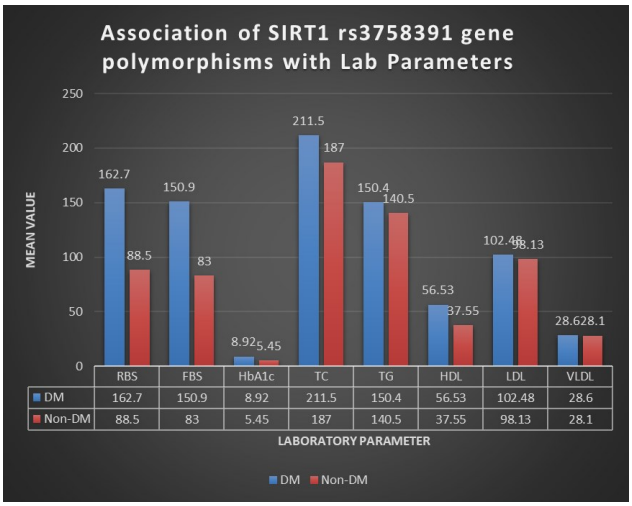

Table-4: Comparative analysis of association of SIRT1 rs10509291 and SIRT1 rs3758391 gene polymorphisms with various Laboratory Parameters in Study and Control groups

Parameter	SIRT1rs10509291 (No=54; DM=42, Non-DM=12)			SIRT1rs3758391 (No=24; DM=20, Non-DM=04)		
	Group	Mean±SD	P	Group	Mean±SD	P
RBS	DM	198.24±86.81	0.000*	DM	162.70±78.81	0.013*
	Non-DM	109.33±17.41		Non-DM	88.50±35.22	
FBS	DM	167.33±73.27	0.000*	DM	150.90±47.02	0.000*
	Non-DM	88.33±4.46		Non-DM	83.00±11.55	
HbA1c	DM	9.53±1.63	0.000*	DM	8.92±1.29	0.000*
	Non-DM	5.18±0.55		Non-DM	5.45±0.17	
TC	DM	213.33±33.77	0.033*	DM	211.50±37.91	0.272
	Non-DM	185.38±49.69		Non-DM	187.00±49.65	
TG	DM	159.81±46.41	0.525	DM	150.40±23.00	0.473
	Non-DM	150.0±46.42		Non-DM	140.50±34.06	
HDL	DM	49.21±17.15	0.515	DM	56.53±11.23	0.003*
	Non-DM	52.70±10.58		Non-DM	37.55±0.00	
LDL	DM	119.13±10.10	0.000*	DM	102.48±20.55	0.695
	Non-DM	93.61±32.62		Non-DM	98.13±16.02	
VLDL	DM	31.17±2.98	0.183	DM	28.60±4.26	0.848
	Non-DM	29.86±2.94		Non-DM	28.10±6.81	
AGE	DM	55.76±11.75	0.049*	DM	58.50±10.12	0.0089*
	Non-DM	65.50±11.52		Non-DM	64.00±6.93	

Table-5 shows aassociation of Diabetic microvascular complication with gene polymorphisms. We found a statistically significant association of SIRT1 rs10509291 and SIRT1 rs3758391 gene polymorphism expression with presence of microalbuminuria (p-0.035 and 0.025 respectively). 36 cases of diabetes had microalbuminuria out of them 22 had positive expression of SIRT1 rs10509291 and 16 had positive expression of SIRT1 rs3758391.We also found significant association of SIRT1 rs10509291 gene polymorphism with presence of retinopathy ($p<0.0003$) but we do not find statistically significant correlation of SIRT1 rs3758391 gene polymorphism with retinopathy ($p=0.714$). 28 cases of diabetes were having non proliferative retinopathy and out of them 26 had SIRT1 rs10509291 ($p<0.0003$) and 10 had SIRT1 rs3758391 polymorphism ($p=0.714$). Diabetic neuropathy was found to be significantly associated with SIRT1 rs3758391 gene polymorphism ($p<0.0253$) but not with SIRT1 rs3758391 gene polymorphism ($p=0.645$). 36 cases of diabetes were having neuropathy and 26 cases had SIRT1 rs10509291 polymorphism and 16 had SIRT1 rs3758391 polymorphism.

Table-5: Association of Diabetic microvascular complication with gene polymorphisms

Complication		SIRT1 rs10509291				SIRT1 rs3758391			
		Positive (n=42)		Negative (N=18)		Positive (N=20)		Negative (N=40)	
		N	%	N	%	N	%	N	%
Diabetic neuropathy	Yes (N=36)	26	72.22	10	27.78	16	44.44	20	55.56
	No (N=24)	16	66.67	8	33.33	4	16.67	20	83.33
	p-value	0.645				0.0253*			
Diabetic retinopathy	Yes (NPRD) (N=28)	26	92.86	2	7.14	10	35.71	18	64.29
	No (N=32)	16	50.00	16	50.00	10	31.25	22	68.75
	p-value	0.0003*				0.714			
Diabetic nephropathy (microalbuminuria)	Yes (N=36)	22	61.11	14	38.89	16	44.44	20	55.56
	No (N=24)	8	33.33	16	66.67	4	16.67	20	83.33
	p-value	0.035*				0.025*			

Table-6: Multivariate regression analysis to find the predictors for gene expression of SIRT1rs10509291

Variable	P	O.R.	95%CI
Age	0.0643	1.1025	0.9942-1.2225
Gender	0.0388*	0.0668	0.0051-0.8695
BMI	0.0029*	0.7066	0.5623-0.8879
TC	0.1883	1.0334	0.984-1.0853
TG	0.0165*	1.1519	0.9318-0.9929
HDL	0.3672	0.9588	0.875-1.0506
LDL	0.0921	0.9494	0.8938-1.0085
VLDL	0.0179*	1.1816	1.0291-1.3566
RBS	0.2085	1.0062	0.9966-1.0159
HbA1c	0.2477	1.1710	0.8961-1.5302
Calorie intake	0.0001*	1.0101	1.0054-1.0148

On multivariate regression analysis of predictor for SIRT1rs10509291 gene, we observed that odds ratio was more than one for age, total cholesterol, triglycerides, VLDL, HbA1c and calorie intake. But statistical significance ($p<0.05$) was found only with triglycerides, VLDL, and calorie intake (Table-6). While on multivariate regression analysis of predictor for SIRT1rs3758391 gene, we observed that odds ratio

was more than one for age, BMI, total cholesterol, triglycerides, VLDL, HbA1c and calorie intake but statistical significance ($p<0.05$) was found only in triglycerides, VLDL, and calorie intake (Table-7).

Table-7: Multivariate regression analysis to find the predictors for gene expression of SIRT1rs3758391.

Variable	p	O.R.	95%CI
Age	0.3858	1.0313	0.9619-1.1058
Gender	0.8939	0.8922	0.167-4.7682
BMI	0.5067	1.058	0.8958-1.2496
TC	0.3813	1.0135	0.9835-1.0445
TG	0.0291*	1.0341	1.0034-1.0657
HDL	0.3126	0.9722	0.9203-1.0269
LDL	0.284	0.9787	0.941-1.018
VLDL	0.0106*	1.0192	0.703-0.9546
RBS	0.2729	0.9921	0.9834-1.0009
HbA1c	0.2492	1.3327	1.0010-1.7744
Calorie intake	0.0453*	1.0024	1.0001-1.0048

DISCUSSION

Diabetes has become a major public health burden all over the world and its prevalence is rapidly increasing in developing countries like India.[6] The mean age of diabetic patients in our study group was 53.33±11.56, younger then reported by Zhuanping et al (2018) who found mean age 65.64±8.71 in their patients.[7] In our study, 80% of our cases were belonging to middle socioeconomic status, higher prevalence of diabetes in this group may be due to multiple risk factors like stressful life (related to job, family adjustment, financial etc.), sedentary life style, lack of self-care and inappropriate nutrition etc. We also found majority of the cases were from urban area explains the diabetes as a disease of urbanisation.[8,9]

The overall prevalence of SNPs SIRT1 rs10509291 was found in 60% subjects (54 out of 90; 60 diabetic and 30 non-diabetic) and SIRT1 rs3758391 polymorphism in 26.67% (24 out of 90). The prevalence of both gene polymorphism was significantly high in diabetic then in control group ($p<<0.006$ and $p<0.043$) (Figure-1). SIRT1 is an important regulator of energy metabolism, and appears to be required for a normal response to calorie restriction. Furthermore, recent reports demonstrate that SIRT1 is downregulated in several cells and tissues in insulin-resistant or glucose intolerance states.[10-12] Therefore, excess energy intake, lead to decreased SIRT1 activity which may contribute to the development of obesity-related conditions including insulin resistance and T2DM. Zhuanping et al also found that SIRT1 gene rs4746720 plays a dominant role in the pathogenesis of T2DM.[7] Han et al (2015) observed that genetic variation of the SIRT1 gene was related to insulin resistance and increase risk of T2DM in Chinese Han population.[13]

In our study, we found that subjects in whom SIRT1 gene polymorphism was present were older than subjects in which SIRT1 gene expression was negative. Kilic et al reported that, absence of significant

change in SIRT1 level between children and adults (from age 3 to 55) may suggest that SIRT1 levels are controlled during a long period of times in our lives and its expression dramatically increases in older ages.[14] Therefore, increased protein level of SIRT1 in older people may be a compensatory mechanism to compete the aging and oxidative stress-related decrease in NAD+ levels and polymorphism in SIRT1 gene may results in metabolic syndrome.[15]

We found statistically significant association of both of the gene polymorphism with lipid profile and blood sugar levels. It has been well-documented that SIRT1 increases insulin sensitivity in major insulin sensitive tissues.[16] Moreover, several studies have shown that Sirt1 overexpression protects against high fat diet (HFD)-induced glucose resistance,[63,64] whereas SIRT1 polymorphism or mutation is associated with impaired glucose tolerance in individuals with metabolic syndrome and T2DM. [17]

We found that subject who showed SIRT1 gene polymorphism had high BMI and more calorie intake as compared to subject in which SIRT1 gene expression was negative. Milne et al showed that calorie restriction extends lifespan and produces a metabolic profile desirable for treating diseases of ageing such as type 2 diabetes.[18] SIRT1 regulates glucose/lipid metabolism through its deacetylase activity on many substrates. SIRT1 in pancreatic β-cells positively regulates insulin secretion and protects cells from oxidative stress and inflammation, and has positive roles in the metabolic pathway via the modulation in insulin signalling. SIRT1 also regulates adiponectin secretion, inflammation, glucose production, oxidative stress, mitochondrial function, and circadian rhythms.[11] Several SIRT1 activators, including resveratrol have been demonstrated to have beneficial effects on glucose homeostasis and insulin sensitivity in animal models of insulin resistance.[19] SIRT1 can regulate energy metabolism under the conditions of caloric restriction and fasting through deacetylation of histones, nuclear transcription factor and related enzymes. The interdiction of SIRT1 activation can affect the development of age and obesity-related diseases, such as diabetes, coronary artery disease and neurodegenerative diseases.[20]

In our study we also found a statistically significant correlation in polymorphism of SIRT1 rs10509291 and SIRT1 rs3758391 gene with presence of microalbuminuria ($p<0.035$; 0.025). In our study we had 60 cases of diabetic and out of them 36 were having microalbuminuria and among them 22 cases had polymorphism of SIRT1 rs10509291 and 16 had polymorphism of SIRT1 rs3758391. Maeda et al also showed that SIRT1-related SNPs and the level of urine protein were associated with ESRD.[21] Similarly, Yue et al also observed that patients having mutation in SIRT1 locus had a higher risk of proteinuria.[22] ElKholy et al found that the mean levels of the serum SIRT1 protein was significantly increasing in the diabetic nephropathy group as compared to the diabetics without diabetic nephropathy and the control group.[23] Their observations indicate that SIRT1 gene is an inherited susceptibility gene for DKD and mutation in the SIRT1 locus result in expression of this gene which increase the risk of DKD. Sun et al reported that The SIRT1 loci rs182180876, rs4746720, and rs2234975 single nucleotide polymorphisms are significantly associated with the risk of diabetic nephropathy. [24]

Letonja et al reported significant association between SIRT1 polymorphism with diabetic nephropathy and diabetic retinopathy in patients with T2DM (p = 0.01).[25] The strong association between diabetic retinopathy and diabetic nephropathy has been shown by many studies done on different populations.[26-28] It is found that SIRT1 has a protective role in the development of diabetic retinopathy.[29]

CONCLUSION

We observed significant association of single nucleotide polymorphism SIRT1 rs10509291 and SIRT1 rs3758391 with type 2 diabetes mellitus and diabetic nephropathy, SIRT1 rs10509291 with diabetic retinopathy and SIRT1 rs3758391 with diabetic neuropathy. Older age, higher body mass index, high cholesterol and high calorie intake were significantly corelated with single nucleotide polymorphism of SIRT1 rs10509291 and SIRT1 rs3758391. Further large scale, multinational, multicentric studies are required to document significance of SIRT1 polymorphism so as to develop therapeutic target for prevention of diabetes and its complications.

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REFERENCE

1. Witka BZ, Oktaviani DJ, Marcellino M, Barliana MI, Abdulah R. Type 2 Diabetes-Associated Genetic Polymorphisms as Potential Disease Predictors. Diabetes Metab Syndr Obes. 2019 Dec 18;12:2689-2706. doi: 10.2147/DMSO.S230061, PMID: 31908510; PMCID: PMC6927489
2. Kitada M, Kume S, Takeda-Watanabe A, Tsuda S, Kanasaki K, Koya D. Calorie restriction in overweight males ameliorates obesity-related metabolic alterations and cellular adaptations through anti-aging effects, possibly including AMPK and SIRT1 activation. Biochim Biophys Acta. 2013;1830(10):4820-7.
3. Kitada M, Zhang Z, Mima A, King GL. Molecular mechanisms of diabetic vascular complications. J Diabetes Invest 2010;1:77–89.
4. Barlovic DP, Cooper ME. Diabetes: RAS inhibition: probably not a one-size-fits-all approach. Nat Rev Nephrol 2009; 5:669–70. DOI: 10.1038/nrneph.2009.189, PMID: 19935810
5. American Diabetes Association. Introduction: standards of medical care in diabetes-2022. Diabetes Care 2022;45(Supplement 1):S1-2.
6. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021 Nov;69(11):2932-2938. doi: 10.4103/ijo.IJO_1627_21. PMID: 34708726; PMCID: PMC8725109.
7. Zhuanping Z, Rifang L, Qing C, Sidong C. The Association between SIRT1 Genetic Variation and Type 2 Diabetes Mellitus Is Influenced by Dietary Intake in Elderly Chinese. Iran J Public Health. 2018 Sep;47(9):1272-1280. PMID: 30320001; PMCID: PMC6174046.
8. Anand K, Shah B, Yadav K. Are the urban poor vulnerable to noncommunicable diseases? A

survey of risk factors for non-communicable in urban slums of Faridabad. Natl Med J India. 2007;20(3):115–20. PMID: 17867614.

9. Misra A, Pandey RM, Rama DJ. High prevalence of diabetes, obesity and dyslipidemia in urban slum population in northern India. Int J Obes Relat Metab Disord. 2001;25(11):1722–9. DOI: 10.1038/sj.ijo.0801748, PMID: 11753596.

10. de Kreutzenberg SV, Ceolotto G, Papparella I, Bortoluzzi A, Semplicini A, Dalla Man C, Cobelli C, Fadini GP, Avogaro A. Downregulation of the longevity-associated protein sirtuin 1 in insulin resistance and metabolic syndrome: potential biochemical mechanisms. Diabetes. 2010 Apr;59(4):1006-15. doi: 10.2337/db09-1187. Epub 2010 Jan 12. PMID: 20068143; PMCID: PMC2844808.

11. Gillum MP, Kotas ME, Erion DM, Kursawe R, Chatterjee P, Nead KT, Muise ES, Hsiao JJ, Frederick DW, Yonemitsu S, Banks AS, Qiang L, Bhanot S, Olefsky JM, Sears DD, Caprio S, Shulman GI. SirT1 regulates adipose tissue inflammation. Diabetes. 2011 Dec;60(12):3235-45. doi: 10.2337/db11-0616. PMID: 22110092; PMCID: PMC3219953.

12. Fröjdö S, Durand C, Molin L, Carey AL, El-Osta A, Kingwell BA, Febbraio MA, Solari F, Vidal H, Pirola L. Phosphoinositide 3-kinase as a novel functional target for the regulation of the insulin signaling pathway by SIRT1. Mol Cell Endocrinol. 2011 Mar 30;335(2):166-76. doi: 10.1016/j.mce.2011.01.008. Epub 2011 Jan 15. PMID: 21241768.

13. Han J, Wei M, Wang Q, Li X, Zhu C, Mao Y, Wei L, Sun Y, Jia W. Association of Genetic Variants of SIRT1 With Type 2 Diabetes Mellitus. Gene Expr. 2015;16(4):177-85. doi: 10.3727/105221615X14399878166195. PMID: 26637398; PMCID: PMC8750030.

14. Kilic U, Gok O, Erenberk U, Dundaroz MR, Torun E, Kucukardali Y, et al. (2015) A Remarkable Age-Related Increase in SIRT1 Protein Expression against Oxidative Stress in Elderly: SIRT1 Gene Variants and Longevity in Human. PLoS ONE 10(3): e0117954. https://doi.org/10.1371/journal.pone.0117954

15. Zhu W, Chen S, Li Z, Zhao X, Li W, Sun Y, Zhang Z, Ling W, Feng X. Effects and mechanisms of resveratrol on the amelioration of oxidative stress and hepatic steatosis in KKAy mice. Nutr Metab (Lond). 2014 Aug 12;11:35. doi: 10.1186/1743-7075-11-35. PMID: 25140191; PMCID: PMC4137107.

16. Cao Y, Jiang X, Ma H, Wang Y, Xue P, Liu Y. SIRT1 and insulin resistance. J Diabetes Complications. 2016 Jan-Feb;30(1):178-83. doi: 10.1016/j.jdiacomp.2015.08.022. Epub 2015 Sep 2. PMID: 26422395.

17. Pfluger PT, Herranz D, Velasco-Miguel S, Serrano M, Tschöp MH. Sirt1 protects against high-fat diet-induced metabolic damage. Proc Natl Acad Sci U S A. 2008 Jul 15;105(28):9793-8. doi: 10.1073/pnas.0802917105. Epub 2008 Jul 3. PMID: 18599449; PMCID: PMC2474520.

18. Milne JC, Lambert PD, Schenk S, Carney DP, Smith JJ, Gagne DJ, Jin L, Boss O, Perni RB,

Vu CB, Bemis JE, Xie R, Disch JS, Ng PY, Nunes JJ, Lynch AV, Yang H, Galonek H, Israelian K, Choy W, Iffland A, Lavu S, Medvedik O, Sinclair DA, Olefsky JM, Jirousek MR, Elliott PJ, Westphal CH. Small molecule activators of SIRT1 as therapeutics for the treatment of type 2 diabetes. Nature. 2007 Nov 29;450(7170):712-6. doi: 10.1038/nature06261. PMID: 18046409; PMCID: PMC2753457.

19. Cao MM, Lu X, Liu GD, Su Y, Li YB, Zhou J. Resveratrol attenuates type 2 diabetes mellitus by mediating mitochondrial biogenesis and lipid metabolism via Sirtuin type 1. Exp Ther Med. 2018 Jan;15(1):576-584. doi: 10.3892/etm.2017.5400. Epub 2017 Oct 30. PMID: 29387206; PMCID: PMC5769236.

20. Kume S, Kitada M, Kanasaki K, Maegawa H, Koya D. Anti-aging molecule, Sirt1: a novel therapeutic target for diabetic nephropathy. Arch Pharm Res. 2013 Feb;36(2):230-6. doi: 10.1007/s12272-013-0019-4. Epub 2013 Jan 30. PMID: 23361587.

21. Maeda S, Koya D, Araki SI, Babazono T, Umezono T, Toyoda M, Kawai K, Imanishi M, Uzu T, Suzuki D, Maegawa H, Kashiwagi A, Iwamoto Y, Nakamura Y. Association between single nucleotide polymorphisms within genes encoding sirtuin families and diabetic nephropathy in Japanese subjects with type 2 diabetes. Clin Exp Nephrol. 2011 Jun;15(3):381-390. doi: 10.1007/s10157-011-0418-0. Epub 2011 Feb 18. PMID: 21331741; PMCID: PMC3110272.

22. Yue XG, Yang ZG, Zhang Y, Qin GJ, Liu F. Correlations between SIRT1 gene polymorphisms and diabetic kidney disease. R Soc Open Sci. 2018 Jun 13;5(6):171871. doi: 10.1098/rsos.171871. PMID: 30110438; PMCID: PMC6030294.

23. Elkholy, O. A., Farouk Attia, G., Salah Ibrahim, W., & Selim, A. (2022). Association of Silent Information Regulator 1 (Sirt1) Gene Polymorphism with the Pathogenesis of Diabetic Nephropathy. International Journal of Scientific Research and Management, 2022; 10(10), 706–720. https://doi.org/10.18535/ijsrm/v10i10.mp02

24. Sun Y, Wang J, Meng Y. Correlation Between Polymorphisms of the SIRT1 Gene microRNA Target Sites and Diabetic Nephropathy. Genet Test Mol Biomarkers. 2021 Jun;25(6):387-398. doi: 10.1089/gtmb.2020.0261. PMID: 34152844.

25. Letonja J, Završnik M, Makuc J, Šeruga M, Peterlin A, Cilenšek I, Petrovič D. Sirtuin 1 rs7069102 polymorphism is associated with diabetic nephropathy in patients with type 2 diabetes mellitus. Bosn J Basic Med Sci. 2021 Oct 1;21(5):642-646. doi: 10.17305/bjbms.2020.5368. PMID: 33577446; PMCID: PMC8381203.

26. Lee WJ, Sobrin L, Lee MJ, Kang MH, Seong M, Cho H. The relationship between diabetic retinopathy and diabetic nephropathy in a population-based study in Korea (KNHANES V-2, 3). Invest Ophthalmol Vis Sci. 2014 Sep 9;55(10):6547-53. doi: 10.1167/iovs.14-15001. PMID: 25205863.

27. Ahmed MH, Elwali ES, Awadalla H, Almobarak AO. The relationship between diabetic retinopa-

thy and nephropathy in Sudanese adult with diabetes: population based study. Diabetes Metab Syndr. 2017 Nov;11 Suppl 1:S333-S336. doi: 10.1016/j.dsx.2017.03.011. Epub 2017 Mar 7. PMID: 28325541.

28. Zhang J, Wang Y, Li L, Zhang R, Guo R, Li H, Han Q, Teng G, Liu F. Diabetic retinopathy may predict the renal outcomes of patients with diabetic nephropathy. Ren Fail. 2018 Nov;40(1):243-251. doi: 10.1080/0886022X.2018.1456453. PMID: 29633887; PMCID: PMC6014304.

29. Karbasforooshan H, Karimi G. The role of SIRT1 in diabetic retinopathy. Biomed Pharmacother. 2018 Jan;97:190-194. doi: 10.1016/j.biopha.2017.10.075. Epub 2017 Nov 6. PMID: 29091865.