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Original Article

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Association of SIRT-1 Gene Polymorphism and Vitamin D Level in Egyptian Patients With Rheumatoid Arthritis

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Abstract

Background: We investigated SIRT-1 genetic variant and its association with vitamin D level in Egyptian patients with rheumatoid arthritis (RA).

Methods: Seventy Egyptian subjects were enrolled in our study and divided into two groups: RA group (n = 50 patients) and healthy control group (n = 20 subjects). Five milliliter blood sample was withdrawn from each subject followed by laboratory investigation and DNA extraction for SIRT-1 gene polymorphism assessment (rs7895833 A>G, rs7069102 C>G and rs2273773 C>T) and vitamin D level expression.

Results: There was statistically significant difference between rheumatoid cases and controls with regard to vitamin D level with 88% of cases showing insufficient vitamin D versus all controls showing sufficient level. SIRT-1 different SNPs rs2273773, rs7895833and rs7069102 genotype frequencies were statistically significant in RA compared to control group (P = 0.001). There was no statistically significant difference between different genotypes of rs2273773, rs7895833 and rs7069102 with regard to vitamin D level.

Conclusion: We concluded that there is a strong association between SIRT-1 polymorphism genotyping and RA. Vitamin D level was insufficient in Egyptian patients with RA.

Keywords: SIRT-1 polymorphism; Vitamin D; Rheumatoid arthritis; Egypt

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease, resulting in a chronic, systemic inflammatory disorder [1]. It is a disease affecting joint cartilage and bone with synovial inflammation and infiltration of inflammatory immune cells [2].

Vitamin D deficiency was shown to have a role in increased levels of proinflammatory cytokines and it plays a very important role in the reduction of inflammation, by suppression of prostaglandin (PG) action, inhibition of p38 stress kinase signaling, and the production of proinflammatory cytokines and inhibition of nuclear factor-κB (NF-κB) signaling [3].

The SIRT-1 gene is located on the 10q21.3 chromosome [4]. SIRTs are a conserved family of NAD+ dependent histone deacetylases (HDACs) and mono-ADP-ribosyltransferases that target histones, transcription factors and coregulators to adapt gene expression to the cellular energy state [5]. HDACs are enzymes inhibiting gene expression by reversing acetylation of histone proteins. In mammals, seven sirtuin genes, SIRT-1 to SIRT-7, have been identified. Among them, SIRT-1 is best characterized so far. It has been shown that it regulates transcription factors such as members of the forkhead transcription factor FOXO family [6], p53 [7], NF-κB [8], the DNA repair factor Ku70 [9], and the transcriptional coactivator p300 [10].

SIRT-1 is found in many tissues such as pancreas, liver, skeletal muscle, brain and adipose tissue. It plays a crucial role in various human diseases such as cardiovascular diseases, inflammation, aging, neurodegenerative disease, non-alcoholic fatty liver disease (NAFLD), amyotrophic lateral sclerosis (ALS), and even cancers [11]. It has been reported that it is a potential therapy for NAFLD [12], ALS [13], kidney disease [14], and pulmonary disease [15].

We, therefore, conducted the SIRT-1 gene polymorphism (rs7895833 A>G, rs7069102 C>G and rs2273773 C>T) in the present study to investigate SIRT-1 genetic variants and its association with vitamin D levels in Egyptian patients with RA.

Materials and Methods

Subjects

The present study included 70 Egyptian subjects who were di-

Table 1. Demographic Characteristics and Routine Investigations in Different Study Groups

Variables	Rheumatoid cases (n = 50), mean ± SD	Controls (n = 20), mean ± SD	P-value
Sex			
Males	38 (76%)	9 (45%)	0.023
Females	12 (24%)	11 (55%)	
Age (years)	40.1 ± 11.5	43.3 ± 9.8	0.289
Complete blood count			
RBCs (g/dL)	92.4 ± 26.6	100.7 ± 16.5	0.199
Hb (g/dL)	13.4 ± 1.9	13.8 ± 1.7	0.429
TLC (10/mm)	6.6 ± 2	5.7 ± 0.98	0.047
PLT (10/mm)	272.9 ± 94.7	239.1 ± 68.6	0.150
Liver function			
ALT (IU/L)	44.6 ± 13.6	32.5 ± 5.7	0.000
AST (IU/L)	52.6 ± 10.1	30.9 ± 5.5	0.000
Total bilirubin (mg/dL)	0.72 ± 0.17	0.85 ± 0.23	0.036
Direct bilirubin (mg/dL)	0.22 ± 0.10	0.23 ± 0.11	0.851
Albumin (g/dL)	4.1 ± 0.48	4.3 ± 0.41	0.058
Other investigations			
Alkaline phosphatase (IU/L)	67.2 ± 26	71.4 ± 23	0.536
Creatinine (mg/dL)	0.91 ± 0.29	0.95 ± 0.18	0.02
CRP (mg/L)	0.24 ± 0.13	0.23 ± 0.09	0.707
INR	1.07 ± 0.10	1.12 ± 0.13	0.143
Anti-CCP (U/ML)	61.7 ± 26	6.9 ± 4.5	0.000
TSH (mIU/L)	1.7 ± 0.99	1.7 ± 0.77	0.799
AFP (ng/mL)	2.9 ± 2.1	1.7 ± 0	0.012
Vit D (ng/mL)	17.9 ± 9.2	42.2 ± 11.8	0.000

Independent *t*-test: Pearson χ^2 (exact). SD: standard deviation.

vided into two groups: RA group (n = 50 patients) and healthy control group (n = 20 subjects).

RA group included 38 men and 12 women with a mean age of 40.1 ± 11.5 years. Patients were clinically diagnosed by physical examination and laboratory investigations at the Faculty of Medicine, Al-Azhar and Cairo Universities. In addition, the control group included nine men and 11 women with a mean age of 43.3 ± 9.8 years. They were recruited from healthy subjects admitted to the same hospital.

Written informed consent was obtained from all subjects enrolled in the study. Approval for this study was not required in accordance with the policy of our institution.

Biochemical investigations

Blood samples of all subjects were centrifuged for 5 min at 4 °C, followed by the removal of plasma and then stored at -20 °C. The following biochemical parameters were determined in both the control and RA groups by standard laboratory methods in the Faculty of Medicine, Cairo University: complete blood picture, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, urea, creatinine, international normalized ratio (INR), and AFP. Whole blood samples of all subjects were analyzed for the genotypes of SIRT-1 and plasma for vitamin D level expression.

DNA isolation

The genomic DNA was extracted from whole peripheral blood sample using QIAamp DNA blood mini-kit extraction kit (Qiagen, Hilden, Germany) following the manufacturer's instructions.

All DNA samples were quantitated using the Nano Drop®-1000 spectrophotometer (Nanodrop Technologies, Inc., Wilmington, USA).

SIRT-1 genotyping

Genotyping was determined using real-time PCR (StepOne, Applied Biosystems, Foster City, USA). SIRT-1 SNPs includ-

Table 2. ANA Titer and Vitamin D Levels in Study Groups

Variables	Rheumatoid cases (n = 50)		Controls (n = 20)		P-value
	No.	%	No.	%	
ANA titer					
Low titer	50	100%	20	100%	-
Vitamin D level					0.000
Deficient (< 10 ng/mL)	3	6%	0	0%	
Insufficient (10 - 29 ng/mL)	44	88%	0	0%	
Sufficient (30 - 100 ng/mL)	3	6%	20	100%	

ing rs7895833 A>G in the promoter region, rs7069102 C>G in intron 4 and rs2273773 C>T in exon 5 (Cat No. 4351379) were analyzed in the extracted DNA by using specific primers and Taqman FAM and VIC probes (Taqman SNP genotyping assays, Applied Biosystems, Foster City, CA). The 25 µL PCR mixture included 20 ng of whole blood genomic extracted DNA and the following reagents: 0.5 µL FAM and VIC probes and primers (Taqman SNP genotyping assays), 12.5 µL Taqman universal master mix II No UNG (Cat No. 4440040) and DNase free water. The thermal cycling profile was 10 min at 95 °C for enzyme activation followed by 40 cycles of 15 s DNA denaturation at 95 °C, 20 s primers and probes annealing at 55 °C, and 30 s at 72 °C for the amplification step. The genotyping was analyzed with StepOne Applied Biosystem version 2.1 soft ware analysis.

Vitamin D serum level assessment

Vitamin D plasma level was detected by ELISA 25-OH vitamin D kit according to instructions of manufactures (DRG, international Inc., USA). The data are expressed as ng/mL. Grading of vitamin D levels was done as follows: ≥ 30 ng/mL (normal); 10 - 30 ng/mL (insufficiency); ≤ 10 ng/mL (deficiency).

Statistical analysis

Data were collected and coded to facilitate data manipulation and double entered into Microsoft Access and data analysis was performed using SPSS software version 18 in windows 7. Simple descriptive analysis in the form of numbers and percentages for qualitative data, and arithmetic means as central tendency measurement, standard deviations as measure of dispersion for quantitative parametric data, and inferential statistic test: Student's *t*-test used to compare measures of two independent groups of quantitative data were conducted. P value ≤ 0.05 was considered the cut-off value for significance.

Results

Fifty patients suffering from RA were enrolled in this study together with 20 subjects as controls. Among the 50 patients, 38 (76%) were men and 12 (24%) were women. The average age was 40.1 ± 11.5 years. In the control group, nine (45%) were men and 11 (55%) were women; the average age was 43.3 ± 9.8 years. While there was no significant difference between groups with regard to age, a significant difference was found as regards gender. The age and gender distribution of the persons included in the study and their P values are given in Table 1. Laboratory investigations in different study groups are given in Table 1 in which there is statistically significant difference with P-value < 0.05 between rheumatoid cases and controls with regard to anti-CCP and vitamin D level, with high mean of anti-CCP, and low mean of vitamin D among RA patients.

Vitamin D level ANA titer

Table 2 illustrates that there is statistically significant difference between rheumatoid cases and controls as regards vitamin D level with 88% of cases showing insufficient vitamin D versus all controls showing sufficient level.

On the other hand, there is no statistically significance difference with P-value > 0.05 as regards ANA titer.

Frequencies of SIRT-1 (rs2273773 C>T, rs7895833 A>G, and rs7069102 C>G) gene polymorphisms

The frequencies of genotypes and alleles in SIRT-1 gene in all groups are shown in Table 3. CC, TC and TT genotype frequencies of rs2273773 were 36%, 38% and 26%, respectively for the group with RA, and these were 60%, 40% and 0%, respectively for the control group (P = 0.000). While the frequencies of C and T alleles of the group with RA were 55% and 45%, these were 80% and 20% for the control group (P = 0.006).

GG, AG and AA genotype frequencies of rs7895833 were 54%, 34% and 12%, respectively for the group with RA, and these were 10%, 30% and 60% for the control group (P = 0.000). While the frequencies of G and A alleles of the group with RA were 71% and 29%, these were 25% and 75% for the control group (P < 0.001).

GG, CG and CC genotype frequencies of rs7069102 were 62%, 26% and 12%, respectively for the group with RA, and these were 0%, 25% and 75% for the control group (P = 0.000). The frequencies of G and C alleles of the group with RA were 75% and 25%, and these were 12.5% and 87.5% for the control

Table 3. Distribution of Genotypes and Allelic Frequency Among Patients and Controls

Variables	Rheumatoid cases (n = 50)		Controls (n = 20)		P-value
	No.	%	No.	%	
rs2273773 C>T					
CC	18	36%	12	60%	
CT	19	38%	8	40%	0.000
TT	13	26%	0	0%	
Allele					
C	55	55%	32	80%	0.006
T	45	45%	8	20%	
rs7895833 A>G					
GG	27	54%	2	10%	
AG	17	34%	6	30%	0.000
AA	6	12%	12	60%	
Allele					
G	71	71%	10	25%	< 0.001
A	29	29%	30	75%	
rs7069102 C>G					
GG	31	62%	0	0%	
CG	13	26%	5	25%	0.000
CC	6	12%	15	75%	
Allele					
C	25	25%	35	87.5%	< 0.001
G	75	75%	5	12.5%	

group (P < 0.001).

Relationship between SIRT-1 gene polymorphisms and levels of vitamin D

There was no statistically significant difference with P-value > 0.05 between different genotypes of rs2273773, rs7895833 and rs7069102 as regards vitamin D level (Table 4).

There was no statistically significance difference with P-value > 0.05 between different genotypes rs2273773, rs7895833, and rs7069102 as regards anti-CCP level (Table 5). There is no correlation between vitamin D levels and any other study variables (Table 6).

Discussion

RA is a chronic inflammatory disease in which there is destruction of joint cartilage and bone. It is characterized by synovial hyperplasia, synovial inflammation, and infiltration of inflammatory immune cells [2].

Our data confirm that vitamin D deficiency is common in our Egyptian patients with RA. Vitamin D levels were found to be insufficient in 88% of cases and deficient in 6% of cases. This result is in agreement with previous reports on patients with RA from other ethnic groups [16, 17].

No relationship was found between 25(OH)D and any other parameter in the routine investigations. This finding is in

Table 4. Comparisons of Vitamin D in Different SIRT-1 Polymorphisms Among Rheumatoid Patients

Variables	Vitamin D		P-value
	Mean	SD	
rs2273773			
TT	17.3	9.5	
TC	16.3	4.7	0.4
CC	20.9	13.1	
rs7895833			
GG	17.4	6.1	
AG	19.9	13.5	0.4
AA	13.9	4.6	
rs7069102			
GG	15.9	4.5	
CG	22.1	15.7	0.2
CC	16.5	5.2	

Table 5. Comparisons of Anti-CCP in Different SIRT-1 Polymorphisms Among Rheumatoid Patients

Variables	Anti-CCP		P-value
	Mean	SD	
rs2273773			
TT	59.6	23.4	
TC	59.1	17.4	0.6
CC	68.5	38.3	
rs7895833			
GG	67.9	29.9	
AG	58.9	18.6	0.07
AA	41.8	13	
rs7069102			
GG	58.2	23.1	
CG	71.7	39	0.3
CC	58.2	18.7	

Table 6. Correlation Between Vitamin D Levels With All Study Variables

Variables	Vitamin D	
	r	P-value
Age (years)	0.19	0.2
Complete blood count		
RBCs	0.15	0.3
Hb	-0.11	0.5
TLC	0.09	0.5
PLT	0.02	0.9
Liver function		
ALT	-0.16	0.3
AST	0.04	0.8
Total bilirubin	0.27	0.09
Direct bilirubin	0.25	0.08
Albumin	-0.26	0.07
Other routine investigations		
Alkaline phosphatase	0.07	0.6
Creatinine	-0.19	0.2
PC	0.04	0.8
CRP	-0.06	0.6
INR	0.14	0.3
Other		
Anti-CCP	0.14	0.4
TSH	-0.16	0.3
AFP	-0.19	0.2

agreement with others studies [18].

It was proved that vitamin D deficiency may have a role in the increased levels of proinflammatory cytokines (IL6, IL17, interferon gamma, TNF alpha, etc.) and it plays a very important role in the reduction of inflammation, including suppression of prostaglandin (PG) action, inhibition of p38 stress kinase signaling, and the production of proinflammatory cytokines and inhibition of NF-κB signaling [3].

Another factor seems to have a role in production of such proinflammatory cytokines which is SIRT-1 gene, which also regulates transcription factors, DNA repair factor Ku70 and the transcriptional coactivator p300 [6, 7, 9, 10].

Thereby, SIRT-1 controls a broad range of cellular processes, including cell survival and inflammation [19]. SIRT-1 was found to be overexpressed in RA synovial tissues and it directly enhances proinflammatory cytokine production of synovial cells and inhibits apoptosis [20].

Therefore, we planned to investigate the different genotypes and allelic frequency of the SIRT-1 gene in patients with RA. In our study, we analyzed rs7895833, rs7069102 and rs2273773 polymorphisms in the SIRT-1 gene and associated these results with levels of vitamin D and anti-CCP in the studied groups.

A significant difference was found between TT, CT and CC genotypes of rs2273773 C>T. The incidence of CC (the wild genotype) was low in patients (36%) than in controls (60%), while the incidence of TT genotypes (the mutant genotype) in patients was higher (26%) than in control (0%).

Moreover, we found a significant difference between GG, AG and AA genotypes of rs7895833 A>G, in which the incidence of GG (the mutant genotype) was higher in patients (54%) than in controls (10%), while the incidence of AA genotypes (the wild genotype) in patients was lower (12%) than in control (60%). The GG (the mutant genotype) genotype of rs7069102 C>G showed higher frequency in patients (62%) than in controls (0%) and the CC (the wild genotype) genotype showed low frequency in patients (12%) than in controls (75%). Thus, the TT genotype of rs2273773, GG genotypes of rs7895833 and GG genotype of rs7069102 are high up in patients than in controls.

Therefore, this result may point out the strong relation of TT genotype of rs2273773, GG genotypes of rs7895833 and GG genotype of rs7069102 with RA. Further investigation is necessary to verify its role in remission and activity.

Regarding the allelic frequency of rs2273773, the C allele was dominant in the control group (80%), and formed about 55% of the RA group, while the T allele which was seen less frequently in the control group (20%), formed about 45% of the rheumatoid arthritis.

On the other hand, the G alleles of both rs7895833 and rs7069102 were dominant in the rheumatoid group (71% and 75%, respectively), and were decreasing in the control group (25% and 12.5%, respectively), while the A allele of rs7895833 and C allele of rs7069102 were seen less frequently in the rheumatoid group (29% and 25%, respectively) and more dominant in the control group (75% and 87.5%).

No information on the expression and function of sirtuins in RA was available until very recently. Niederer et al reported the overexpression of SIRT-1 in RA synovial tissue and despite evidence for an anti-inflammatory role of SIRT-1 in animal models of inflammation, they showed that SIRT-1 directly enhances

proinflammatory cytokine production of synovial cells [20].

SIRT-1 deficient mice display systemic lupus erythematosus-like manifestations, suggesting that SIRT-1 may have a role in autoimmune processes. SIRT-1 targets two major proinflammatory pathways, the NF-κB and AP-1 pathways, both of which are implicated in the pathogenesis of chronic arthritis. Therefore, SIRT-1 may play a role in the pathogenesis of RA and other forms of arthritis. Research on SIRT-1 in arthritis is still at an early stage. The published data have confirmed that SIRT-1 is overexpressed in RA and is involved in the inflammatory process in the RA synovium.

Macrophages from myeloid SIRT-1 knockout mice showed increased inflammation produced by NF-κB indicating an anti-inflammatory activity of SIRT-1 [21].

Furthermore, the application of HDAC inhibitors causes genome-wide acetylation of histones, which improve the symptoms in lupus-prone mice [22] and mice induced to develop RA [23], while hyperacetylation of a variety of genetic loci in human SLE is associated with disease severity [24].

Supporting to our results studies in animal models of arthritis have shown useful effects of HDAC inhibitors; Grabiec et al evaluated the effects of different HDAC inhibitors in monocyte-derived macrophages, synovial explants and synovial fluid macrophages of patients with RA [25]. They used NAM, a non-specific inhibitor of sirtuins. Addition of NAM to cultured macrophages of healthy individuals reduced LPS- and TNF-α-induced production of IL-6 and LPS-induced TNF-α production. The findings of Grabiec et al were unexpected, as the data obtained with SIRT-1 deficient or SIRT-1 transgenic mice rather suggested that SIRT-1 has anti-inflammatory effects by inhibiting NF-κB activation. Fernandes et al have used J774 macrophages to study the effect of the sirtuin inhibitors sirtinol and cambinol. They found significantly decreased LPS-induced expression of IL-6, TNF-α, and the chemokine Rantes [26].

Studies of resveratrol in synovial cells may be of relevance for understanding the role of SIRTs in RA. Byun et al have shown that treatment of synovial fibroblasts was derived from patients with RA with resveratrol induces apoptosis. This apoptosis was independent of p53 but required activation of caspase 8 [27]. Also, Yang et al explored the effect of resveratrol on the levels of sirtuin 1 (SIRT-1), and they found that resveratrol increases sirtuin 1 expression in peripheral blood mononuclear cells [28].

No previous data associated different genotypes of SIRT-1 polymorphism with RA; we concluded that SIRT-1 polymorphisms may play a role in the development RA. Further studies are needed to explain the role of SIRT-1 in chronic joint inflammation. Moreover, research needs to concentrate on the other members of the sirtuin family. Increased understanding of the impact of sirtuins on immune pathways is needed to be able to design therapeutic strategies targeting sirtuins. In more prospective studies, the SIRT-1 gene expression and mutations should be analyzed with a bigger RA group.

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