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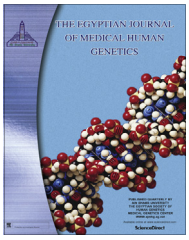

ORIGINAL ARTICLE

Sirtuin 1 gene rs2273773 C > T single nucleotide polymorphism and protein oxidation markers in asthmatic patients

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KEYWORDS

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Abstract *Background:* Sirtuin-1 (SIRT-1), a protein has been found to protect the cells against oxidative stress due to its deacetylase activity.

In this investigation, we aimed to study SIRT-1 gene rs2273773 C > T single nucleotide polymorphism and markers of serum protein oxidation (protein carbonyl and sulfhydryl groups) in asthmatic patients.

Subjects and methods: 120 asthmatic patients and 120 healthy controls were genotyped for SIRT-1 gene rs2273773 C > T SNP using polymerase chain reaction – confronting two pair primer method (PCR-CTPP). Serum protein carbonyl and sulfhydryl groups were measured using colorimetric methods.

Results: SIRT-1 gene rs2273773 C > T SNP genotyping revealed that the TT genotype was significantly higher in the patients compared to the controls ($P < 0.05$), while there were no significant differences regarding the genotypes TC and CC between the patients and the controls ($P > 0.05$). T allele was significantly higher in the patients compared to the controls ($P = 0.017$). The distribution of the genotypes didn't differ among the atopic and the non-atopic asthmatic patients, also no difference was found in the genotype distribution according to the severity of asthma ($P > 0.05$). Serum protein carbonyl group concentration was significantly higher in the patients compared to the controls ($P < 0.001$), while serum protein sulfhydryl group content decreased significantly in the patients compared to the controls ($P < 0.0001$). No differences in markers of protein oxidation according to SIRT-1 gene rs2273773 C > T genotype were found.

Conclusion: SIRT-1 gene rs2273773 C > T SNP was associated with asthma but not with protein oxidation markers in Egyptian population.

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1. Introduction

Asthma is a chronic inflammatory disease of the airways with a complex etiology [1]. The interaction of genes and environmental factors affects the development of asthma and determines the expression or progression of the disease [2]. Epigenetic mechanisms such as DNA methylation and histone modification control the accessibility of the genome and manage gene transcription in response to the environment in a heritable fashion. Recent evidence suggests that these mechanisms play a role in allergy and asthma [3]. SIRT-1 is a NAD + −dependent nuclear deacetylase of 747 residues, involved in various important metabolic pathways. It down-regulates p53 activity, rising lifespan, and cell survival and deacetylases peroxisome proliferator-activated receptor-gamma and its coactivator 1 alpha, promoting lipid mobilization [4]. SIRT-1 can directly modify chromatin, silence transcription and modulate the cellular proliferation. It possesses a probable antiaging effect through increasing the genomic stability suppressing recombinant DNA recombination [5,6]. SIRT-1 gene is located to chromosome 10 (10q21.3) and has many single nucleotide polymorphisms (SNPs), of which the SNP rs2273773 C > T, a silent mutation in exon 5, was found to be associated with many diseases including chronic obstructive pulmonary disease, hypertension, type 2 diabetes and cardiovascular disease [7–9]. Oxidative stress was found to play an important role in asthma pathogenesis [10]. Reactive oxygen species (ROS) attack proteins causing their oxidation by forming carbonyl groups. The amino acids; lysine, arginine, proline, and histidine are the most liable to modification [11]. The bulk of protein sulfhydryl in plasma is represented by Cys-34 of albumin. Protein sulfhydryl acts as an antioxidant reacting with ROS, protecting cells against the damage induced by them [12].

In this investigation, we aimed to study SIRT-1 gene rs2273773 C > T SNP and serum markers of protein oxidation (protein carbonyl group concentration and protein sulfhydryl group content) in asthmatic patients. Also, we studied the association between SIRT-1 gene rs2273773 C > T SNP and the type and severity of asthma.

2. Materials and methods

2.1. Study population

The study was approved by the Ethics committee of Sohag Faculty of Medicine and was in accordance with the Helsinki Declaration of 1975. An informed written consent was obtained from all individuals included in the study. 120 asthmatic patients and 120 healthy controls were enrolled in the study. The patients were recruited from the chest disease department of Sohag University Hospital, the diagnosis of asthma was according to the clinical history, physical examination, and pulmonary function tests, including reversibility testing and measurement of bronchial reactivity. Patients were classified into atopic and non-atopic and further as having mild intermittent, mild moderate or severe persistent asthma. Atopic asthma and non-atopic asthma were defined based on the presence or absence of atopy (any skin prick test $\geqslant$3 mm). In addition, IgE antibodies and eosinophil count were evaluated for all the participants to differentiate between atopic and non-atopic asthma [13]. The exclusion criteria were the presence of hypertension, diabetes mellitus or any other chronic disease, as SIRT-1 gene rs2273773 C > T SNP has been established to be associated with blood pressure and hyperglycemia in previous studies [7,9].

2.2. Blood samples and laboratory investigations

Fasting blood samples (about 5 ml) were collected from the patients and the controls via the venipuncture of an antecubital vein. Samples were divided into two parts; one taken in tubes containing Na2-EDTA (final concentration 1 mg/ml) for genomic DNA extraction and the other part was taken into plain tubes and the serum of it was used for the routine laboratory investigations (blood glucose and lipid profile) and for the estimation of IgE antibodies, protein carbonyl and sulfhydryl groups. Total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG) and fasting glucose were determined using an enzymatic method on Cobas C 311 analyzer (Roche diagnostics, Germany). Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula. IgE was measured using an ELIZA kit (ab108650), according to the enclosed instructions. The assay range of the kit was from 5 to 800 IU/ml.

2.3. Assay of serum protein carbonyl group concentration

Protein carbonyl group concentration was measured according to the method of Reznick and Packer [14] with some modifications; as follows, two tubes of 200 µL serum were taken, one as a test and the other as a control. After that, 1.0 ml of 10 mM 2,4 dinitrophenyl-hydrazine (DNPH) prepared in 1.25 M HCl was added to the test sample and 1.0 ml of 2.5 M HCl alone was added to the control sample. The contents were mixed and incubated in the dark at room temperature for 1 h and shaken intermittently every 15 min. Then 1.25 ml of 20% trichloroacetic acid (TCA) (w/v) was added to both tubes and the mixture left in ice for 10 min. The samples then underwent centrifugation at 3500 rpm for 20 min to get the protein pellet and the supernatant carefully discarded. This was followed by a second wash with 10% TCA. Finally the precipitates were washed three times with 1 ml of ethanol: ethyl acetate (1:1, v/v) to remove unreacted DNPH and lipid remnants. The final protein pellet was dissolved in 1 ml of 6 M guanidine hydrochloride (GuHCL) and incubated at 37 °C for 10 min. The insoluble materials were removed by centrifugation. Carbonyl concentrations were determined from the difference in absorbance at 370 nm between the test and the control samples, with $\varepsilon 370 = 22{,}000\ M^{-1}\ cm^{-1}$ (the molar extinction coefficient of DNPH). Carbonyl levels were expressed as nmol/mg protein.

2.4. Assay of serum protein sulfhydryl group content

It is determined according to thiol/disulfide reaction of thiol and Ellman's reagent (5,5′-dithiobisnitrobenzoic acid, DTNB) [15]. 50 µL of serum was mixed with 1 ml 0.1 M Tris, 10 mM EDTA PH 8.2, constituting the blank reaction and assessed at 412 nm. After that, we added 40 µL 10 mM DTNB in methanol and the absorption was read at 412 nm after stable color formation (1–3 min). The concentrations of protein sulfhydryl groups were calculated using a molar extinction

coefficient of 13.600 M^{-1} cm^{-1}. Protein sulfhydryl groups were expressed as nmol/mg protein.

2.5. DNA isolation

Genomic DNA was isolated from the buffy coat of the samples taken in Na2-EDTA tubes (final concentration 1 mg/ml) after centrifugation at 3000 rpm for 15 min at room temperature using DNA isolation kit (illustra blood genomic Prep Mini Spin Kit, supplied by GE Healthcare), according to the manufacturer's instructions. The DNA isolated using the kit has a characteristic band size of approximately 20 kb on an agarose gel. The yield of genomic DNA was measured by UV absorbance and the purity of it was measured by A_{260}/A_{280} (less than 1.7).

2.6. Determination of SIRT1 gene polymorphism

SIRT1 rs2273773 C > T SNP in exon 5 was analyzed using PCR-CTPP (polymerase chain reaction–confronting two pair primer) assay as described previously [8]. Two pairs of primers; forward 1 (F1), reverse 1 (R1), forward 2 (F2) and reverse 2 (R2), synthesized by eurofins Genomics, were used for the amplification. Table 1 showed the primers sequences, their melting temperature, G-C content and the products obtained.

Briefly; 25 μL total PCR mixtures containing 100–200 ng DNA, 10.0 pmol of each primer, 1.0 mM dNTP (deoxynucleotide triphosphates), 25 mM $MgCl_2$ and 2.5U Taq DNA polymerase in the supplied reaction buffer (Taq Buffer with $(NH_4)2SO_4$) were prepared. The PCR cycling conditions were as follows; initial denaturation at 95 °C for 10 min., 30 cycles of 95 °C for 1 min., 63 °C 1 min., and 72 °C for 1 min. and additionally the final step at 72 °C for 5 min. PCR products were separated on a 2% agarose gel stained with ethidium bromide and genotyped. Three genotypes were defined by 3 distinctive banding patterns 314, 228 bp for CC genotype; 314, 228, 135 bp for CT genotype; and 314, 135 bp for TT genotype (Fig. 1).

2.7. Statistical analysis

Genotype distribution was tested for HWE (Hardy–Weinberg equilibrium) by x^2 analysis. The association between asthma and genotype was calculated using the Chi-square test. Student's t test was used to compare the differences between controls and patients regarding the demographic and laboratory data. Anova test was used to compare the differences among the patients' groups. Results were expressed as mean ± SD or number and percent. A two-tailed value of $P < 0.05$ was considered statistically significant. All statistical calculations were performed using the computer program SPSS (Statistical Package for the Social Science; SPSS, Chicago, IL, version 16 for Microsoft Windows, USA).

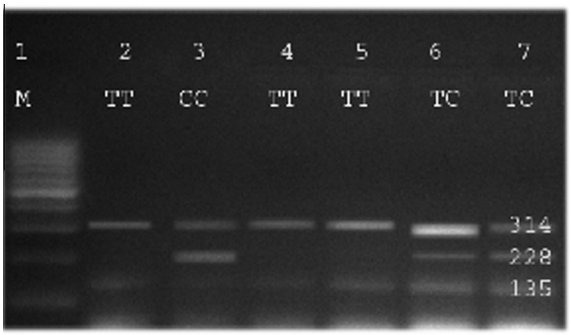

Figure 1 Representative agarose gel electrophoresis showing SIRT-1 gene rs2273773 C > T SNP, lane 1; 100 bp marker, lanes 2, 4 and 5 represent TT genotype, lane 3 represents CC genotype, lanes 6 and 7 represent TC genotype.

3. Results

SIRT-1 gene rs2273773 C > T SNP was in Hardy–Weinberg equilibrium for both the patients and the controls. The results of the investigation revealed that there were no significant differences between the patients and the controls regarding age, sex, blood pressure, blood glucose, total cholesterol, triglyceride and LDL-C. However, there were significant differences in HDL-C, eosinophil count and IgE level ($P < 0.05$). Protein carbonyl group concentration increased significantly ($P < 0.001$), while protein sulfhydryl group content decreased ($P < 0.0001$) in asthma patients compared to controls, Table 2. SIRT-1 gene rs2273773 C > T SNP genotyping revealed that the TT genotype was significantly higher in the patients compared to the controls ($P < 0.05$) and there were no significant differences regarding the genotypes TC and CC ($P > 0.05$), however, TC genotype was higher in the controls but didn't reach the significant level ($P = 0.07$). T allele was significantly higher in the patients compared to the controls ($P = 0.017$), Table 3. The distribution of the genotypes didn't differ among the atopic and the non-atopic asthmatic patients, Table 4. No difference was found in the genotype distribution according to the severity of asthma ($P > 0.05$), Table 5. The markers of protein oxidation didn't differ according to the genotype in both the patients and the controls ($P > 0.05$), Fig. 2.

4. Discussion

In this investigation, the association between SIRT-1 gene rs2273773 C > T single nucleotide polymorphism, protein oxi-

Table 1 Primers used for the amplification.

Primers	Sequence	Tm	GC-content (%)	Products
Forward-1 (F-1)	5-GTGTGTCGCATCCATCTAGATAC- 3	60.6 °C	47.8	314, 228 bp for CC
Forward-2 (F-2)	5-CTCTCTGTCACAAATTCATAGCCT-3	59.3 °C	41.1	314, 228, 135 bp for CT
Reverse-1 (R-1)	5-GTAGTTTTCCTTCCTTATCTGACAG-3	59.7 °C	40	
Reverse-2 (R-2)	5-CTGAAGTTTACTAACCATGACACTG-3	59.7 °C	40	314, 135 bp for TT

Table 2 Clinical and laboratory data of the participants.

Character	Controls, $n = 120$	Patients, $n = 120$
Age (years)	45.5 ± 11	46.6 ± 10.8
Systolic Bp (mmHg)	120 ± 11	125 ± 10
Diastolic BP(mmHg)	70 ± 8.6	75 ± 7.6
Glucose (mg/dl)	90 ± 5.5	100 ± 4.7
Total cholesterol (mg/dl)	191.9 ± 12.2	195 ± 8.7
Triglyceride (mg/dl)	111 ± 28.4	95.4 ± 20.5
HDL-C (mg/dl)	39.4 ± 3.5	28.7 ± 3.6*
LDL-C (mg/dl)	103.7 ± 14.3	112.5 ± 11.5
Eosinophils/mm^3	178.5 ± 65.4	400 ± 201***
Type of asthma		
Atopic, *n* (%)	–	79 (66)
Non-atopic, *n* (%)	–	41 (34)
Severity of dis.		
Mild, *n* (%)	–	55 (46)
Moderate, *n* (%)	–	35 (29)
Severe, *n* (%)	–	30 (25)
IgE (IU/ml)	70 ± 20	135.6 ± 40**
Protein carbonyl (nmol/mg)	2.5 ± 0.63	3.75 ± 0.9**
Protein sulfhydryl (nmol/mg)	324.7 ± 33.4	202.8 ± 19.8***

* $P < 0.05$.
** $P < 0.001$.
*** $P < 0.0001$.

Table 3 Genotype distribution in the participants.

Genotype	Controls, $n = 120$	Patients, $n = 120$	X^2	P
TT, *n* (%)	22 (18.33)	42 (35)	8.5	0.0035*
TC, *n* (%)	70 (58.33)	56 (46.7)	3.27	0.07
CC, *n* (%)	28 (32.33)	22 (18.3)	0.9	0.34
T-allele, *n* (%)	114 (47.5)	140 (58.3)	5.56	0.017*
C-allele, *n* (%)	126 (52.5)	100 (41.7)		

* $P < 0.05$.

Table 4 Genotype distribution in atopic and non-atopic asthma.

	Atopic, $n = 79$	Non-atopic, $n = 41$	X^2	P
TT, *n* (%)	27 (34.1)	15 (36.6)	0.07	0.8
TC, *n* (%)	36 (45.6)	20 (48.8)	0.11	0.7
CC, *n* (%)	16 (20.3)	6 (14.6)	0.57	0.45
T-allele, *n* (%)	90 (57)	50 (61)	0.36	0.55
C-allele, *n* (%)	68 (43)	32 (39)		

dation markers and bronchial asthma in Egyptian population was examined. Our results showed that there was an association between TT genotype and T-allele and asthma. Protein carbonyls increased while protein sulfhydryl decreased in asthmatics compared to controls.

Table 5 Genotype distribution according to the degree of asthma.

	Mild, $n = 55$	Moderate, $n = 35$	Severe, $n = 30$	X^2	P
TT, *n* (%)	20 (36.4)	12 (34.3)	10 (33.3)		
TC, *n* (%)	30 (54.5)	14 (40)	12 (40)	8.5	0.39
CC, *n* (%)	5 (9.1)	9 (25.7)	8 (26.6)		
T-allele, *n* (%)	70 (63.6)	38 (54.3)	32 (53.3)		
C-allele, *n* (%)	40 (36.4)	32 (45.7)	28 (46.7)		

X^2 and P of chi-square for 3 × 5 table.

SIRT-1 gene polymorphism was studied and found to be associated with many diseases [7–9]. SIRT-1 gene rs2273773 C > T SNP, a silent mutation in exon 5, was found to be associated with hypertension and hyperglycemia in Japanese [9]. In another study, TT genotype and T-allele were found to be increased in cardiovascular disease patients as compared to controls and the risk of having cardiovascular disease increased 1.9 times in carriers of T-allele [7]. However, a study on the genetic variation of SIRT1 and its effects on human longevity revealed that, the mortality rate didn't differ among the genotypes of SIRT-1 gene rs2273773 C > T SNP after 18 years follow up in cohort of white individuals of Dutch in The Netherlands [16]. The association between SIRT-1 gene rs2273773 C > T SNP and bronchial asthma may be due to the effect on SIRT-1 protein expression, which in turn affects the inflammation occurring in asthma [8].

Bronchial asthma represents a serious health problem as it was found that 5% to 10% of the population suffer from asthma. Many genes have been found to be implicated in the pathogenesis of asthma. In identical twins if one is affected, the probability of the other having the disease is approximately 25%. By the end of 2005, 25 genes had been associated with asthma in more than six populations [17]. The hallmarks of bronchial asthma are the increase in responsiveness and infiltration of airways by the inflammatory cells which is exacerbated by the cytokines produced by T-helper cells. SIRT1 is a NAD+ dependent histone deacetylase [18]. It also, deacetylates several transcription factors, responsible for metabolism, endocrine signaling, and inflammation, including peroxisome proliferator-activated receptor-γ (PPAR-γ), PPAR-γ coactivator 1-α [19], forkhead box transcription factor, p53 [20], and nuclear factor kB (NF-kB) [21–22]. SIRT1 regulates hypoxia-inducible factor 1-α (HIF1-α) activity and stabilization [23–24]. Studies in cultured renal medullary interstitial cells have shown that SIRT1 protects from oxidative injury and hypoxia via deacetylation and activation of HIF1-α [25]. SIRT1 has been shown to regulate pro-inflammatory mediator release in sustained inflammation and aging of the lungs. It was reported that SIRT1 protein expression and enzyme activity were increased in a murine model of allergen-induced airway inflammation [24]. It was reported that mice lacking SIRT1 catalytic activity exhibited an exaggerated response to hypoxia within 1 week of exposure compared to the wild type mice [26]. SRT1720, a pharmacological SIRT1 activator was found to protect against Type II alveolar epithelial cells apoptosis in rats with emphysema induced by exposure to cigarette

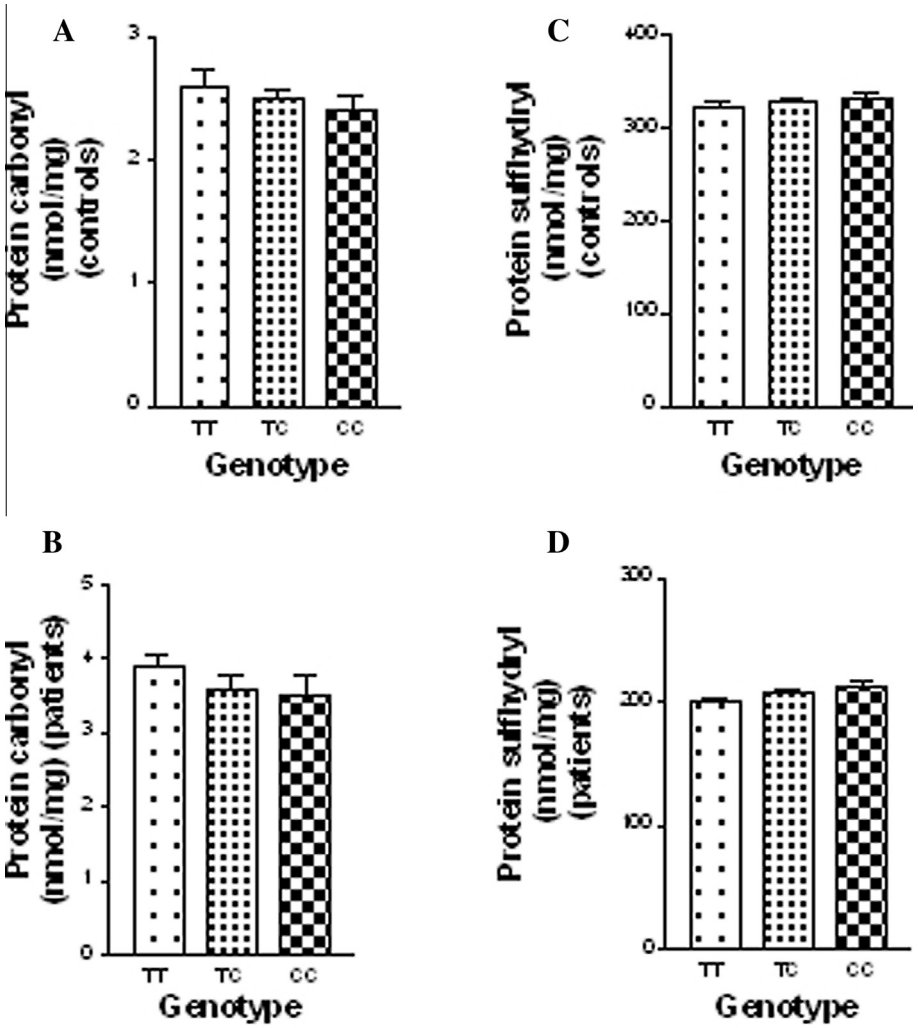

Figure 2 No significant difference in protein group concentration (nmol/mg protein) in the controls (A) and patients (B) according to the genotype ($P > 0.05$). Also, no difference in protein sulfhydryl content (nmol/mg protein) in controls (C) and patients (D) according to the genotype ($P > 0.05$).

smoke and in vivo intratracheal instillation of lipopolysaccharide. SRT1720 improved lung function including airway resistance and pulmonary dynamic compliance. Treatment mice with SRT1720 up-regulated the levels of surfactant protein (SP)A, SPC, SIRT1 and forkhead box O 3, increased SIRT1 activity, down-regulated the level of p53 and inhibited type II alveolar epithelial cells apoptosis [26].

This investigation revealed increased protein oxidation in asthmatic patients represented by an increase in protein carbonyls and a decrease in protein sulfhydryls. Oxidative stress (oxidant-antioxidant imbalance) has been increasingly recognized as a major factor contributing to the chronic inflammation present in asthmatics and was reported by many investigators [10,27–28].

This is the first study of SIRT-1 gene rs2273773 C > T SNP in asthmatic Egyptian population. The limitation of the study was the low number of participants, so further studies in which larger population and the mechanisms by which SNP in SIRT1 gene affect asthma pathogenesis are required.

5. Conclusion

The study revealed an association between SIRT-1 gene rs2273773 C > T SNP and asthma in Egyptian population.

Conflict of interest

The authors declare that there were no conflicts of interest.

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