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Regular paper

Associations between rs2241766 and rs3774261 polymorphisms in *ADIPOQ* gene and atopic dermatitis

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Atopic dermatitis (AD) is a common skin condition that affects both children and adults. Adipokines have been shown to play a role in the pathogenesis of AD. In the current study, the association between adiponectin gene (*ADIPOQ*) polymorphisms and AD was investigated. In addition, changes in serum adiponectin levels in AD patients were examined. Restriction fragment length polymorphism-PCR technique was used to genotype *ADIPOQ* SNPs. The ELISA assay was used to measure serum Adiponectin levels. A total of 324 participants (162 AD and 162 healthy controls) were included in the study. The frequency of the GG genotype of rs3774261 was higher in the AD group (44.5%) than in the control group (32.7%, *P*<0.05). Regarding the rs2241766 SNP, the frequency of the GG genotype was higher in the AD group (10.5%) than in the control group (3.1%), while the frequency of the TT genotype was lower (*P*<0.001) in the AD group (35.8%) than the control group (57.4%). Moreover, the GG haplotype of rs3774261 and rs2241766 significantly increased the risk of AD by about 2-fold (*P*<0.05). Finally, serum adiponectin levels were lower in the AD group than in the control group (*P*<0.05). These results indicate an association of the rs2241766 and rs3774261 SNPs with the risk of developing AD among the population examined.

Keywords: Atopic dermatitis, *ADIPOQ*, adiponectin, polymorphism, rs3774261, rs2241766

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Abbreviations: AD, atopic dermatitis; *ADIPOQ*, adiponectin gene; SNPs, single nucleotide polymorphisms

INTRODUCTION

Atopic dermatitis (AD) is a common form of eczema that affects both children and adults (Frazier & Bhardwaj, 2020; Waldman *et al.*, 2018). In a recent systematic review, the prevalence of AD in adults ranged from 1.2% in Asia to 17.1% in Europe (Bylund *et al.*, 2020). In the United States, the prevalence of AD is about 7% with an estimated annual burden of more than 5 billion per year (Drucker *et al.*, 2017). Patients with AD have dry, scaly and itchy skin with red-gray patches distributed in different parts of the body such as the hands, feet and knees (Fishbein *et al.*, 2020). AD is thought to be caused by a combination of factors that include the immune response, genetic variability, exposure to certain stimuli such as skin irritants, air pollution, tobacco smoke, and skin infection. (Chiesa Fuxench, 2017; Kantor & Silverberg, 2017; Nutten, 2015). In addition, an association between obesity and AD has been reported (Ali *et al.*, 2018; Hirt *et al.*, 2019).

The link between obesity and AD has been shown to be mediated in part by adipokines (Jaworek & Szepietowski, 2020; Jeong *et al.*, 2015; Kelishadi *et al.*, 2017). Adipokines include many peptides that are secreted from adipose tissue into the bloodstream and target other organs of the body to modify their function (Fasshauer & Blüher, 2015). Adiponectin is the most abundant adipokine in the circulation (Fang & Judd, 2018). Adiponectin plays an important role in the body's energy balance by regulating fatty acid oxidation in muscles and glucose production in the liver. (Fang & Judd, 2018). In addition, adiponectin has anti-inflammatory properties that protect the body's organs from chronic inflammation (Choi *et al.*, 2020). It has been shown that Adiponectin levels are significantly reduced in patients with AD compared to healthy people (Jung & Kim, 2020). Furthermore, lower adiponectin levels have been reported in extrinsic AD compared to intrinsic AD patients (Han *et al.*, 2016). In inflammatory human epidermal equivalents in vitro model of AD, adiponectin has been shown to inhibit the expression of key inflammatory mediators and increase the expression of filaggrin (Seo & Seong, 2019). In the animal model of AD, adiponectin expression was found to be significantly lower in the group of mice that developed severe dermatitis (Jeong *et al.*, 2015). Adiponectin signaling has been linked to the regulation of sebum production by human sebaceous glands and thus can be used in the management of clinical conditions such as atopic dermatitis where sebum secretion is significantly reduced (Jung *et al.*, 2017). Thus, previous literature suggested a role for low adiponectin level in the pathology of AD.

Adiponectin is encoded by the *ADIPOQ* gene located on chromosome 3. Several single nucleotide polymorphisms (SNPs) are present in the *ADIPOQ* gene and have been shown to be of clinical interest. Among *ADIPOQ* SNPs are rs2241766 and rs3774261. The rs2241766 (45T/G) is a synonymous variant that affects the level of adiponectin and has been shown to be associated with several conditions such as cancer, cardiovascular disease, and asthma. (Ding *et al.*, 2015; Zhou *et al.*, 2013). The rs3774261 (712 G/A) is also associated with plasma adiponectin level and has been shown to be associated with clinical conditions such as diabetes, cardiovascular disease, and metabolic syndrome (de Luis Roman *et al.*, 2021; Kanu *et al.*, 2016; Saleh & Tayel, 2020; Yao *et al.*, 2016). In the current study, the association between *ADIPOQ* rs2241766 and rs3774261 SNPs and AD was investigated. The expected findings may enhance our

knowledge regarding the role of adipokine genes in the development of AD.

MATERIALS AND METHODS

Study participants

A total of 162 patients with AD disease were recruited into this case-control study. In addition, 161 healthy subjects were recruited to serve as a control group. The control group was selected to roughly match the AD group in age, BMI, and gender. Participants' ages ranged from 1 year to 60 years. Participants were drawn from King Abdullah University Hospital, the Health Center of the Jordan University of Science and Technology, and the hospitals of the Ministry of Health in northern Jordan. The diagnosis of AD was made by dermatologists according to the UK Working Party's Diagnostic Criteria (Williams *et al.*, 1994). Exclusion criteria for the patient group include uncontrolled concomitant systemic disease, presence of other skin diseases, pregnant or lactating women, and a BMI of 30 or more. Written informed consent was obtained from the participants in accordance with the guidelines of the Institutional Review Board of Jordan University of Science and Technology. A structured questionnaire interview was conducted to collect data on the demographics of the study participants.

Blood sampling

Two blood samples were obtained from each person. Five milliliters of whole blood were collected in an EDTA tube for molecular analysis and another five milliliters were collected in a plane tube for biochemical analysis. After coagulation, blood serum was obtained by centrifugation of samples at 500×*g*. The storage condition for EDTA samples was –20°C and for serum samples was -80°C.

DNA Extraction

DNA extraction from whole blood was achieved using a Promega DNA Purification Kit (Cat #: A1125, Madison, USA) according to the manual provided by the manufacturer.

Genotyping of *ADIPOQ* SNPs

The rs2241766 and rs3774261 SNPs were genotyped using restriction fragment length polymorphism-PCR technology. PCR reactions were performed using a master mix obtained from Promega and 5ng of template DNA and 1 μM of each primer. For rs2241766, the primers were forward: 5'-GCAGCTCCTAGAAGTAGACTCTGCTG-3' and reverse: 5'-GCAGGTCTGTGATGAAAGAGGCC-3'. For rs3774261, the primers were forward: 5'-TGGCATTCAACCACATTTAC-3', and reverse: 5'-AAGCCTTCATTCTTCATCAG-3'. PCR conditions for both SNPs were 5 min at 95°C, followed by 35 cycles: denaturation for 40s at 95°C, annealing (58°C for rs3774261, and 60°C for rs2241766) for 45s, and extension at 72° Celsius for 45s. The cycles were then followed by a final 5 min extension at 72°C. The amplified PCR fragments (372 bp and 217 bp for rs2241766 and rs3774261 respectively) were detected by agarose (1%) gel electrophoresis and visualized using UV light and ethidium bromide. The PCR products were then digested with *SmaI* for rs2241766 and *Rsal* for rs3774261. Details regarding the restriction conditions and the sizes of the digested fragments were as previously described (Bruno *et al.*, 2021; Zhou *et al.*, 2015).

Measurement of plasma adiponectin level

Adiponectin was measured in plasma using an ELISA kit obtained from R&D Systems for Research Purposes (DuoSet; Minneapolis, MN, USA) according to the manual provided by the manufacturer. Changes in optical density were measured at 450 nm using an ELx800 microplate reader (BioTek Instruments, Winooski, VT, USA). Adiponectin levels were measured in the samples based on the use of a serial standard provided with the kit (Khabour *et al.*, 2018).

Statistical analysis

Associations of ADIPOQ SNPs with AD, and Hardy–Weinberg equilibrium of rs2241766 and rs3774261 SNPs were performed using SNPstat statistical program. Adiponectin serum levels between the AD group and the control group were compared using the Student t-test. Categorical analysis was computed using the Chi-square test. A *p*-value of <0.05 was used to conclude statistical significance. All collected data are presented in the manuscript.

RESULTS

A total of 324 participants (162 AD and 162 healthy controls) were included in the study. The percentage of male participants in the AD group was similar to that of the control group (50.5%, Table 1). The majority of participants were children (75.3% in the control group and 76.5% in the AD group, $P=0.792$). The BMI (±S.D.) for the AD group was 22.3±4.9 and the BMI for the control group was 21.9±5.2 ($P=0.476$). Thus, all demographic variables were similar between the two groups. Regarding serum adiponectin, the levels in the AD group (2161±1021) were significantly lower ($P=0.036$, Table 1) than those in the control group (2412±1130).

Table 2 shows the genotypes and alleles of the *ADIPOQ* SNPs. Regarding the rs3774261 SNP, the frequency of the GG genotype was higher in the AD group (44.5%) than the control group (32.7%), while the frequency of the AA genotype was lower in the AD (11.7%) group than the control (20.4%) group (OR [95% CI]: 2.36 [1.21–4.60], $P<0.05$). In addition, the frequency of the rs3774261 G allele was enriched in the AD (66.4%) group compared to the control (56.2%) group (OR [95% CI]: 1.54 [1.12–2.12], $P<0.01$). These results

Table 1. Demographics of the study sample

Variable	Control N (%)	Patient N (%)	*P*-value
Gender			
Male	82 (50.6)	82 (50.6)	1.00
Female	80 (49.4)	80 (49.4)	
Total	162	162	
Age groups			
1–18 years	122 (75.3)	124 (76.5)	0.792
> 18 years	40 (24.7)	38 (23.5)	
BMI (mean ±S.D.)	21.9 (5.2)	22.3 (4.9)	0.476
Serum adiponectin (ng/mL)	2412±1130	2161±1021	0.036

Table 2. Genotype and allele frequencies of rs3774261 and rs2241766 of *ADIPQ* gene in AD subjects and controls

Genotypes /Alleles	Patient N (%)	Control N (%)	OR (95% CI)	*P*-value
rs3774261 SNP				
GG	72 (44.5)	53 (32.7)	1.00	
GA	71 (43.8)	76 (46.9)	1.45 (0.90–2.35)	0.0320
AA	19 (11.7)	33 (20.4)	2.36 (1.21–4.60)	
Allele G	215 (66.4)	182 (56.2)	1.00	0.0078
Allele A	109 (33.6)	142 (43.8)	1.54 (1.12–2.12)	
rs2241766 SNP				
TT	58 (35.8)	93 (57.4)	1.00	
TG	87 (53.7)	64 (39.5)	0.46 (0.29–0.73)	<0.001
GG	17 (10.5)	5 (3.1)	0.18 (0.06–0.52)	
Allele T	203 (62.7)	250 (77.2)	1.00	<0.001
Allele G	121 (37.3)	74 (22.8)	0.49 (0.35–0.70)	

Table 3. Haplotype analysis of the rs2241766 and rs3774261 SNPs and AD

	rs3774261	rs2241766	Frequency	OR (95% CI)	*P*-value
1	A	T	0.31	1.00	–
2	G	T	0.39	0.63 (0.40–1.00)	0.053
3	G	G	0.22	1.75 (1.01–3.03)	0.047
4	A	G	0.08	1.58 (0.92–3.57)	0.082

indicate an association between the rs3774261 SNP and the risk of developing AD. Regarding the rs2241766 SNP, the frequency of the GG genotype was higher in the AD group (10.5%) than in the control (3.1%) group (OR [95% CI]: 0.18 [0.06–0.52], $P<0.001$), while the frequency of the TT genotype was lower in the AD group (35.8%) than the group control subjects (57.4%). In addition, the frequency of the rs2241766 G allele (OR [95% CI]: 0.49 [0.35–0.70], $P<0.001$) was enriched in the AD group (37.3%) compared to the control group (22.8%). These results indicate an association between the rs2241766 SNP and the risk of developing AD.

Regarding the effect of the s examined polymorphism on serum adiponectin levels, the GG genotype of rs2241766 had lower levels than other genotypes in both the AD and control groups ($P<0.05$). However, serum levels of adiponectin were similar in the different genotypes of the rs3774261 SNP ($P>0.05$).

When the haplotypes of the rs3774261 and rs2241766 SNPs were considered (Table 3), the GG haplotype significantly increased the risk of AD by about 2-fold ($P=0.047$).

DISCUSSION

In the current study, the association between *ADIPOQ* rs3774261 and rs2241766 SNPs and AD was examined. The results showed that the G allele in both SNPs was associated with an increased risk of AD in the examined population.

Adiponectin is an abundant protein in the human body that is secreted by adipose cells (Fang & Judd, 2018). The level of adiponectin has been shown to play a role in the pathology of many conditions and diseases such as obesity, diabetes, cardiovascular disease, chronic inflammation, and others. (Maeda *et al.*, 2020; Nguyen, 2020; Parida *et al.*, 2019; Yang *et al.*, 2019). This role is attributed to its effect on energy homeostasis and inflammation in the body (Choi *et al.*, 2020).

The rs3774261 and rs2241766 are common polymorphisms in the *ADIPOQ* gene and have been shown to be of clinical interest. The G allele of rs2241766 has been reported to decrease the level of adiponectin in the circulation and is associated with an increased risk of metabolic syndrome, heart diseases (Saleh & Tayel, 2020), kidney diseases (Han *et al.*, 2020), and colorectal cancer (Li *et al.*, 2014). Similarly, the G allele of rs3774261 has been reported to decrease the level of adiponectin in the circulation and be associated with an increased risk of heart disease (Kanu *et al.*, 2016), diabetes (Howlader *et al.*, 2021; Ramya *et al.*, 2013), and prostate cancer (Dhillon *et al.*, 2011). Moreover, in a body weight loss intervention, non-G-allele carriers for the rs3774261 SNP showed a significant improvement in adiponectin level, lipid profile and inflammatory markers compared to G-allele carriers. (de Luis Roman *et al.*, 2021). In the current study, the G allele of rs2241766 and rs3774261 was found to be associated with an increased risk of AD. In support of this, the GG haplotype was found to increase the risk of AD by approximately twofold. The reported effect of these SNPs on the level of adiponectin could explain the associations observed with AD.

The present results showed lower levels of adiponectin in the serum of AD patients compared to healthy subjects. This finding is consistent with previous literature that has indicated a role for adiponectin in the development of AD (Han *et al.*, 2016; Jaworek & Szepietowski, 2020; Jung *et al.*, 2017). In addition, the expression of the *ADIPOQ* gene was reported to be significantly reduced in a mouse model of AD (Jeong et al., 2015). Moreover, in an *in vitro* model of AD, the addition of adiponectin to epidermal cells has been shown to

diminish the expression of inflammatory mediators (Seo & Seong, 2019). Adiponectin signaling enhances sebum secretion and subsequent protection of the skin against AD (Jung *et al.*, 2017). It has also been shown that levels of other adipokines such as resistin and leptin affect the risk of AD (Banihani *et al.*, 2018; Farag *et al.*, 2020; Jaworek & Szepietowski, 2020; Kovács *et al.*, 2020; Seo & Seong, 2019). Thus, a considerable amount of literature supports the role of adipokines in AD disease.

The current study has some limitations. The *ADIPOQ* gene contains several polymorphisms and in the current study, only rs2241766 and rs3774261 were examined. Thus, the inclusion of other SNPs in the *ADIPOQ* gene is highly recommended in future studies. The majority of AD patients in the study were children. Due to the limited sample size, the stratification of patients into different age groups could not be applied. Thus, it is possible that the associations observed may differ in children versus adults. Therefore, the current findings in different age groups need to be confirmed. The current study was conducted in Jordan and the results may be influenced by the genetic background of the population. Therefore, the results of the study should be confirmed in other populations.

In conclusion, the rs2241766 and rs3774261 SNPs of the *ADIPOQ* gene may be associated with atopic dermatitis among the Jordanian population.

Declarations

Conflict of Interest. The authors have nothing to declare.

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