Association between polymorphisms in adiponectin, leptin and leptin receptor genes with COVID-19 disease severity among Jordanian population

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Running title: Adipokines genetic variations and COVID-19 disease

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Abstract

Introduction: Variations in genetic makeup can affect COVID-19 disease susceptibility and severity. Adipokines, including leptin and adiponectin, are protein hormones synthesized in the adipose tissues. Adipokines are implicated in the regulation of body metabolism and immunity. Here, the study investigated the relationships between single nucleotide polymorphisms in adiponectin (*ADIPOQ*: rs1501299 and rs822396), leptin (*LEP*: rs7799039) and leptin receptor (*LEPR*: rs1137101) and COVID-19 susceptibility/severity in Jordan.

Materials and Methods: A cross-sectional, case-control design was adopted. The study included 427 subjects who never experienced COVID-19 disease (controls), and 434 subjects with COVID-19 disease history (cases). Cases included 268 subjects who experienced mild/moderate symptoms and 166 subjects who experienced severe symptoms. Genotyping of genetic variants was performed using "polymerase chain reaction-restriction fragment length polymorphism technique (PCR-RFLP)" technique. Cross-tabulation and multivariate regression analysis were used in data analysis.

Results: No statistical differences were found between distribution of genotypes of the studied genetic variations and susceptibility to COVID-19 ($P>0.05$). Regarding disease severity, the *ADIPOQ* rs1501299 polymorphism exhibited an association with COVID-19 severe form of the disease ($P<0.05$). The frequency of GT genotype was lower ($P<0.05$) among patients with a severe form of the disease than among the patients with a non-severe form of the disease. Finally, the AGGA haplotype of rs822396, rs1501299, rs1137101, and rs7799039 polymorphisms was higher among patients with severe form of the disease than among patients with non-severe form of the disease ($P<0.01$).

Conclusion: the *ADIPOQ* rs1501299 polymorphism and the AGGA haplotype of rs822396, rs1501299, rs1137101, and rs7799039 may contribute to COVID-9 disease severity among Jordanian people. The current results can be integrated in the management of COVID-9 disease severity.

Keywords: adipokines, genetic variations, SARS-CoV-2, virus

1. Introduction

COVID-19 is a serious contagious infection caused by "severe acute respiratory syndrome coronavirus (SARS-CoV-2)". Symptoms range from asymptomatic infection to a life-threatening complicated pneumonia [1]. The virus invades various tissues in the body, primarily the respiratory system, and then spreads to other body systems such as the neuronal system, gastrointestinal tract, and circulatory system [2]. Symptoms include sore throat, fever, hypoxia, dyspnea, diarrhea, and others. The variability of disease symptoms is attributed to several factors, including age, health status, and genetic factors [1].

Adipokines play a role in regulating body's metabolism and immunity [3]. The most important adipokines are adiponectin and leptin [4]. Adiponectin is the product of *ADIPOQ* gene in the adipose tissue that circulates in the bloodstream to the target cells. Adiponectin has anti-inflammatory and antioxidant properties and enhances insulin sensitivity in the human body [5]. Like adiponectin, leptin is a protein produced by adipose tissues and circulates in the bloodstream. It is encoded by *LEP* gene and involved in regulating appetite, energy expenditure, and immune response [6]. Some investigations have examined the relationship between COVID-19 and adiponectin and leptin blood concentrations, with conflicting results [7]. Most studies agree on an inverse relationship between circulating adiponectin concentration and the

degree of COVID-19 severity [8, 9]. Regarding leptin, elevated adiponectin levels are associated with an excessive inflammatory response and the resulting severe form of COVID-19 [8, 10, 11]. In addition, adipose tissue expresses ACE2, the major receptor for the "SARS-CoV-2".

Adiponectin and leptin levels are impacted by "single nucleotide polymorphisms" (SNPs). These include rs822396 (-3971A>G) and rs1501299 (276G>T) in *ADIPOQ* gene, rs7799039 (2548A>G) in *LEP* gene, and rs1137101 (A>G: Q223R) in leptin receptor (*LEPR*) gene. The rs822396 and rs1501299 SNPs influence the expression level of adiponectin and have been reported to affect the risk to several long-lasting illnesses such as metabolic syndrome, diabetes, and asthma [12]. Similarly, rs7799039 in the *LEP* gene influences leptin levels and is linked to diabetes, obesity, and cancer. The rs7799039 has also been shown to affect COVID-19 severity in the Egyptian population [13]. Finally, rs1137101 in the *LEPR* gene is an important polymorphism that impacts leptin function and has been shown to be associated with several chronic diseases . Therefore, the aim of this investigation was to study the contribution of rs822396, rs1501299, rs7799039, and rs1137101 to susceptibility/severity of COVID-19 disease in Jordan.

2. Materials and Methods

2.1. Study Subjects

The "case-control design" was adopted in the current investigation. The case group included 434 participants who previously infected with COVID-19. The control group included 427 participants without a history of COVID-19. Both groups were recruited from northern Jordan and were age- and sex- matched. COVID-19 history was confirmed through participants' medical records. Cases were stratified into: non-

severe and severe subgroups, using the severity scale described previously [14]. Non-Jordanians and children (<18 years old) were not allowed to participate.

2.2. Ethical issues

The "Institutional Review Board (IRB) of Jordan University of Science and Technology" approved the study protocol (approval ID: 20/160/2023). Participants were given written informed consent in accordance with IRB and international research ethical regulations.

2.3. Blood Sampling

Blood samples were drawn from participants in EDTA blood collection tubes. Blood was stored in the freezer for DNA extraction and genotyping.

2.4. Anthropometric Measurements

Participant's height (H) was measured using a stadiometer, while their weight (W) was obtained using a medical scale. BMI was deducted from W(kg) and H($m^{2)}$) as previously described. Body fat percentage was measured using a smart medical scale obtained from ICOMON (China).

2.5. Molecular Analysis

DNA was extracted using a "G-spin™ genomic DNA extraction kit" (iNtRON Biotech) as described in the kit datasheet. DNA quantity and quality were measured using a nanodrop spectrophotometer (Bio-Rad, USA).

Genotypes of rs7799039, rs1137101, and rs822396 variants were detected via "polymerase chain reaction-restriction fragment length polymorphism technique". Amplification conditions and restriction conditions are shown in Table 1. After PCR-RFLP procedure, the digestion products were electrophoresed on 3% agarose, visualized using EtBr under UV light.

Table 1. PCR and restriction conditions of examined polymorphisms of included genes.

Item	rs7799039	rs1137101	rs822396
F primers	5'TTTCTGTAATTTTCCCGTGAG3'	5'GGCCTGAAGTGTTAGAAGAT3'	5'GGTCTTGGAAACTTCTGAGGCT3'
R primers	5'AAAGCAAAGACAGGCATAAA3'	5'CTGCTCTCTGAGGTGGGAAC3'	5'AAACCTTGGAGAGAGGGCAA3'
PCR product	242 bp	642 bp	245 bp
PCR conditions	94˚/5min then 34 cycles: 94˚C/30s, 52˚C/45s, and 72˚C/45s, then a final extension of 72˚C/5min	94˚/5min then 32 cycles: 94˚C/30s, 58˚C/30s, and 72˚C/30s, then a final extension of 72˚C/5min	94˚/3min then 35 cycles: 94˚C/30s, 55˚C/25s, and 72˚C/30s, then a final extension of 72˚C/5min
Restriction conditions	10 units of *HhaI*/10uL of PCR product incubated at 37˚C overnight	10 units of *MspI*/10uL of PCR product incubated at 37˚C overnight	10 units of *MseI*/10uL of PCR product incubated at 37˚C overnight
Restriction products	AA: 242bp GG: 181/61bp	AA: 642bp GG: 469/173bp	GG: 245bp, AA: 181 + 64

The genotypes of *ADIPOQ* rs1501299 were determined using the polymerase chain reaction-allele refractory mutation system (PCR-ARMS). Amplification of region flanking rs1501299 was performed using forward (5'GAGCTGTTCTACTGCTATTAGCTCTGC3') and reverse primers (5'GAATATGAATGTACTGGGAATAGGGATG3'). Internal forward primer for the G allele was: 5'CCTCCTACACTGATATAAACTATATGAGGG'3 and the internal reverse primer for the T allele was: 5'TGTGTCTAGGCCTTAGTTAATAATGAACGA3'. PCR conditions were 95˚/5min then 32 cycles (95˚C/0.5min, 58˚C/0.5min, and 72˚C/1min), followed by 72˚C/5min [15]. After PCR, fragments were electrophoresed on 3% agarose, visualized using EtBr under UV light. The PCR fragments were: 476bp for the "control band", 244bp for the "G allele", and 292bp for the "T allele".

2.6. Statistics

The "SNPStats" program was utilized to determine rs7799039, Q223R, rs822396, and rs1501299 distribution and relationship with susceptibility/severity of COVID-19. The alignment of the examined polymorphisms with Hardy–Weinberg equilibrium was also assessed using "SNPStats". Study measures are presented as mean (±SD) or percentages, and they were compared between groups using SPSS (version 22). The cutoff p-value for significant was ≤0.05. Sample size was computed using "GPower-3.1 software" (intermediate effect/alpha=0.05/1-betta=0.9). The minimum required sample=470 participants.

3. Results

The study included 434 participants with a history of COVID-19 disease (cases) and 427 subjects without a history of COVID-19 disease (controls). No statistical difference (P>0.05) was observed between cases and controls regarding age, and gender ratios. However, differences were found between cases and controls concerning BMI, body fat percentage, and the presence of chronic diseases (P<0.05, Table 2). The incidence of chronic diseases and body fat percentage were significantly higher among the case group, while BMI was slightly higher among the control group.

Table 2: Demographic Characteristics of the overall subjects:

Variables	Case (n=434)	Control (n=427)	P-value
Gender ratio (male: female)	41.9:58.1	46.1:53.9	0.210
Age (years)	46.0±13.4	47.2±12.3	0.180
BMI (kg/m^2)	30.4±5.8	31.5±8.3	<0.05
% body fat	36.6±9.24	32.4±8.33	<0.01
Having a chronic disease	171(39.4%)	139(32.6%)	<0.01

The distribution of genotypes of the included variants among participants is shown in Table 3. The AA genotype (71.7%) of rs822396, the GG (42.6%) genotype of the

rs1501299, AG genotype (49.1%) of rs7799039, and AA genotype of rs1137101 were common in the study sample. None of the examined polymorphisms were associated (P>0.05) with COVID-19 susceptibility.

Table 3: Genotype distribution of rs822396 based on susceptibility to COVID-19

Polymorphism	Genotype	Case	Control	OR (95% CI)	P-value
rs822396	**AA**	311 (71.7)	334 (78.2)	1.00	0.068
	AG	113 (26)	83 (19.4)	1.46 (1.06-2.02)	
	GG	10 (2.3)	10 (2.3)	1.07 (0.44-2.62)	
rs1501299	GG	214 (49.3)	182 (42.6)	1.00	0.096
	GT	158 (36.4)	185 (43.3)	0.73 (0.54-0.97)	
	TT	62 (14.3)	60 (14.1)	0.88 (0.59-1.32)	
rs1137101	**AA**	209 (48.2)	202 (47.3)	1.00	0.97
	AG	182 (41.9)	182 (42.6)	1.03 (0.78-1.37)	
	GG	43 (9.9)	43 (10.1)	1.03 (0.65-1.65)	
rs7799039	GG	122 (28.1)	102 (23.9)	1.00	
	AG	213 (49.1)	228 (53.4)	1.28 (0.93-1.77)	0.323
	AA	99 (22.8)	97 (22.7)	1.17 (0.80-1.72)	

Next, we examined the association between rs822396, rs1501299, rs7799039, rs1137101 haplotypes and susceptibility to COVID-19. Similar to genotypes, none of the haplotypes were associated with COVID-19 susceptibility.

The case group was stratified into two categories according to COVID-19 severity. As shown in Table 4, the *ADIPOQ* rs1501299 polymorphism was associated with severe form of COVID-19. The frequency of GT genotype was lower among the severe subjects compared to non-severe ones. However, rs822396, rs7799039, and rs1137101 did not impact COVID-19 severity (P>0.05).

Table 4: Genotype distribution of adiponectin polymorphisms within the case subgroups based on COVID-19 severity.

Polymorphism	Genotypes	Severe	Non-severe	OR (95% CI)	P-value
rs822396	**AA**	117 (70.5)	194 (72.4)	1.00	
	AG	46 (27.7)	67 (25.0)	1.14 (0.73-1.77)	0.730
	GG	3 (1.8)	7 (2.60)	0.71 (0.18-2.80)	
rs1501299	**GG**	91 (54.8)	123 (45.9)	1.00	0.038
	GT	48 (28.9)	110 (41.0)	0.59 (0.38-0.91)	
	TT	27 (16.3)	35 (13.1)	1.04 (0.59-1.84)	
rs7799039	**AA**	46 (27.7)	53 (19.8)	1.00	0.160
	GA	77 (46.4)	136 (50.8)	1.04 (0.65-1.66	
	GG	43 (25.9)	79 (29.5)	1.59 (0.93-2.74)	
rs1137101	**AA**	71 (42.8)	138 (51.5)	1.00	0.210
	AG	77 (46.4)	105 (39.2)	1.43 (0.95-2.15)	
	GG	18 (10.8)	25 (9.3)	1.40 (0.72-2.74)	

The association between rs822396, rs1501299, rs7799039, rs1137101 haplotypes and COVID-19 severity are presented in Table 5. The frequency of AGGA haplotype was higher among the "severe group" (0.126%) than among the "non-severe group" (0.046%, OR [95%CI]: 2.95 [1.41 - 6.16], P<0.01). On the other hand, none of the other haplotypes were significantly associated with COVID-19 severity.

Table 5. Haplotype analysis of rs822396 (A/G), rs1501299 (G/T), rs1137101 (G/A), and rs7799039 (A/G), polymorphisms and COVID-19 disease severity.

	Non-severe	Severe	OR (95% CI)	P-value
AGAG	0.22	0.2075	1	---
AGAA	0.1723	0.1579	0.95 (0.52 - 1.75)	0.86
ATAG	0.1124	0.0971	0.97 (0.49 - 1.89)	0.92
ATAA	0.112	0.0882	0.87 (0.46 - 1.65)	0.67
AGGG	0.0974	0.0758	0.75 (0.33 - 1.70)	0.49
AGGA	0.0462	0.1264	**2.95 (1.41 - 6.16)**	**<0.01**
ATGG	0.051	0.0595	1.18 (0.47 - 2.96)	0.72
GGAA	0.0574	0.0536	1.08 (0.44 - 2.66)	0.87
ATGA	0.0377	0.0311	0.86 (0.22 - 3.36)	0.83
GGAG	0.0368	0.024	0.63 (0.15 - 2.71)	0.54
GGGA	0.0152	0.0206	1.86 (0.48 - 7.12)	0.37
GTAA	0	0.0313	1.21 (0.27 - 5.40)	0.81
GGGG	0.019	0.0271	3.82 (0.22 - 65.75)	0.36
GTGG	0.012	0	0	-
GTGA	0.0107	0	0	-

4. Discussion

COVID-19 can be expressed in different forms with a range of clinical signs. Previous literature indicates that certain variants in genes can impact individual susceptibility to COVID-19 and its severity. Here, the relationship between *ADIPOQ* (rs1501299 and rs822396), *LEP* (rs7799039) and *LEPR* (rs1137101) variants with COVID-19 susceptibility/severity was examined. No associations were observed between genotypes of the examined variants and susceptibility to COVID-19. When disease severity was considered, the *ADIPOQ* rs1501299 was found to impact COVID-19 severity. Additionally, AGGA haplotype of rs822396, rs1501299, rs1137101, and rs7799039 was found to be associated with disease severity.

Adipokines are a group of proteins produced by adipose tissues and circulate in the bloodstream. Adipokines such as adiponectin and leptin, are implicated in the regulation of body metabolism and immunity [5]. Levels of these cytokines have been shown to be associated with the etiology of many disease conditions, such as obesity, diabetes, heart disease and cancer [12]. These conditions have been shown to modulate outcomes of COVID-19 infection. In addition, circulating adiponectin and leptin levels have been shown to impact severity and outcomes of COVID-19 [16-18]. The present results showed no impact for *ADIPOQ*, *LEP*, and *LEPR* variants on susceptibility to COVID-19. Furthermore, none of haplotypes of examined polymorphisms were associated with susceptibility to COVID-19. The limited literature addressing genetic variations in adipokine genes and COVID-19 susceptibility make comparisons with literature inapplicable. Adiponectin receptors (such as adipoR1 and adipoR2) are expressed in various parts of the respiratory system including epithelial cells, smooth muscle cells and lung macrophages. Similarly, leptin receptor is expressed in lung epithelial cells and airway muscle cells.

A previous study showed that leptin did not involve in “SARS-CoV-2” infection ability in laboratory models of lung infection [19]. Additionally, adiponectin level was reported to be low in COVID-19 patients [20]. The absence of a relationship between the examine SNPs and COVID-19 susceptibility suggests that these adipokines may not be involved in binding to or entrance of “SARS-CoV-2” into body cells.

The present results reported an impact of *ADIPOQ* rs1501299 and COVID-19 severity. Additionally, AGGA haplotype of rs822396, rs1501299, rs1137101, and rs7799039 was found to be associated with disease severity. Limited literature has examined the relationship of adipokine gene polymorphisms with COVID-19 disease severity. A previous study in Egypt showed an impact for *LEP* rs7799039 on COVID-19 disease severity [13]. A study that was conducted in Iraq reported no relationship between *ADIPOQ* rs266729 variant and COVID-19 disease severity [21]. On the other hand, the relationship between adiponectin and leptin blood levels and the severity of COVID-19 has been well investigated, and studies have shown conflicting results. Regarding adiponectin, literature has indicated an association between high [22], low [23, 24] or unchanged [25] adiponectin levels in severe form of COVID-19. Regarding leptin, literature has indicated an association between high [8, 10, 11, 24], low [23] or unchanged [25] leptin levels in severe form of COVID-19. A study showed that gender and underlying diseases influence the relationship between adiponectin protein level and severe form of COVID-19 [26]. In addition, it has been shown that adiponectin/leptin ratio influences COVID-19 disease severity, rather than individual level of adiponectin or leptin [27]. Additionally, blood adiponectin level at hospital admission was inversely related to death and lung dysfunction in COVID-19 [28]. The consensus in literature is that severe COVID-19 is related to lower circulating adiponectin level and higher circulating leptin level.

Among the study limitations is that it was conducted in Jordan, therefore, it is recommended to expand its scope to include other populations in other countries. In addition, circulating adiponectin and leptin levels were not investigated, and deceased patients were not included due to adopted retrospective approach.

5. Conclusion

The *ADIPOQ* rs1501299 polymorphism may contribute to COVID-9 disease severity in the Jordanian population. Additionally, the AGGA haplotype of SNPs rs822396, rs1501299, rs1137101, and rs7799039 may be associated with disease severity. These findings support the relationship between circulating adiponectin level and leptin level with COVID-19 disease severity.

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Ethics

Approval of the study protocol was granted from "Institutional Review Board of Jordan University of Science and Technology".

Authors' Contribution

ZO: "Methodology, investigation, data curation, writing-original draft".

OK: "Methodology, supervision, funding acquisition, writing-review and editing".

Conflict of Interest

Authors have no "conflict of interest" to declare

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Availability of data

"Data are available on reasonable request from the corresponding author".

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