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Research Article

Effect of High-Altitude on Serum-ISG-15 Levels in Influenza Patients

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Abstract

Introduction: Influenza worldwide outbreaks are common, and the mortality rate is high. In high-altitude symptoms are shared with those from respiratory infections, these like tachycardia, cough, and shortness of breath. ISG-15 is effective in ISGylation process involved in the active suppression of much viral infection such as HIV, HCV, and RSV, dengue. This study aims to evaluate if serum ISG15 levels in influenza patients are different between high and low altitude cities.

Materials and methods: 38 serum samples were collected from patients with influenza; serum ISG-15 levels were evaluated by ELISA.

Results: Serum ISG15 was significantly higher in Taif patients than Makkah; also, males from Taif have more serum ISG15 levels than Makkah.

Discussion and conclusion: high-altitude can lead to increase the cellular release of ISG15 in response to influenza viral infection.

Keywords: ISG-15; High-Altitude; Influenza; IFN-α; Low-Altitude

Abbreviations

ISG15: Interferon Stimulated Gene 15; IFN-α: Interferon Alpha.

Introduction

Influenza is an acute respiratory viral infection. Worldwide outbreaks are common, and the mortality rate is high. The spread of influenza is rapid due to high number of viral particles present on droplets that spread by sneezing, coughing and touching.

ISG-15 is effectively induced by several effects such as type-I-IFN [1], and viral infection [2]. ISG-15 is secreted from several cells and induce the production of IFN-γ [3]. ISG-15 is effective in ISGylation process involved in the active suppression of many viral infection such as HIV [4], HCV [4,5], and RSV [6], dengue [7].

ISG-15 deficient mice are more susceptible to several viral infections such as herpes simplex virus-1, Chikungunya virus, vaccine virus and sindbis virus [8-12]. Moreover, ISG-15 levels have up-regulated *in vivo* following influenza A and B infection [12]. ISG15 antiviral activity is processed via its conjugation to the cellular protein [13].

In high-altitude symptoms are shared with those from respiratory infections, these like tachycardia, cough, and shortness of breath [14]. Moreover, another study showed threefold increase in the mortality rate in high-altitude between 2000 - 2499 m above sea levels due to pneumonia-influenza infection [15,16].

Taif is 1879 m above the sea level and Makkah is 277 m. This study aims to evaluate if serum ISG15 levels in influenza patients is different between those two cities. A previous study has shown significant difference in cytokines levels between those two cities in type-I-diabetic children against non-diabetic children, they have shown that IFN-γ, TNF-α, IL-6, IL-1β, IL-4, and IL-10 are significantly higher in Type-I diabetic children from Taif than Makkah [17].

Materials and Methods

Study group

Serum was obtained from a panel of 38 healthy volunteers showing symptoms of influenza aged between 18 and 52 years (20 men, 18 women), following written informed consent. 16 participants from Taif and 22 from Makkah. Subjects are free from autoimmune, malignant or immunosuppressive disease. About 3 ml of blood was taken into red-tube and centrifuged at 1500 rpm, and then serum was collected and stored at -20°C for serum ISG-15 analysis. Ethical approval was provided from Taif university ethical committee.

ISG-15 serum levels

ISG-15 serum levels will be analysed for the 38 samples from both groups of patients. ELISA kit for assay of ISG-15 levels was purchased from BT-laboratory cat number E1988Hu and the detection sensitivity between 10 ng to 3000 ng. The analysis was performed on Bio-Rad xMark™ micro plate spectrophotometer.

Statistical analysis

ISG-15 serum levels have been compared using t-test between Taif and Makkah patients and the results were compared by Paired t-test via GraphPad prism 5.03.

Results

ISG-15 protein levels

This study has quantified the levels of serum-ISG15 between Taif and Makkah influenza patients. In figure 1 the relative difference between Taif and Makkah patients are illustrated. Patients from Taif have shown significantly more serum ISG15 than Makkah.

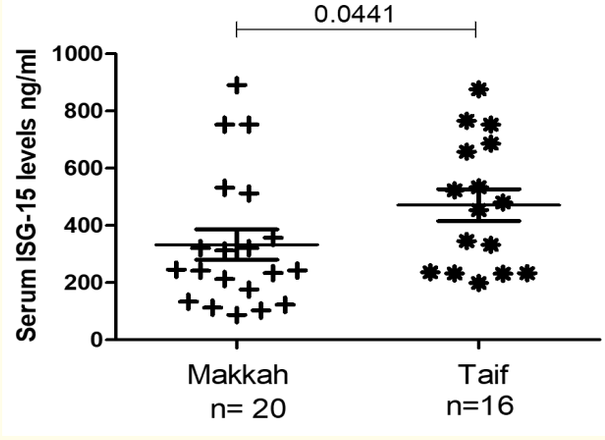

Figure 1: Relative levels of serum ISG15 was quantified and compared between influenza patients between Makkah and Taif. Significant difference was calculated showed more ISG15 levels in Taif patents than Makkah (P. value = 0.0441).

Serum ISG-15 according to gender

Serum ISG-15 levels were compared according to gender (Figure 2). Taif males were shown significantly more serum ISG15 than Makkah males (P. value = 0.0092). However, comparing females and males in Makkah, and females from Taif with Makkah has shown no significant difference.

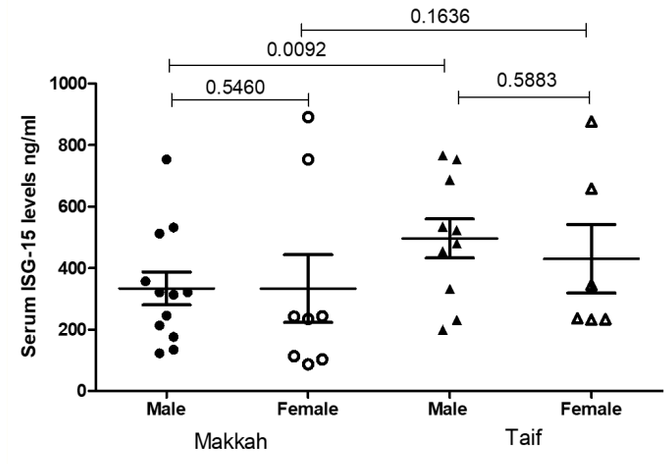

Figure 2: Serum ISG-15 levels were found to be significantly higher in Taif males than Makkah (P. value = 0.0092).

Discussion

Due to antigenic drift and shift in influenza, outbreaks or seasonal epidemics are common. Clinical symptoms of influenza are common and can be diagnosed particularly in winter session. This study has aimed to evaluate the difference between serum ISG-15 levels in influenza patients from Taif and Makkah. ELISA test for detection of serum ISG-15 levels has shown that Taif patients have significantly more serum ISG15 levels than Makkah. As described earlier Taif is a high-altitude city 1879 m and Makkah is 277 m above sea level. Moreover, males from Taif displayed more serum ISG-15 levels than those from Makkah. Viral detection lead to the activation of type-I IFN which is then play a major role in innate immune response and in activating of several interferon stimulated genes involving ISG15 [8]. Induction of ISG15 is supported by type-I-IFN levels, up-regulation of ISG-15 expression occur due stress on cells by illness such as viral infection [18,19] and in our study this has been done by influenza virus. IFN-α is highly effective on ISG-15 expression and against influenza, a study has found that IFN-α administration has reduced Influenza in rhesus macaques [20]. When age grouped were compared according to serum ISG15 levels, no significant difference where detected. Overall, ISG15 was identified as universal suppressor of viral infection. Antiviral action related with protein ISGylation by ISG-15 has been detected and studied for both DNA and RNA viruses, like influenza A and B [21],

Sindbis [22], hepatitis B, herpes simplex type-1, murine γ-herpesvirus, RSV [5], HIV-1 [5,23] and Ebola virus [24,25].

Recommendation and Conclusion

Our study is consistent with previous findings reported by others suggesting expansion in the levels of ISG15 due to viral response and in this case influenza [8,12]. Even more, high-altitude can induce ISG15 production [16]. This finding can be further studied by involving USP18 serum levels. The study can conclude that ISG-15 serum levels are affected by high-altitude.

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Conflict of Interest

There is no conflict of intertest.

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