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Comparative study of Resistin and Glucose levels in COVID-19 patients

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***Abstract*---**Since the end of 2019, coronavirus disease 2019 caused by severe acute respiratory syndrome coronavirus 2 has spread worldwide, it causes risks to public health. Adipokines perform a hormonal function and the most important adipokines that have received research interest are resistin, which is an important link between insulin resistance, and diabetes. This study aimed to estimate the level of Resistin and level of glucose and their relationship to diabetes in Covid-19 patients. The study was conducted on 65 patients with covid-19 and 23 healthy individuals in a control group, Resistin was assessed by the ELISA technique, it was resistin levels in male and female Covid-19 patients high(737.5714±103.44982, 638.5000±85.20096 respectively pg\ml) when compared to healthy males and females (363.7692±26.83405, 394.0000± 30.59412 respectively pg\ml).An elevated glucose level was observed in male and female patients (122.2000±9.703, 145.6667±11.55 mg/dl respectively)when compared to healthy males and females (90.8462±6.346, 102.3000±7.701 mg /dl respectively), This research found a high level of Resistin in Covid-19 patients.Therefore, it can be used as an important indicator to signify the complications of COVID-19 disease as well as for diagnosis, this hormone may have a relationship in causing new diabetes after infection Covid-19.

***Keywords*---** adipokine, COVID-19, diabetes mellitus, insulin resistance, resistin.

Introduction

COVID-19 is a new viral disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an enveloped RNA beta coronavirus. COVID-19 was first reported in China (C. S. G.of the International, 2020)in December 2019 and rapidly spread globally, infecting over 180,000,000 and causing over 3,800,000 deaths as of June 25, 2021(Hidalgo *et al.* 2021).The majority of infected individuals are asymptomatic or have mild to moderate symptoms. However, approximately 5–20% of hospitalized subjects require treatment in an intensive care unit (ICU) because of respiratory failure (Guan *et al.*, 2020) Resistin (or 'resistance to insulin') was originally discovered in mice in 2001 and named for its ability to resist (interfere with) insulin action at that time, Resistin , which was originally described as an adipocyte-specific hormone, has been suggested to be an important link between obesity, and diabetes insulin resistance. (Jamaluddin *et al.*, 2012)Although its expression was initially defined in adipocytes, significant levels of resistin expression in humans are mainly found in mononuclear leukocytes, macrophages were found to be produced and released from white adipose tissue into the circulation.

(Dutta *et al.*, 2021) It was observed that it is expressed at very low levels in endothelial cells, preadipocytes, and vascular smooth muscle cells but is abundantly expressed in the bone marrow and the peripheral mononuclear cells (Taouis and Benomar,2021) resistin is secreted mainly by macrophages rather than adipocytes.(Ebihara *et al.*, 2021)Diabetes mellitus (DM) is a major global public health challenge, and diabetes comprises a heterogeneous etiology of the disease characterized by elevated blood glucose and many systemic manifestations that cause a number of complications that reduce the quality of life of sufferers. Diabetes mellitus occurs as a result of a defect in the secretion of insulin from the pancreas in individuals.(Makrilakis, 2019) The amount of insulin that is secreted may be less than what is required, or it may completely stop its production, and this condition is called insulin deficiency, or in some cases, the amount secreted is large as individuals with obesity, but there is resistance by tissues and cells in the body that impairs the function of insulin, and this is called The condition is insulin resistance(Su *et al.*, 2019).

Mellitus Insulin resistance (IR) is due to a reduced tissue sensitivity to insulin and refers to the inability of the pancreas to secrete sufficient insulin for blood glucose regulation(Page and Johnson 2018). Failure of glucose regulation leads to diabetes.(Davids *et al.*, 2020) COVID-19 has raised public health concerns in recent days around the world. Diabetes has been reported to be one of the most common comorbidities and is associated with a high mortality rate(Zhou and Tan, 2020). These manifestations of diabetes pose challenges in clinical management and suggest complex pathophysiology of diabetes associated with Covid-19 (Hamming *et al.*, 2004) This study aimed to estimate the serum level of Resistin hormone, and the level of glucose and its relationship to diabetes in Covid-19 patients, and this hormone could give an important indication on complications of the COVID-19 epidemic in males and females Patients.

Materials and Methods

Study design and patients characteristics

This randomized study was conducted on Iraqi patients with covid-19 in the Fallujah Teaching Hospital. The study was conducted on 65 patients diagnosed with covid-19 patients who were diagnosed as having SARS CoV-2 (based on a positive RT-PCR test) and pneumonia (based on computed tomography imaging) and symptoms. and 23 healthy individuals as a control Under the same age group and gender. Human samples enrolled in this study were subdivided into males and females. They were (35) male and (30) female inpatient groups, and the range of age of participants was (20-75) years, where Pregnant women were excluded from this study.

Collection of samples
Blood samples

Venous blood samples were collected by using strict aseptic technique Venipuncture was performed and 5 ml of blood was withdrawn, then the blood was put into a gel tube, and the gel tubes were centrifuged at 3000 rpm for five minutes to obtain serum.

Determination of Human Resistin concentrations in serum

Resistin was determined by the ELISA technique and using a device (Diagnostic Automation, Inc., USA) and Kit from(Elabscience, USA), In accordance with the manufacturer's instructions, the test was carried out. From a standard curve, the concentration of Resistin was calculated.The enzyme-Linked Immunosorbent Assay technique for the sandwich method is one of the acceptable serological tests for easiness and fineness in measuring . It is based on the interaction between the antibodies in the wells of the test’s plate and specific antigens in the patient's serum.

Determination of Glucose Levels

The serum glucose was determined by the enzymatic colorimetric (GOD-PAP) method, using the kit supplied by Spinreact, Spain, In accordance with the manufacturer's instructions, this test was done.

Statistical Analysis

The data was analyzed using the complete random design C.R.D in one way, and the significant differences between the means were tested using the L.S.D test at the level of 0.05, as well as the study of the simple correlation between the different characteristics, the data analysis was conducted using the statistical program SPSS, as well as the Excel program, was used to display Results.(Steel and Torrie, 1960).

Results and Discussion

Resistin Hormone Level in male and female Covid-19 patients and control groups

The results of the current study showed a highly significant increase in the level of the hormone resistin in male and female Covid-19 patients (737.5714±103.44982, and 638.5000±85.20096 respectively pg\ml) when compared to the control group for males and females (363.7692±26.83405, and 394.0000± 30.59412 respectively pg\ml) There are no statistically significant differences between female and male patients, p-value = 0.05 as shown in figure 1.

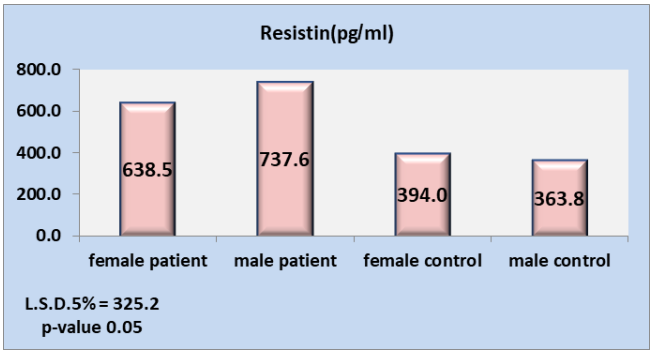

Figure 1. Resistin Hormone Level in male and female Covid-19 patients and control groups

Glucose Level in male and female Covid-19 patients and control groups

The means of glucose showed a highly significant increase in male and female Covid-19 patients (122.2000±9.703, and 145.6667±11.55 mg/dl respectively) when compared to the control group for males and females (90.8462±6.346, and 102.3000±7.701 mg /dl respectively), The glucose level in female patients is slightly higher than in male patients p-value 0.05 as shown in figure 2

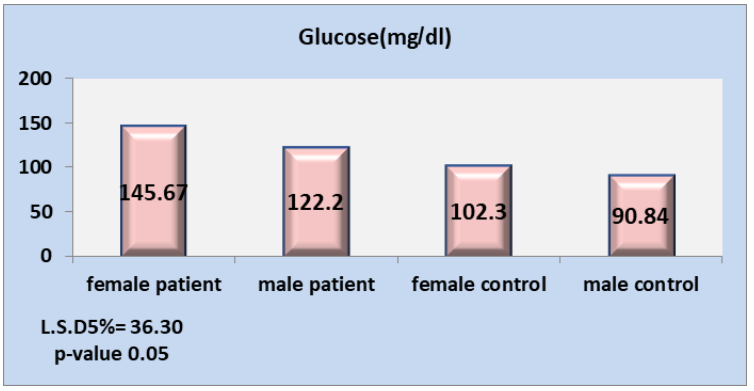

Figure 2. glucose Level in male and female Covid-19 patients and control groups

The results of the current study showed significant differences in the hormone resistin in patients with Covid-19, as this hormone was significantly higher in patients compared to healthy, There are no statistically significant differences between female and male patients. The results of the current study agreed with what was stated by Ebihara et al Which showed that resistin was elevated in COVID-19 patients compared to healthy people and it formed a network of cytokines and markers of endothelial damage, which may be involved in the pathogenesis of COVID-19.(Ebihara *et al.*, 2021) A recent study demonstrated that resistin is associated with severity and prognosis, suggesting that systemic inflammation and endothelial damage caused by the resistin-associated network may contribute to a fatal outcome in COVID-19 patients. (Martin *et al.*, 2021)Also, the current results agreed with another study by Perpiñan et al Which showed it is possible to use the hormone resistin to predict the development of inflammation in patients with Covid-19 .

The patients were suffering from high levels of resistin, and are at high risk of the need for mechanical ventilation therefore that resistin is the best indicator of the need for mechanical ventilation in Covid-19 disease. (Perpiñan *et al.*, 2022)Resistin, which is secreted from white adipose tissue, has been implicated in metabolic, inflammatory, and autoimmune diseases (Musovic *et al.*, 2021)Studies have found that resistin is expressed in several types of cells such as the intestinal epithelium, skeletal muscle cells, astrocytes, and adipocytes (Jumli and Nadeem, 2021) ACE2 was recognized as the receptor for the entry of SARS-CoV-2 into host cells(Zhang and Hashimoto, 2020)(Ziegler *et al.*, 2020). High expression of ACE2 (eg in the bronchial epithelium) has been shown to contribute to patterns of morbidity and severity of COVID-19 but limited studies have not looked at adipose tissue. (Edler *et al.*, 2020).

Where another study demonstrates that ACE2 expression in adipose tissue is higher than that in lung tissue, a major target tissue affected by SARS-CoV-2 infection.(Santos *et al.*, 2020). Complex interactions occur between adipose tissue and the immune system. Overexpression of inflammatory adipokines can affect the immune response. These events may be another reason for the rise in the hormone resistin. there are multiple mechanisms by which the adipose tissue may contribute to the development of COVID-19. (Malavazos *et al.*, 2020). According to studies the fast clinical worsening and significant mortality risk in severe COVID-19 have been linked to cytokine storm. COVID-19 had higher blood levels of cytokines such as IL-1ß, IFN-γ, IFN-γ induced protein 10 (IP10), and monocyte chemoattractant protein 1 (MCP1)patients admitted to the intensive care unit (ICU) exhibited greater cytokine levels of IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, macrophage inflammatory protein 1-, and T NF-α. (Huang *et al.*, 2020).

Increased levels of resistin correlated with an increase in pro-inflammatory cytokines Release of human resistin is mediated by inflammatory events, such as stimulation with lipopolysaccharide or the cytokines, IL-1, IL-6, and TNF-α (Dasari and Raghunath, 2018)Several studies have also reported that increased resistin levels correlated with increased C-reactive protein levels and TNF-α. All these data led to the conclusion that increased levels of resistin were related to increased inflammation.(Amato et al., 2014) The results of the current study showed significant differences in the glucose level in patients with Covid-19, as this

glucose level was significantly higher in patients compared to healthy, The study also showed that the glucose level in males is higher than in females,The results of the current study are consistent with a previous study that explained by Rajpal and Ismail Hyperglycemia, even in the absence of diabetes, can lead to increased susceptibility for the infection. In addition, Covid-19 may show severe levels of high blood sugar or new diabetes. (Rajpal, and Ismail, 2021)It also agrees with another study by Rubino et al showed that there is Patient mechanisms leading to severe hyperglycaemia have been observed in individuals without a prior history of diabetes(Rubino *et al.*, 2020).

According to a previous study by Wilson, high blood sugar is due to several reasons, among which a possible mechanism is that the Coronavirus can directly infect and damage or kill the cells of the pancreas that make insulin. Some studies have shown that these cells have an ACE2 receptor that the virus uses to enter cells. Or the cells of the pancreas can be damaged due to the high level of inflammation caused by the immune system's response to the virus (Wilson ,2022) Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of disease (Yang et al., 2010)Sugar may also rise due to Alternatively, many kinds of illness, including other viral infections, stress the body in various ways and so cause blood sugar levels to rise (Wilson, 2022) In the current study, the hormone resistin may have a role in the high level of glucose in patients.

The results of this study showed there is a positive correlation between the hormone resistin level and glucose level in covid-19 patients. But it's not a big relationship, According to previous studies,An increase in hormone resistin can cause a rise in glucose levels, Hung et al pointed out that the hormone resistin is linked to obesity and insulin resistance, and diabetes(Hung *et al.*, 2021) inflammation might be the process that links resistin to insulin resistance. also, Previous studies have pointed out that resistin plays a role in pro-inflammatory processes. and that the expression of resistin has been the result of the production of the pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) (Su *et al.*, 2019) pointed out Darif etal there is a severe clinical condition in COVID-19 called cytokine storm caused by systemic hyper-inflammation and excessive secretion of pro-inflammatory cytokines(Darif *et al.*, 2021)This leads to an increase in the hormone resistin ,besides, resistin could also stimulate the expression of pro-inflammatory cytokines,so Chronic inflammation is a major and well-known cause of insulin resistance (Raimundoa *et al.*, 2021)

Al-Harithy and Al-Ghamdi reported that resistin levels positively correlated with insulin resistance only in people with higher resistin levels (Al-Harithy and Al-Ghamdi, 2005) The study indicated by Gual et al that resistin levels might be the principal factor that induced insulin resistance at high levels (Gual *et al.*, 2003)Insulin resistance (IR) is due to a reduced tissue sensitivity to insulin and refers to the inability of the pancreas to secrete sufficient insulin for blood glucose regulation(Govender *et al.*, 2021).and Insulin is a hormone secreted by the islets of Langerhans in the pancreas; it stimulates glucose transport to muscle, adipose tissue, and the liver(Davids *et al.*, 2020). Failure of glucose regulation leads to

diabetes (Lauterbach and Wunderlich ,2017)Therefore, it is High baseline levels of resistin have been associated with an increased risk of type diabetes2(Parafiniuk *et al.*, 2022) Interestingly, resistin is also expressed inside the β-cells of pancreatic islets, in association with insulin. In T2DM, a significant increase in resistin expression within the β-cells occurred, which suggested a role for resistin in pancreatic β-cell regulation(Dasari and Raghunath, 2018)Recently, several studies have proven that diabetes increases morbidity and mortality in diabetic patients with COVID-19 Emerging information suggests that individuals with diabetes are at increased risk for complications including death(Hill and Sowers, 2020)

Conclusion

This research found an increase in the level of the hormone resistin in Covid-19 patients compared to healthy people,there is no difference in the level of the hormone resistin between male and female patients. Therefore, it can be used as an important predictive sign of the complications of Covid-19 disease and diagnosis. also through this research, it was found high glucose levels in Covid-19 patients, and there is a positive correlation between increasing the hormone resistin levels and glucose in Covid-19 patients, It is possible that this hormone may have a role in causing high glucose levels in Covid-19 patients.

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