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# Comparative study of Apelin and Glucose levels in COVID-19 patients

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***Abstract*---**A novel coronavirus, known as Severe Acute Respiratory Syndrome- Coronavirus 2, has just emerged as an epidemic danger to worldwide public health, Diabetes increases the severity and mortality rate of COVID-19. Adipokines perform a hormonal function including apelin is the newest finding among adipokines and has drawn much Research interest about its functions. This study aimed to estimate the level of apelin hormone in Covid-19 patients and the relationship of this hormone to the level of glucose. The study included 65 patients and 23 healthy as a control group. Apelin hormone was determined by ELISA technique, the level of the hormone Apelin elevated in male and female Covid-19 patients (3752.8571±81.60529, and 3786.3333±96.92097 respectively pg\ml) when compared to the control group for males and females (112.8462±7.79287, and 151.3000±22.20913 respectively pg\ml), High level of glucose 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 study shows a very high increase of apelin hormone in Covid-19 patients compared to healthy. it can be used as a predictive biomarker for the risk of deterioration and disease progression. also, It has an important role in managing COVID-19 patients. There is a possibility that the rise in the hormone apelin will cause a high level of glucose in patients with Covid-19.

***Keywords*---**adipokine, apelin, COVID-19, diabetes mellitus, glucose.

**Introduction**

A novel coronavirus, known as Severe Acute Respiratory Syndrome- Coronavirus 2 (SARS-CoV-2), has just emerged as an epidemic danger to worldwide public health. The SARS-CoV-2 disease has been dubbed COVID-19 (Coronavirus Disease 2019) by the World Health Organization (WHO). COVID-19 was discovered in Wuhan, Hubei Province, China, at the end of 2019, and it is now a true pandemic, with nations all over the world reporting a large surge in COVID-19 cases. (Liu *et al* .,2020; Nadjib,2020) This virus continues to pose serious health risks, resulting in the deaths of many people as well as significant social, psychological, and economic consequences. This virus began as zoonotic and was transferred to people via animals such as bats and others, Then it develops to pass from one person to another.(Phan et al.,2020) Patients present a complicated clinical picture that can lead to respiratory, hepatic, gastrointestinal, and neurological health problems, as well as death in severe cases. The underlying pathophysiological processes are complicated and diverse and have been characterized as an inflammatory/cytokine storm triggered by an immune system hyper response. The illness is particularly severe in elderly patients, especially those with pre-existing cardiovascular, metabolic, renal, and pulmonary disorders, resulting in prolonged hospitalization in intensive care units (ICU) and an elevated high death rate.

(Ferreira and Reis,2020) Diabetes mellitus is a chronic condition resulting in high blood glucose levels either because of the failure of insulin secretion or action (Mounika *et al.*,2021; Erener,2020). Globally, approximately 463 million individuals suffer from diabetes, and this figure is estimated to reach 700 million by 2045 (Saeedi *et al.*,2019). Poor glycemic control among patients with diabetes increases their chances of getting infections; therefore, these individuals need to be more cautious than the general population (Carey *et al.*,2018; Norouzi *et al.*,2021). Diabetes increases the severity and mortality rate of COVID-19(Singh *et al.*,2020;*Wu et al.*,2021). Additionally, it was also confirmed that patients with diabetes have a higher mortality rate due to COVID-19 than non-diabetic patients(Alguwaihes *et al.*,2020). Therefore, for patients with diabetes, compliance with preventive guidelines related to COVID-19 becomes even more important (Pal *et al.*,2021) Insulin sensitivity and secretory function are Important properties of WAT.actually, adipose tissue acts as an endocrine organ-like pancreas and takes part in the pathogenesis of T2DM and obesity (Lee *et al.*,2014). WAT not only stores excess energy in the form of triglycerides but also Works as an endocrine organ that secretes adipocytokines. So, nowadays scientists consider adipose tissue as an important endocrine organ that causes a major effect on health (Fairbridge *et al.*,2015;Mohammadzadeh and Zarghami,2011).

apelin is the newest finding among adipokines, it has drawn much attention and extended studies have been done on possible biological and molecular functions. (Alipour *et al*,.2017)Apelin, also known as APLN, is the intrinsic linker of the apelin receptor (APJ, angiotensin II-like receptor 1), an orphan G protein-coupled protein-coupled receptor (GPCR) (Estienne *et al.*,2021) APJ, also known as APLNR, in (1993) was originally discovered by O'Dowd et al. The APJ receptor consists of 380 amino acid residues, the sequence of which is very similar to the angiotensin II type 1 (AT1) receptor (54% for transmembrane domains and 30%

for the entire sequence). However, angiotensin II is not associated with APJ. Apelin is an endogenous peptide, first isolated from bovine gastric extracts (Lv *et al.*,2020). The APJ receptor is widely distributed throughout the body including skeletal muscle, cardiac muscle, pulmonary tissue, mammary glands, ovaries, brain, kidneys, pancreas, and adrenal glands. (Kawamata *et al.*,2001) Thus, indicating a role for apelin in a range of physiological processes including regulation of fluid homeostasis, blood pressure, and metabolic control. (Roberts *et al.*,2009; Bertrand *et al.*,2015) . The current study aimed to estimate the level of apelin hormone in patients with Covid-19, and the relationship of this hormone to the level of glucose. This hormone may be used as a biomarker to indicate the development of Covid-19 complications. as well as to monitor disease progression in Covid-19 patients.

## Materials and Methods

### Study design and characteristics of patients

This randomized study was conducted on 65 Iraqi patients infected with COVID-19 from Fallujah Teaching Hospital, including (35) males and (30) females, 23 healthy individuals who do not suffer from comorbidities under the same age group and gender as a control group. The ages of the participants ranged from ( 20-75 )years old, and the biomass index ranged from 14.7 to 38.5 of the participating patients. Pregnant women were excluded from this study, patients were diagnosed with COVID-19 based on a positive RT-PCR test and pneumonia (based on computed tomography). ) as well as symptoms.

### Collection of samples
### Blood samples

Each participant in this study had 5 milliliters of whole venous blood drawn, via venipuncture with syringes after the region was disinfected with 70% ethanol. then the blood was put into a gel tube, and the gel tubes were Centrifugation at 3000 rpm for 5 minutes to obtain serum, Then the serum is used for the ELISA test.

### Determination of Human Apelin concentrations in serum

Apelin was determined using an ELISA kit according to the manufactured company (Elabscience, USA), and using a device (Diagnostic Automation, Inc., USA) It was Determined the optical density (OD value) for each well at once with a micro-plate reader set to 450 nm. By the ELISA Reader, the standard curve was then drawn as a relationship between the standard concentrations and the absorbance on the graph paper, and absorbance values of the samples were projected onto the curve to find out the hormone concentration for each sample. This technique relies on the interaction between the antibodies in the wells of the test's plate and specific antigens in the patient's serum. This technique is considered one of the accepted serological tests for the ease and accuracy of measurement.

**Determination of Glucose Levels**

The level of glucose in the blood , of each participant in the current study, was estimated based on a kit equipped with(Spinreact, Spain) and the test was conducted according to the manufacturer's protocol by the enzymatic colorimetric (GOD-PAP) method, Where is done in this method, glucose was oxidized by glucose oxidase (GOD) to gluconate and H2O2. The formed H2O2 then reacts under the catalysis of peroxidase with phenol and 4-aminophenazone to yield a red-violet quinonimine dye that matches the glucose concentration.

**Statistical Analysis**

The data were analyzed using the SPSS statistical program as well as the Excel program to display the results. The analysis of the data was carried out 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 0.05 level, as well as the study of the simple correlation between the different characteristics. (Steel and Torrie, 1960).

**Results and Discussion**

**Apelin Hormone in male and female Covid-19 patients and control groups**

The results of the current study showed a very highly significant increase in the level of the hormone Apelin in male and female Covid-19 patients (3752.8571±81.60529, and 3786.3333±96.92097 respectively pg\ml) when compared to the control group for males and females (112.8462±7.79287, and 151.3000±22.20913 respectively pg\ml), This hormone is very high in males and females patients at the same rate approximately ,p-value = 0.05. as shown in figure1

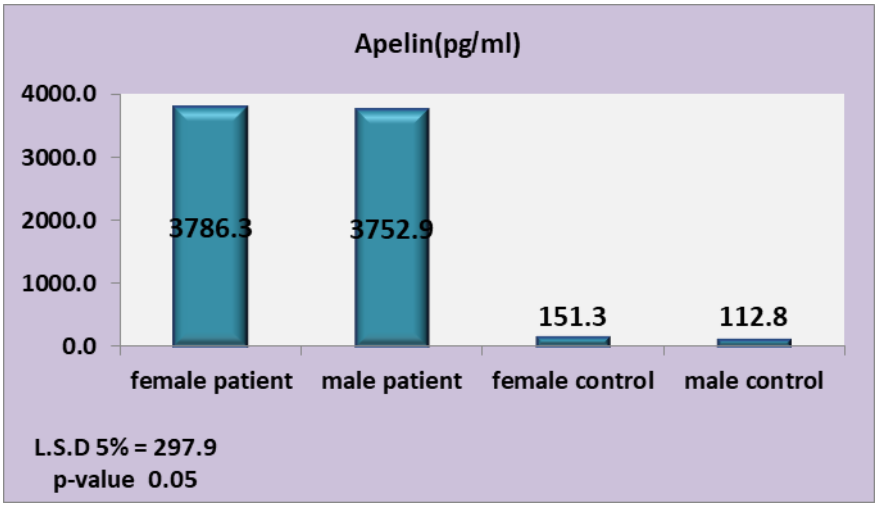


Figure 1. Apelin Hormone in male and female Covid-19 patients and control groups

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

The results of this study showed a significant increase in glucose levels in Covid-19 patients, males, and females. (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), and, there is a slight difference in the average glucose between females and males patients. p-value = 0.05 as shown in figure 2.

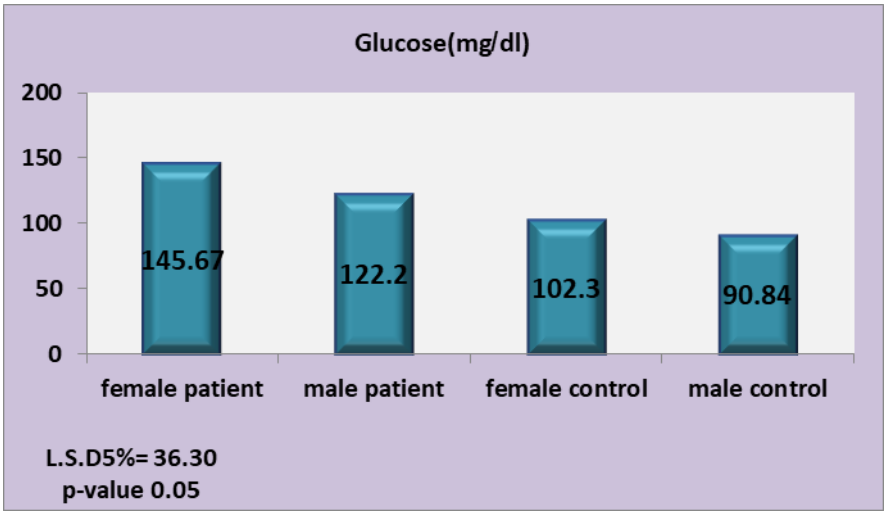


Figure 2. glucose Level in male and female Covid-19 patients and control groups.

Apelin is an endogenous peptide identified as a ligand of the G protein-coupled receptor APJ.( Kuba *et al.*,2019) Apelin belongs to the family of adipokines, which are bioactive mediators released by adipose tissue (Wysocka *et al.*,2018). the apelin peptide was expressed in the spinal cord and several human brain regions and is highly expressed in chondrocytes, endothelial cells, the heart, skin, brain, spleen, thymus, and lungs. also, the expression level of apelin was found in skeletal muscle. In the liver, pancreas, and kidney(Mlyczyńska *et al.*,2020). The wide tissue distribution of apelin and its receptors suggests that it can be involved in many physiological processes including blood pressure regulation, endocrine stress response, and body fluid homeostasis. cardiac contractility, angiogenesis, and energy metabolism. Additionally, this peptide participates in pathological processes, such as heart failure, obesity, diabetes, and cancer(Wysocka *et al.*,2018).

Through the results, it was found that the level of the hormone apelin is very high in female and male patients with Covid-19. The results of the current study agree with a previous study by McGrail et al which clarified Increased expression of apelin,the apelinergic system is activated, which results in a suppression of several molecules involved in the immune system, including inflammatory cytokines, which has led to consider apelin a potential target in COVID-19(McGrail *et al.*,2022) As evidenced by a different study by Salles, et al., apelin may be useful as a biomarker that predicts the probability of deterioration and illness progression. As a pharmacodynamic biomarker, apelin may play a

significant and sensitive role by offering a biological readout to track the effectiveness of a treatment intervention. These findings may be especially important for the management of COVID-19 because apelin is also a substrate for ACE2 (Salles *et al.*,2020) Recent studies have also indicated that An excessive cytokine response during a particularly bad case of "Covid-19" can harm the lungs and kill patients.

Apelin has been shown to reduce this response or reduce respiratory distress syndrome in adults, acute respiratory distress syndrome, acute lung, and acute respiratory distress by suppressing inflammatory responses that are stimulated by several factors secreted by cells such as IL-18, Apelin, which is produced in the heart, lungs, brain, and blood, functions as master regulator that helps maintain blood pressure.to control blood pressure, it collaborates with the enzyme receptor Angiotensin-converting enzyme 2 (ACE2). is the same means by which “Covid-19” enters human cells, and impairs the normal function is angiotensin-converting enzyme 2. Coronavirus interrupts the working relationship between ACE2 and apelin, preventing them from allowing blood vessels to relax, and hijacking cells to produce more viruses. Reduced levels of ACE-2 have a direct impact on apelin production, lowering the body's natural defense mechanisms. organs connected to the lungs.

It has been demonstrated that AngII controls the secretion of many adipokines, including apelin. Apelin secretion is stimulated by high amounts of AngII but inhibited by low quantities of AngII. (Saravi and Beer,2020; O'Dowd *et al.*,1993) There are several studies confirming the importance of apelin hormone in treatment and diagnosis, as mentioned by the authors' Fan, et al apelin is assumed to be essential in reducing Ang-II-mediated acute lung and cardiovascular injuries as well as prothrombotic events in COVID-19 patients because SARS-CoV-2 binds to and down-regulates ACE2, which in turn activates Ang-II-mediated pathological pathways in endothelial and epithelial cells in the lung, heart, and vasculature. Preclinical studies show that apelin or its analogues can lessen the severity of ALI by reducing lung fluid accumulation, cytokine secretion, and hypoxemia, which occur in COVID-19-associated ARDS and cause downstream injury to the heart, kidney, and other organs.

Despite the lack of basic and clinical evidence supporting the therapeutic effects of apelin or its analogues on COVID-19 infection and the severe complications associated with it, these peptides have been shown (Fan *et al.*,2015).which experimental and clinical studies indicate that Ang-II mediates inflammation systemically in the heart, lung, and vascular endothelial cells. Furthermore, ACE2, the receptor for SARS coronavirus, has been identified as a regulator of acute lung injury and heart failure (Sato *et al.*,2013). Another study by Yang et al noted the role of apelin in reducing complications of Covid-19 infection, these peptides may prevent the acute effects of COVID-19, and their beneficial effects may extend to protecting other organs from a cytokine storm and reducing deaths (Yang *et al.*,2015). As reported in a previous study by author Yan et al, apelin expression is enhanced in response to acute respiratory distress syndrome, and activation of the apelin/APJ system protects against Ang-II-induced endothelial inflammation and coagulation event.

Thus, apelin may have anticoagulant effects. In addition to therapeutic effects, apelin can act as an indicator in the development of coagulopathy and cardiovascular disorders, including pulmonary embolism (PE) (Yan *et al.*,2020). In addition to therapeutic effects, Brame et al. explained that apelin can be a plasma marker for lung and heart injuries(Brame et al.,2015). It was also observed in this study that the level of glucose levels increased in patients compared to healthy ones. Previous studies mentioned several reasons that may lead to high glucose, but in this study, we address another reason that may be involved in causing high glucose, which is the hormone apelin. The current study showed there is a positive correlation between the hormone Apelin level and glucose level in patients. Through this relationship, we explain that the rise in the hormone apelin in patients with Covid-19 after infection leads to a rise in glucose levels in patients, so it is possible that the patient will develop diabetes after a period of infection with Covid-19, and this requires several studies to clarify the relationship more.

Adipokines regulate many vital functions and play an important role in the pathophysiology of insulin resistance, inflammation, and diabetes (Yamauchi *et al.*,2014). According to previous studies, the apelin/APJ system plays a physiological role in energy metabolism and glucose metabolism and is involved in many diseases, including metabolic syndrome and diabetes (Li *et al.*,2014) Apelin is a lipid with insulinmimic activity that is produced and released by adipose tissue. (Olszanecka *et al.*,2012) It is one of the fatty substances that affect metabolism, especially metabolic syndrome, which is closely related to cardiovascular physiology and insulin sensitivity (Bełtowski, 2006). The results of the current study are in agreement with a previous study by Ebrahimzadeh et al showed an increase in the hormone apelin in patients with diabetes. (Ebrahimzadeh et al.2019)The results are also consistent with a previous study by Ma et al showed that high apelin levels were reported to be associated with an increased incidence of type 2 diabetes(Ma *et al.*,2014) Noori et al also mentioned in their study that high apelin levels were observed in people with type 2 diabetes compared with control subjects (Noori *et al.*,2019).

Another study showed that the hormone apelin has a role in regulating insulin levels(Boucher *et al.*,2005) Apelin plays a beneficial role in energy metabolism by increasing glucose uptake and insulin sensitivity (Bertrand *et al.*,2015) Apelin could also be involved in the regulation of blood glucose levels by AMPK activation and cAMP decrease (Alipour *et al.*,2017) In diabetic patients, apelin concertation was increased (Habchi *et al.*,2014), extending susceptibility to diabetes (Zheng *et al.*,2016), thus, examining plasma apelin levels could be used as a method to predict the development of type 2 diabetes (Ma *et al.*,2014; Hu *et al.*,2016) Therefore, it is possible that apelin has a role in causing diabetes in patients with Covid-19.

**Conclusion**

This study shows a very high increase of apelin hormone in patients with Covid-19 compared to healthy people, there is no significant difference in the level of this hormone between male and female patients, Due to the very high level of this hormone, therefore, the apelin hormone is considered one of the important

hormones that can be used as a predictive biomarker for the risk of deterioration and disease progression. also, It has an important role in managing COVID-19 and monitoring the effectiveness of treatment in patients. apelin may play a role in limiting the acute effects of COVID-19and their beneficial effects may extend to protecting other organs from the cytokine storm and reducing mortality. It may be used as a treatment for COVID-19 patients in the future. also, there is a positive relationship between the apelin hormone and the level of sugar, the rise of the apelin hormone after infection with the Coronavirus may cause a rise in glucose and thus may cause diabetes in patients with Covid-19.

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