Effect of COVID-19 Infection on kidney Function and some Related Hormones

Abstract

Aims: The current study aimed to find out the influence of infection with COVID-19 on kidney function and the levels of some related hormones.

Materials & Methods: Urea, Uric acid, Creatinine and ADH, EPO were estimated in patients' serum samples of with severe COVID-19 were admitted to hospital of Ibn Al-Khatib for isolation in Baghdad city. During the period May 2020-October 2020, the total number of positive cases were 60 patients they compared with 31 healthy adults.

Findings: The results showed a significant increment in all parameters levels of patients except in Ca (Calcium level), in respect to the gender all parameters showed a significant elevation in male than female patients in Calcium and urea and non-significantly elevation in serum ADH and EPO level in male as compared to female.

Conclusion: We concluded that rhEPO can be used in a treatment to reduce syndrome and confront the SARS-COV-2. The gender role in the infection severity with COVID-19 between males and females.

Introduction

From the time of 5 decades, the numerous coronaviruses emergence which lead to an extensive variety of animal and human diseases has been occurred. Such viruses are created from genetic substance inside a coating protein that are so small germs that lead to acquainted infectious diseases i.e., flu, common cold, and warts or leads to serious illnesses i.e., Spanish influenza, Ebola, and COVID-19 [1]. Such a virus which leads to COVID-19 is not the mostly lethal pandemic in comparison to other viruses. The Corona viruses that lead to SARS-COV-2 and respiratory syndrome in the Middle East might resulting in death in few circumstances. COVID-19 is a newly infectious discovered disease which has extent all the way through the sphere [2]. Although COVID-19 is principally a respiratory disease, the kidney might be among the target infection organs with SARS-COV-2. Kidney involvement records of COVID-19 patients are quiet so limited. Nevertheless, there are additional patients are infected globally [3]. Infection with this virus showed obvious sex-specific severity and mortality greater level of death in males in comparison to females. Differences of sex in their immunity response to the foreign antigen's distinctions in innate and adaptive immune responses [4]. Many documents have revealed that renal dysfunction is an aggregate clinical COVID-19 propagation indicator. Proteinuria is the mostly communal clinical manifestation that is detected in further than ½ of the COVID-19 patients, additionally to hematuria, raised blood urea N, and raised serum creatinine [5]. Numerous endocrine cases of disturbances in relation to all endocrine glands dysfunction after and during infection of SARS-CoV-2 were described. Therefore, it has been proposed that infection by SARS-CoV-2 might as well result in disturbances of endocrine system. Indeed, angiotensin-converting enzyme 2 (ACE2) receptors, that mark the SARS-CoV-2 penetration location into cells in large numbers, are localized in the endocrine tissues. Therefore, it was proposed that infection of SARS-CoV-2 and COVID-19 may result in the development of hormonal disturbances [6].

A study found that the physical, emotional, or psychological stresses and pain linked with infections (i.e., COVID-19) stimulate the axis of hypo-thalamohypophysial, resulting in release of Antidiuretic hormone (ADH). Otherwise, stress triggers the cortical neurons that encourage the hypothalamus for ADH secretion [7].

ADH or vasopressin or arginine vasopressin (AVP) is a non-peptide made in the hypothalamus. It was documented that it has an essential function in the osmotic body balance control, regulation of BP, Na homeostasis, and functioning of the kidney. Given its essential task in many functions, there is no wonder that ADH has excessive clinical implications. Primarily, ADH affects the kidney ability to re-absorb H_2O; If existing, ADH induces H_2O transport proteins expression in the collecting duct and late distal tubule to upsurge H_2O reabsorption. Numerous states of disease ascend if the body loses ADH secretion control or replies to its attendance [8].

Erythropoietin (EPO) is a produced hormone/cytokine mostly through the kidneys by hypoxia-inducible factor-2 as its prime factor of transcription, and over RBC apoptosis of precursors inhibition, upsurges the mass of RBC cells. Nevertheless, EPO has other advantageous cyto-protective effects i.e., anti-ischemic, anti-apoptotic and regenerative effects in a diversity of tissues i.e., cardiac muscle, lung, nervous system, kidney, pancreas, retina, and endothelial cells. By EPOR-βcR, as a special receptor; It conducts its defensive influences after trauma and in censoriously ill patients [9].

In COVID-19 patients, responses of disordered inflammatory be the cause of end-organ injury. Increased interleukin levels (i.e., IL-6 and IL-1β) are associated independently with severity/mortality of the disease, and therapies targeting IL-6 and IL-1β effects display encouraging results. Studies revealed that the effect of EPO as an immune-regulator including inhibiting IL-6 and IL-1β synthesis by monocytes and prompting regulatory survival T-cells. Furthermore, growing proof founds global tissue-protective anti-apoptotic EPO effects, particularly in targeted organs by COVID-19. Reliable with such, a report of current case ascribed amelioration of respiratory distress in an anemic 80-year-old man to the use of EPO [10]. The current work tries to detect the infection effect with the Corona virus on kidney function and the level of some hormones related to it.

Materials and Methods

COVID-19 severe patients were admitted to the hospital of Ibn Al-Khatib for isolation in Baghdad City, during the period May 2021-October 2021. The total number of positive cases were 60 patients (31 males and 29 females) their age ranged from 20-54 years old, they compared with 31 healthy adults (17 males and 14 females) with estimated age 22-57 years (Table 1).

Table 1. Total number of patients (positive COVID-19) and control subjects

Groups number	Male	Female	Total
Patients	31	29	60
Control	14	17	31
Total	91		

Laboratory methods

The Xpert Xpress SARS-COVID-2 test (GeneXpert from Cepheid/USA) was used for detection in the throat and nasal swabs by using the kit form. The in vitro test as automated diagnostic for qualitative nucleic acid detection from COVID-2 as SARS and performed on a system of gene pert instruments, that is integrate and automate sample preparation, extraction of nucleic acids, amplification and target sequences detection in samples utilizing assays of RT-PCR. Serum separated from five ml of venous blood were obtained from the patients and control groups to assessed EPO and Anti-diuretic hormones using ELISA kit form (Elab Science, China). A clinical diagnosis and examination were carried out for every patient by the consultant medical staff and the examination results of the biochemical laboratory as a routine work were measured (serum creatinine, blood urea, serum Ca and uric acid).

Data analysis

The findings were evaluated in an SPSS data sheet version 20 that was used to perform analysis. The differences of significant M±SD were measured by Mann-Whitney, Independent-Samples T-test and the associations between variables were estimated by correlation of Person. A probability of p-value<0.05 is regarded as significant.

Findings

The results displayed a significant increment in all parameter levels of patients except in Ca (calcium level). Whereas, female patients and control were significantly different in uric acid levels and the two other hormones. While male patients and control revealed significant differences in Creatinine and both hormones. In respect to the gender Calcium and urea presented a significant elevation in male than female patients in Table 2.

Table 2. Renal function biomarker levels in COVID-19 patients and control (male and female)

Renal function Parameters sig. (2-tailed)	Groups	COVID-19 patients (n=60) M±SD	Controls (n=31) M±SD	r
Urea (mg/dl)	Total	33.28±7.08	30.19±9.24	0.040 S
	Male	35.90±7.78	31.23±10.29	0.070 NS
	Female	30.48±5.01	28.92±7.97	0.370 NS
	Male vs. female	Male 35.90±7.78 Female 30.48±5.01	-	0.002 S
Creatinine (mg/dl)	Total	0.61±0.41	0.74±0.17	0.009 S
	Male	0.54±0.34	0.76±0.17	0.004 S
	Female	0.69±0.46	0.71±0.18	0.422 NS
	Male vs. female	Male 0.54±0.34 Female 0.69±0.46	-	0.245 NS
Uric acid (mg/dl)	Total	6.31±1.95	5.14±1.34	0.009 S
	Male	6.77±2.15	5.47±1.47	0.059 NS
	Female	5.81±1.61	4.73±1.09	0.044 S
	Male vs. female	Male 6.77±2.15 Female 5.81±1.61	-	0.053 NS
Ca (mg/dl)	Total	10.11±0.44	9.91±0.54	0.085 NS
	Male	10.23±0.39	9.94±0.51	0.069 NS
	Female	9.98±0.45	9.88±0.60	0.391 NS
	Male vs. female	Male 10.23±0.39 Female 9.98±0.45	-	0.038 S
EPO H. (IU/ml)	Total	101.18±22.75	50.37±9.95	0.000 HS
	Male	103.83±23.11	52.48±9.99	0.000 HS
	Female	98.34±22.40	47.80±9.64	0.000 HS
	Male vs. female	Male 103.83±23.11 Female 98.34±22.40	-	0.379 NS
Anti-diuretic H. (IU/ml)	Total	110.25±24.34	57.31±10.52	0.000 HS
	Male	113.54±24.80	60.18±11.90	0.000 HS
	Female	106.73±23.76	53.82±7.56	0.000 HS
	Male vs. female	Male 113.54±24.80 Female 106.73±23.76	-	0.264 NS

NS=Non-Significant; S=Significant; HS=High Significant

The correlation in renal function parameters also was assessed and revealed a positive relationship between age and creatinine and the positive link has been indicated at 0.01** level between urea and uric acid, whereas, the relevance was at level 0.05* with the two hormones EPO H and Anti-diuretic H. Also, uric acid with Ca and the two hormones records a similar link at level 0.01** (Table 3).

Table 3. Correlations among renal function parameters in both groups

Renal function parameters Sig. (2-tailed)	**Age**	**Urea** (mg/dL)	**Creatinine** (mg/dL)	**Uric acid** (mg/dL)	**Ca** (mg/dL)	**EPO** (IU/ml)	**H. Anti-diuretic H.** (IU/ml)
1. Age	1						
2. Urea (mg/dL)	0.227	1					
3. Creatinine (mg/dL)	0.048*	0.487	1				
4. Uric acid (mg/dL)	0.886	0.003**	0.202	1			
5. Ca (mg/dL)	0.281	0.739	0.636	0.00**	1		
6. EPO H. (IU/ml)	0.867	0.032*	0.128	0.174	0.804	1	
7. Anti-diuretic H. (IU/ml)	0.798	0.023*	0.070	0.092	0.799	0.000**	1

Person's correlation, ** Correlation is significant at the 0.01 level (2-tailed), * Correlation is significant at the 0.05 level

Discussion

The function of the kidneys is a fundamental human body functioning part; Whichever damage is able to impairment such cycles and disturb the metabolism of human. The kidney is amongst the diverse organs which are afflicted significantly through the infection by SARS-CoV-2. Reports have revealed that numerous COVID-19 pneumonia patients have presented multiple kidney injuries types, whereas others who were passed away from illness of COVID-19 presented austere kidney injury [11]. Regarding to Table 2, a significant increase was there in Serum Urea Nitrogen, Creatinine and Uric acids levels of patients except in Ca (Calcium level). These findings were in consistence with the documents that revealed that dysfunction of the kidney is a growing clinical COVID-19 propagation indicator. proteinuria is the mostly mutual clinical manifestation that is detected in more than ½ of the COVID-19 patients, besides to hematuria, raised blood urea N, and elevated serum creatinine [5].

The involved mechanism in the BUN increase level following infection by SARS-CoV-2 has not been elucidated fully. Given that ACE2 is the principal cellular SARS-CoV-2 receptor and expressed highly in epithelial renal cells, it is probable that the viral infection might lead directly to a SARS-CoV-2 interaction with its receptor in the kidney to decrease ACE2 expression, leading to abnormal renin-angiotensin-aldosterone system (RAAS) activation [12, 13]. The RAAS as activated able to increase significantly the water absorption by tubules of the kidney whereas enhancing the urea resorption and causing elevated levels of BUN [14]. The BUN level elevation is not just a dysfunction of kidney indicator nevertheless it also can reflect the status of inflammation, N equilibrium, catabolism, sepsis, and renal hypo-perfusion from hypovolemia, or minimized cardiac output, numerous where have been stated to be associated closely with the opposing outcomes in COVID-19 patients [15, 16].

The high levels of serum creatinine (SCr) may be due to the austere cases across the disease course, backup the level of SCr as a danger factor foreseeing mortality in coronavirus-infected [17].

Also, the elevation of serum uric acid (SUA) can be attributed to patients with a history of other diseases such as type 1 diabetes or smoking as SUA is the greatest plentiful antioxidant molecule in the plasma and this result agrees with [18]. High levels of SUA in humans signify an evolutionary benefit that is able to enhance antioxidant defense, upsurges levels of SUA, which is related to the upsurge in the capacity of serum antioxidants. UA returns endothelial tasks in patients with T1DM and smokers as regular through the response to antioxidant stress. Consequently, the antioxidant SAU effect might be advantageous potentially in circumstances considered by OS, even though the molecular mechanisms are not understood fully. SUA is believed to have a defensive effect on both the prime angle-closure glaucoma and the central nervous system against oxidative injury.

Additionally, table 2 revealed high significant elevation in EPO and ADH hormones serum level in comparison to the control group. Elevation of high significant in the serum ADH level may be associated with fever, pain, stress and dehydration that the patient may suffer during the infection with COVID-19. This result agrees with [19], who studied Vasopressin System Activation throughout COVID-19. Their findings indicate, that the vasopressin system activation plays a key function for the osmotic maintenance, cardiovascular, and stress concerning the serum EPO level increment. This can be attributed to the kidneys attempt to compensate the lack of oxygen, especially since this hormone is responsible for the RBC production that is responsible for transporting O_2 to all body parts. The

finding comes along with [20], who found that hypoxia and EPO increased EPO receptors, increased protein levels and EPOR gene expression in human microvascular endothelial cells (HMVEC-L). Furthermore, EPO dose- and time-dependently stimulated NO production. Such NO stimulation was obvious although hypoxia induced endothelial NO synthase eNOS gene expression reduction.

In respect to the gender all parameters showed a significant elevation between male and female patients in Calcium and urea and a non-significant elevation in the level of uric acid in male than female group (Table 2). This is in line with the study of [21], who revealed that rates of infectious are greater in males than in females, and that might be because of sex hormones which contribute to diverse immunologic responses in males and females: As an overall rule, estrogens encourage both adaptive and innate immune responses that resulting in faster pathogens clearance and more vaccine efficacy. Contrariwise, testosterone has mainly suppressive influences on immune function that might elucidate the more susceptibility to infectious diseases perceived in males.

A study reported that COVID-19 has tended to be a global health disaster since its 1st advent in Wuhan, China. Epidemiological reports propose that COVID-19 influence elderly people with numerous comorbidities i.e., obesity, hypertension, and diseases of chronic lung [22]. The variances in the COVID-19 severity and incidence are probable to be multi-faceted, and reliant on numerous social, biological, and economical aspects. Precisely, the socio-economic variances and psychological COVID-19 impact affecting females and males are vital in pandemic preparedness and mitigation. Preceding clinical reports have revealed that women are less vulnerable to obtain viral infections and minimized cytokine synthesis [23]. Females have a greater neutrophil and macrophage activity besides antibody creation and response [24].

Additionally, in-vivo ACE2 studies presented greater expression in the male than female patients' kidneys that might clarify the variances in COVID-19 progression and susceptibility between male and female patients. Nevertheless, it rests unidentified if the ACE2 expression varies in female or male patients' lungs. Differences in the socio-economic status and access to healthcare among ethnic groups might affect the rates of COVID-19 [25]. Ethnic groups frequently have greater medical comorbidities levels and lower socio-economic status, that might elevate their contracting COVID-19 risk by weak immunity as cell-mediated. In a study, was examined the existing literature on the racial differences gender among patients of COVID-19 and additional exam for the conceivable biological mechanisms underlying such variances [26]. Such is consistent with the results of our research in the table 2.

Table 3 shows the correlations between renal function parameters in both groups. It revealed a positive relationship between age and creatinine, and this reflects that age affects kidney function, especially in the case of infection with the Corona virus, and some routinely measured biochemical parameters, and it is expected that creatinine in the blood is one of them.

The present study consistent by a study of [17] who exposed that the high serum creatinine (SCr) levels may be due to the austere cases across the disease course, backup the level of SCr as a threat factor expecting death in COVID-infected patients.

Also, positive relationship level between urea and uric acid, whereas, the relevance was at level 0.05* with the Anti-diuretic in the same table, which indicates that the clearance of uric acid and urea relies upon an operative intravascular volume. In the unsuitable SIADH (a state syndrome augmented intravascular volume) uric acid clearance is elevated and the urea is elevated just if excretion of salt is low [27].

Finally, uric acid has a positive correlation with Ca shown in Table 3. Perhaps the reason is that corona patients suffer from inflammation in the kidneys and joints, and these cases of inflammation are linked to the relationship between uric acid and calcium.

The present study agreed with a study of [28] who revealed that concentration of Ca is correlated positively with inflammation. Few reports presented that hypercalcemia is associated with diseases of inflammation. Few critical inflammatory cytokines, i.e., IL-1β, and IL-6, able to upregulate the receptor of Ca-sensing, that able to control homeostasis of blood Ca and is an inflammation responder and promoter. For the moment, TNF-a and IL-6 are necessary cytokines of inflammation, associated positively with levels of SUA (30-32). Consequently, if UA crystallizes in joints, an increased SUA level might result in inflammatory arthritis. Based on the foregoing analysis, we guess that the mechanism of inflammation might affect the +ve association between SUA and total Ca. Generally, additional studies must be directed to find out the association mechanism between SUA and total Ca.

Conclusion

It can be concluded that rhEPO might weaken distress syndrome of respiratory system and oppose the SARS-COV-2.

Recommendations

1- Disturbances diagnostics of endocrine system according to clinical symptoms must be considered in both patients with COVID-19 and post-COVID-19 syndrome.

2- Supplementary studies require to correlate the incidence and pathogenesis of ADH in COVID-19.

3- The well-organized designation of clinical trials along with cautious EPO administration consideration in anemic COVID-19 patients to more evaluate its clinical assistances in such life-threatening patient population group.

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