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COVID-19 Infection Causes Insulin-Resistance between Hospitalised Patients in Najaf Governorate

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Abstract.A novel epidemic infection Coronavirus-19 (COVID-19) considered as one of the challenges in sustainable development. A new-onset of hyperglycaemia has been observed between many COVID-19 patients. The clear explanation of this elevation in fasting plasma glucose (FPG) was debuted. Here we investigate whether this increase is due to impaired insulin secretion or insulin resistance. 269 participants, group 1 (control, n=46) group 2 (COVID-19 patients, n= 223). 27 Patients were excluded due to missing of their FPG results. FPG, liver enzymes (ALT, AST, and Alk. Phosphatase), b.urea, s.creatinine, s. insulin, C-peptide, D-dimer, and s.ferritin were measured. Our results showed that FPG was increased in 82% (161) patients and this increase was positively correlated with ferritin ($r^2$0.039, *P-value 0.0013*). There is no correlation between FPG with liver enzymes (ALT and AST). The level of insulin hormone and c-peptide were normal. Because there were no increase in insulin or c-peptide and the only relationship was between FPG and ferritin. Therefore, we concluded that COVID-19 infection could cause insulin resistance.

Keywords. (COVID-19, T2D, Ferritin, HOMA-IR, QUICKI)

INTRODUCTION

A novel Severe Acute Respiratory Syndrome (SARS-CoV-2) infection has been discovered late in 2019 in Wuhan, China. The world health organization (WHO) announced the rapid spread of this infection as a globular epidemic early in 2020 [1, 2]. Signs and symptoms were appeared in 15% of infected patients. COVID-19 infection was disparate from mild, moderate and sever [2, 3]. Many laboratory parameters are increased in COVID-19 infection. Inflammatory markers such as (Interleukin-6 (IL-6), Tumour necrotic factor-α TNF α) are increased in COVID-19 patients [4-7]. Biomarkers such as (C-reactive protein, D-Dimer, and ferritin) are elevated. The severity of illness was determined by the level of (D-dimer and CRP) as proposed by [4, 8]. Diabetes increases the prevalence and incidence of COVID-19 [9-11]. It is clear that the severity of infection is pronounced with metabolic disorder (Diabetes, hypertension, myocardial disorder) [9, 10, 12]. The new-onset hyperglycaemia was observed in many patients suffering from COVID-19 infection [13-15]. There was no clear explanation of why glucose increased in COVID-19 patients without any diabetic history, and whether this is due to insulin secretion defect or due to insulin resistance. Homeostasis model assessment-Insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) are useful tools to assess insulin-resistance and insulin sensitivity, respectively [16-20]. Because COVID-19 infection is one of the challenges of sustainable development. Therefore, our aim was to investigate whether the new-onset of hyperglycaemia in COVID-19 patients could be explained by insulin resistance

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PATIENTS AND METHODS

Patients

This study included 269 participants two groups were included in this study, group 1 (control, n=46) group 2 (COVID-19 patients, n= 223). 27 Patients were excluded due to missing of their FPG results. The ethics committee (IRB), the college of Science, Kufa University, Iraq approved this worked (347/2020). This is compatible with the International Guideline for Human Research, declaration of Helsinki. We clarify the aim of the project to all patients and they gave their acceptance by signing the consent form.

Materials

Kits for Aspartate aminotransferase (Cat. No 12211), Alanine aminotransferase (Cat. No 12212), alkaline phosphatase (Cat. No.12217), blood urea (Cat. No. 10505), creatinine (Cat. No. 10051), and glucose (Cat. No. 10260) were purchased from the Human Gesellschaft for Biochemical and Diagnostic mbH company, Germany. While other kits such as D-Dimer (Ref. CFPC-25), Ferritin (Ref. CFPC32) were purchased from the Boditech Med Incorporated, Republic of Korea. Insulin (Ref DE2935) and C-peptide (Ref DE3920) were purchase from demeditec, Germany. The protocols followed the instruction of manufacture. Results are presented as mean± mean standard error. GraphPrism-8.3 was performed for statistical analyses. A two-sided P-value < 0.05 was considered statistically significant.

HOMA-IR calculation: The calculation of HOMA-IR was performed by using the following formula

HOMA-IR = [fasting Plasma glucose (mg/dl) x Fasting insulin (µIU/ml)/2430][17, 21]

QUICKI calculation: QUICKI was calculated according to the below formula

QUICKI = 1/[log FPG (mg/dl) + log FPI (µIU/ml)] [17, 18]

RESULTS

In this study two hundred sixty-nine participants were recruited. Group 1 (control, n=46 participants) and group 2 (Hospitalised COVID-2, n= 196 participants). The mean age for the control group was 58.2±1.8, while hospitalised COVID-19 patients was 61.6±10.86. Female represented 57% (n=20) and 39% (n=77), in control and Hospitalized SARS-CoV-2 respectively. Our results showed that the concentration of ferritin was significantly increase 785± 25.6 vs 107.8±10 and D-dimer was also increase significantly 2.9±0.23 vs 0.52±0.14, respectively in all COVID-19 patients (table 1). Previous studies showed that the enzymes activity of the liver increased in COVID-19 patients [8, 22]. Our results also showed that liver enzymes (ALT and AST) were increase significantly 38.9±1.9 vs 26±2.18 and 37.2±1.9 vs 25.5±3.03, respectively, as expected (table 1).

Next we tested whether there is any correlation between increased in D-dimer and/or ferritin and liver injury. There was a positive correlation between ALT and D-Dimer (r^2 0.064, *P-value 0.005*) (figure 1 A). Ferritin was also correlated positively with ALT (r^2 0161, *P-value 0.0001*) (figure 1 B). Moreover, AST was also show a positive correlation with D-dimer (r^2 0.15, *P-value 0.0001*) and with ferritin (r^2 0.21, *P-value 0.0001*) (figure 2 A and B, respectively). The above results indicated that the severity of COVID-19 infection associated with the injury of the liver.

It has been reported that a new-onset of hyperglycaemia is associated with COVID-19 patients [15, 23, 24]. Here we investigate the level of fasting plasma glucose (FPG) in COVID-19 patients and compared it with control and whether the increase in FPG could be explained by liver injury. Our results showed that FPG levels were increased significantly in COVID-19 patients (table 1). However, the increased was not pronounced in all COVID-19 patients. Only 161 out of 196 (82%) patient had high FPG levels (table 2).

A correlation between increased FPG and enzymes activity was tested. The results showed that the increased in FPG did not correlated with either ALT (r^2 0.0006, *P-value 078)* (figure 3 A) or with AST (r^2 0.00001, *P-value 0.92*) (figure 3 B). Although, only 88 (45%) out of 196 COVID-19 patients had high FPG and high ALT activity. While only 72 (37%) out of 196 COVID-19 patients had increase in AST level and high FPG (table 2). This indicated that increased FPG in COVID-19 patients cannot be explain by liver injury.

Because liver injury did not explain the increment in FPG in COVID-19 patients. Our next aim was that whether the increased in FPG could be explain by increase in biomarkers that elevated with SARS-CoV-2 patients (Ferritin and D-Dimer). A positive correlation between s. ferritin and FPG ($r^2$0.039, *P-value 0.0013*) was found (figure 3 C). D-dimer showed no correlation with FPG ($r^2$0.99, *P-value 0.99*) (figure 3 D). These results suggested that the elevation of plasma glucose is associated with increased in ferritin. Later, we investigate whether the increased in FPG is due to insulin-resistance or insufficient insulin secretion. HOMA-IR is considered as a marker of insulin-resistance, therefore, we measured the HOMA-IR for patients and compared them with HOMA-IR for control. The results showed that HOMA-IR was significantly increased (0.89±0.08 vs 0.4±0.1, respectively) (Table-1). Moreover, QUICKI, the marker of insulin sensitivity showed no difference between COVID-19

TABLE 1. The biomarkers of participants

	Control (n=46)	**COVID-19 (n=196)**	
	M±SE	**M±SE**	***P-value***
Age	58.2±1.8	61.6±0.86	0.073
Gender			
Female (n) %	(20) 57%	(77) 39%	
Male (n) %	(26) 43%	(119) 61%	
Ferritin (ng/ml)	107.8±10	785±25.6	0.000002
D-Dimer (µg/ml)	0.52±0.14	2.9±0.23	0.000019
ALT (U/L)	26±2.18	38.9±1.9	0.010
AST (U/L)	25.5±3.03	37.2±1.9	0.025
Alk. Phosph. (U/L)	86.6±2.8	127±6.6	0.084
FPG (mg/dl)	116±4.9	219±7.7	0.000000
insulin (µIU/ml)	8.8±1.02	9.9±0.7	0.93
C-peptide (ng/ml)	1.1±0.2	1.23±0.2	0.43
HOMA-IR	0.4±0.1	0.89±0.08	0.04
QUICKI	1.28±0.05	1.37±0.03	0.244
B. urea (mg/dl)	44.4±4.1	62±3.4	0.029
s. Creatinine (mg/dl)	0.8±0.04	0.9±0.05	0.307

Abbreviation: ALT Alanine aminotransferase; AST Aspartate aminotransferase; Alk. Phosph. Alkaline phosphatase; FPG Fasting plasma glucose; HOMA-IR Homeostasis model assessment-Insulin resistance; QUICKI The quantitative insulin sensitivity check index.

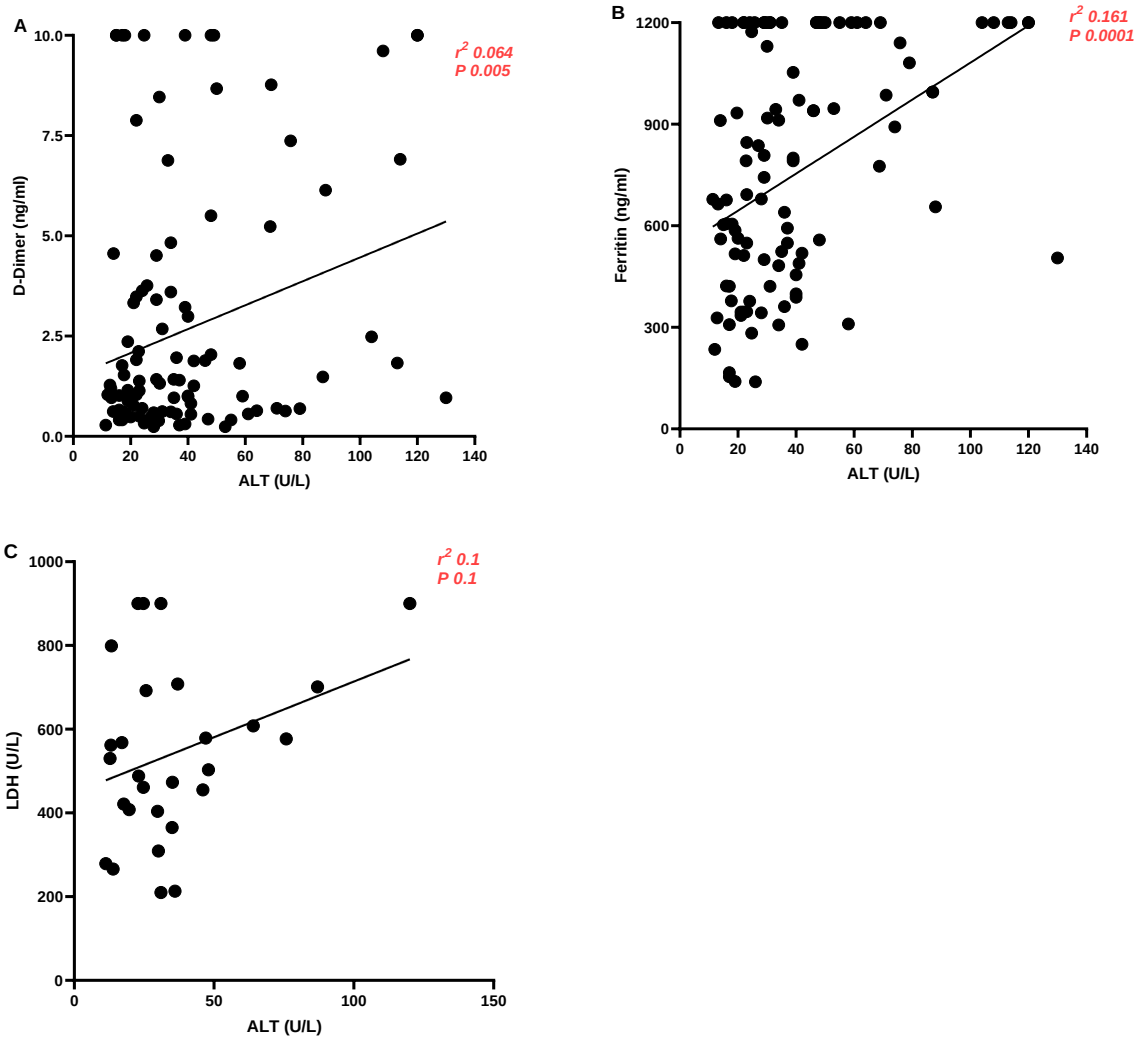

FIGURE 1. Correlation between ALT with D-Dimer and Ferritin

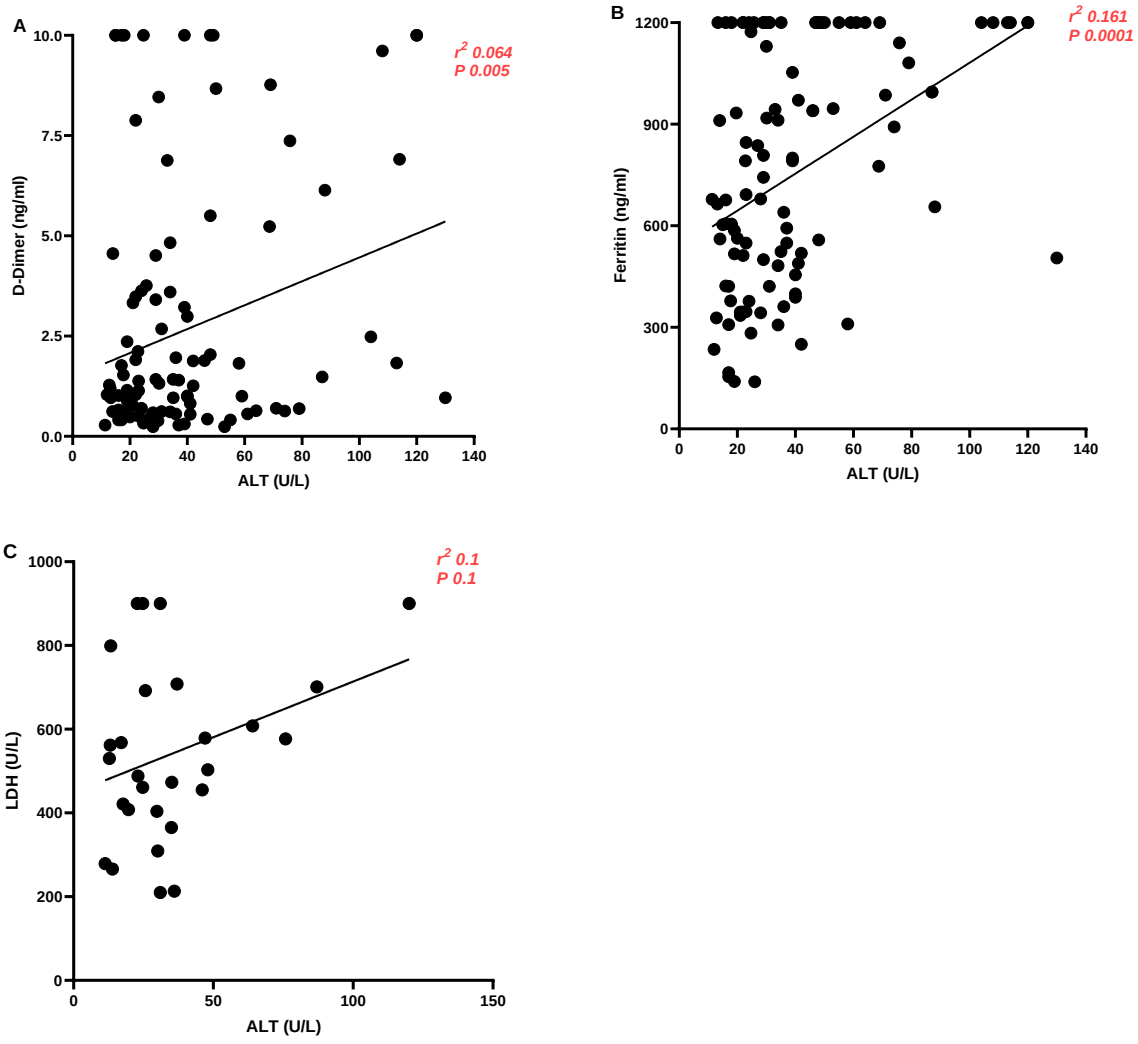

FIGURE 2. Correlation between AST with D-dimer and ferritin

TABLE 2. Number and percentage of COVID-19 patients who had abnormal metabolic biomarkers

	COVID-19 (n=196)	
	No.	**% from total COVID-19 patients**
FBS	161	82%
ALT	88	45%
AST	72	37%
b. Urea	60	31%

and control (1.37±0.03 vs 1.28±0.05, respectively) (Table 1). Altogether, the plausible conclusion from the above results is that the new-onset of hyperglycaemia between COVID-19 patients could be due to insulin-resistance.

DISCUSSION

The rapid spread of novel SARS infection (COVID-19) early in 2020 encouraged the WHO to announced it as a globular infection [1]. Evidences of new-onset of increase plasma glucose were noticed with COVID-19 infection [15, 25-27]. However, the real explanation of the elevation of plasma glucose in non-diabetic patients infected with COVID-19 was elucidate. One of the explanation was that glucose increased due to damaging of beta-islet cells by SARS-CoV-2 virus. The expression of ACE2 receptor is presented in many tissues such as liver, pancreatic cells, tongue, and kidney. ACE2 receptor is also expressed in the lung [28]. Here we aimed to investigate whether the elevation of plasma glucose in non-diabetic patients who were admitted to hospital with COVID-19 infection could be explain by insulin-resistance or insulin sensitivity.

The liver enzymes were elevated in most COVID-19 patients as expected form previous studies [8, 22]. Elevation of plasma glucose was not associated with elevation in liver enzymes which indicated that elevation of plasma glucose cannot be explain by liver injury. Although, damaging of beta-islet cells cannot be the possible explanation of hyperglycaemia in COVID-19 because, the two biomarkers of β-islet cells [29, 30], insulin hormone and C-peptide did not increase in COVID-19 patients (table 1). Our results revealed that there is a positive correlation between FPG and the iron storage protein (ferritin). Many studies reported the association of s.ferritin with metabolic syndrome [31]. Ferritin is a biomarker for iron storage in the body, it is elevated with inflammation and many disease such as metabolic syndromes (T2D, hyperglyceridemia, obesity) [32-34]. Progression of insulin resistance is detected from HOMA-IR[19, 20, 35]. We calculated HOMA-IR and the results suggested that the new-onset of hyperglycaemia between COVID-19 patients is due to insulin resistance.

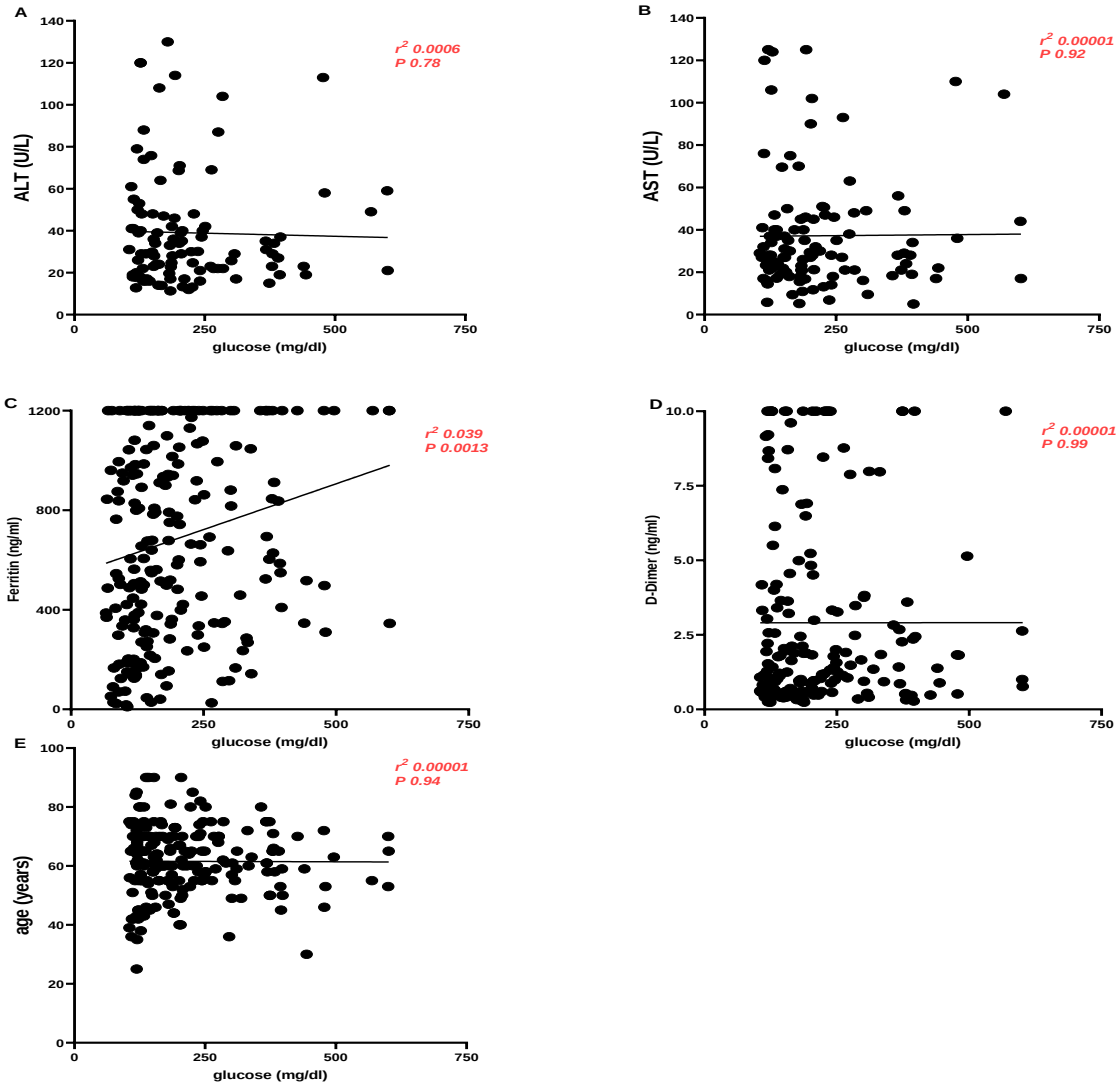

FIGURE 3. Correlation between glucose with liver enzymes, D-Dimer and ferretin

CONCLUSION

We concluded that patients infected with COVID-19 virus had increased FPG and ferritin without increased in insulin and c-peptide hormones. HOMA-IR, but not QUICKI, was elevated in COVID-19 patients indicated that the new-onset of hyperglycaemia could be due to insulin resistance. Follow-up investigations are highly recommended.

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