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Comparative Analysis of Glucose Biomarkers During Acute and Recovery Phases in COVID-19 Patients

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Abstract

COVID-19, or the disease caused by the SARS-CoV-2 virus, affects glucose metabolism to a great extent. Recent studies have reported that hyperglycemia and glucose control disorders among patients with COVID-19 can increase the severity of infection, mainly in individuals with prior chronic non-fatal conditions including diabetes. The aim of this study is to assess some glucose biomarkers as Random Blood Sugar and Fructosamine levels that might be useful in COVID-19 patients during acute phase of infection and recovery. This study included 150 participants: 100 COVID-19 patients (50 males, 50 females) and 50 controls in Baghdad from November 2021 to June 2022. Blood samples were collected during the acute (1-3 weeks) and recovery phases (4-6 weeks) of infection. Random Blood Sugar, Glycated Hemoglobin, and Fructosamine levels were measured using a fully automated biochemical analyzer (INTEGRA-400 plus by Roche). The significant sex differences in glucose biomarkers in acute and recovery phases of COVID-19 patients were shown by this study. In the acute phase, Random blood sugar (RBS) levels were significantly more elevated in males to 382.98 ± 160.37 mg/dl compared with females 207.96 ± 65.38 mg/dl while similar trends were seen in HbA1c and fructosamine level respectively.) During recovery phase high glucose levels persist in males as well which clearly indicate the stronger effect of COVID-19 on glucose metabolism might be more in males. These results highlight the need to follow the glucose profiles in individuals with COIVID-19, and especially in men. The study reveals that COVID-19 patients often experience compromised glucose regulation, particularly in males. Compared to females, males have higher blood RBS, HbA1c, and fructosamine levels, making them more susceptible to high blood glucose levels. Post-recovery, glucose profiles remain elevated, especially in males, making them more susceptible to diabetes and other metabolic complications. Fructosamine is more useful as a follow-up indicator.

Introduction

As 2019 was coming to an end, in the fourth quarter, an alternation in Wuhan, China, occurred in one of the ancient viral families, the Coronaviridae, which later caused a worldwide catastrophe. Coronaviruses (CoVs) are a highly diversionary family of single-stranded RNA (ss-RNA) that use these characteristics to infect humans, they have posed and will continue to pose a serious threat to public health due to financial and veterinary reasons. [1] *Coronaviridae* has a further subfamily classification; *Orthocoronaviridae*;which consists of four genera; (α – *Coronaviridae* & β – *Coronaviridae*) mostly; or exclusively; infects mammals, where (γ – *Coronaviridae* & δ –*Coronaviridae*) especially affect many avian species; therefore;

this made human & his animals under heavy burden infections due to both direct relationships with its effects on nutrition by most means [2,3]. Symptoms of COVID-19 varies among people, some feeling with only general tiredness, others with dyspnea, some suffer arthralgia and/or diarrhea, while headache & fever mastered the signs & symptoms, in addition to loss senses like taste & smell [4-6]. The most common indicators of pancreas infection or inflammation include nausea, vomiting, and epigastric discomfort, along with fever, hypothyroid crumps, and even jaundice if the infection or inflammation spread from a gallstone obstruction. Pancreas infections and inflammations can be either chronic or acute, depending on the cause [7].

The "Pancreatic Islets" are segments of the internal tissue that have various secretions and functions. Patients with certain features, such as advanced age, male sex, obesity, hyperglycemia, and the presence of comorbidities (diabetes mellitus (DM), cardiovascular disease (CVD), and chronic renal disease), can be identified as being at a higher risk of developing severe COVID-19 symptoms and death. Patients with diabetes mellitus are often more vulnerable to severe SARS-CoV-2 infection, and inadequate glucose management raises the risk of hospitalization and death. As seen in human monocytes, where higher glucose levels directly increased SARS-CoV-2 replication, hyperglycemia can promote viral multiplication [7–9]. Hypoxia-inducible factor-1α and mitochondrial reactive oxygen species are produced during glycolysis, which sustains SARS-CoV-2 replication [10-12].

The study aimed to find correlation and linkage of some biochemical and immunological tests as markers for patients with COVID – 19 during and after recovery in Baghdad & surrounding governorates in Iraq Several tests were taken under considerations of linkage among them as profiles in order to make it as a certain of “role” for diagnosis & follow up in next waves and/or for the future attacks of epidemic or even pandemic cases.

Method and Method

Patients’ data collection

Patient data collection began after obtaining a positive (+ve) result for COVID-19 within the period November 2021 until Jun2022, which consisted of name, age, medical history & habitat area. After the patient's COVID-19 infection was confirmed by real-time polymerase chain reaction (RT-PCR) Around 5.0 milliliters of venous blood were extracted. Each sample was divided into 2 parts, different tubes (E.D.T.A-K and gel tube) The gel tube centrifuged for 10 min. at 5000 rpm**.**

Study design

The patients were divided into two groups: one group consisted of 50 controls, the other group consisted of 100 patients with COVID-19 in both acute and convalescent stages. Most of the patients were from friends, the National Center for Teaching Laboratories, and Baghdad Medical City, who wished to try to keep patients alive and be in contact for follow-ups during the critical stages of their recuperation. The basis for the research design was the creation of assays that may offer a crucial signal to identify the COVID-19 infection line, the strength of the illness, and its duration for two weeks during the acute phase and four to six weeks during the recovery phase. Data collection for patients commenced when their COVID-19 test resulted in a positive (+ve). The study design was based on the manifestation of tests that can

indicate an important signal towards deciding the linage of infection with COVID-19, degree of incidence & intensity.

Biochemical Tests ((Random Blood Sugar, Glycated glucose levels and fructosamine): These tests were done by using fully automated biochemical analyzer "INTEGRA – 400 plus by Roche.

Random blood sugar

Random samples were taken according to the difficulty of getting fasting samples to patients with COVID – 19, who eat or drink juices or flavored medicines with different sweeteners. The steps of testing using "Hexokinase", which was described by German scientist Otto Heinrich Warburg in 1930**,** The steps of testing using "Hexokinase", which was described by German scientist Otto Heinrich Warburg in 1930

Glycohaemoglobin

The test was done by using automated biochemical analyser "HLC-723 – G8 "by TOSOH.The sample was whole blood collected via vain blood into an E.D.T.A (K_2) tube, homogenized on a tube roller mixer for about 10 minutes before testing [13,14].

Serum Fructosamine

The steps of testing using Formazan method [15].

Ethics Committee Approval

Before beginning research and gathering samples, experimental study involving humans or animals must receive approval from the Institutional Review Board, Ministry of Higher Education and Scientific Research, University of Anbar, Scientific study Ethics Committee, number 189, date 3-5-2021. In order to strictly preserve the patient's identity and privacy in the article, no specific photos of patients, healthy individuals, or any portion of them, were used in the research.

Statistical analysis:

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 24.0 for Microsoft Windows. Data were presented as mean ± standard deviation (SD). To compare differences between groups, an independent samples t-test was applied. A P-value of less than 0.05 was considered statistically significant, whereas a P-value of less than 0.01 was regarded as highly significant.

Result and discussion

The results of the study show a comparison of glucose profiles (Random Blood Sugar, HbA1c, and Fructosamine) between male and female COVID-19 patients in the acute phase over 1-3 weeks. The data indicate significantly higher Random Blood Sugar levels in males (382.98 ± 160.37 mg/dl) compared to females (207.96 ± 65.38 mg/dl), with a p-value < 0.01 suggesting high significance. Similarly, HbA1c levels were higher in males (6.7 ± 0.88) % compared to females (5.9 ± 0.6) %, also showing high significance with a p-value < 0.01. Fructosamine levels, assessed for both genders together, showed an average of 299.9 ± 58.1 µmol/L, with a p-value < 0.01, indicating a statistically significant difference across the

groups. These findings suggest a pronounced gender disparity in glucose regulation among COVID-19 patients during the initial weeks of infection, showm table 1.

Table 1: Comparison levels of glucose profile (RBS, HbA1c and fructosamine) between male and female in acute phase during (1-3) weeks COVID-19 patients.

Pancreatic	Sex	Mean ±Std.	t-test	P-Value
RBS (mg/dl)	Female	207.96±65.38	8.044	.000 (P<0.01 HS)
	Male	382.98±160.37		
HbA1c (%)	Female	5.9±0.6	5.555	.000 (P<0.01 HS)
	Male	6.7±0.88		
Fructosamine (µmol/L)	Both	299.9±58.1	5.34	.000 (P<0.01 HS)

For a study examining glucose profiles—namely Random Blood Sugar (RBS), Hemoglobin A1c (HbA1c), and fructosamine—across age groups in patients with COVID-19 during the acute phase (1-3 weeks). It reports the mean values and standard deviations for RBS, HbA1c, and fructosamine as 291.95 ± 148.56 mg/dl, 6.15 ± 0.91%, and 230.90 ± 20.00 µmol/L, respectively, with an average age of 36.93 ± 9.24 years. The t-test values provided are significant ($p < 0.01$), highlighting a high statistical significance across all parameters studied. This data might be used to understand the impact of COVID-19 on glucose metabolism better, which could be critical for managing diabetic or hyperglycemic patients during their infection as shown in table 2.

Table 2: Comparison between the levels of glucose profile (RBS, HbA1c and fructosamine) and age for acute phase during (1-3) weeks COVID-19 patients.

	Age (year)	RBS (mg/dl)	HbA1c (%)	Fructosamine (µmol/L)
Mean ±Std.	36.93±9.24	291.95±148.56	6.15±0.91	230.90±20.00
t-test		19.105	36.945	33.165
P-Value		.000 (P<0.01 HS)	.000 (P<0.01 HS)	.000 (P<0.01 HS)

The aforesaid criteria and tests had an expectation curve that was predictable and compatible with the signs and symptoms that were recorded by doctors throughout hospitalization or quarantine periods, where the specificity of RBS reached its full optimistic value of (100%) of link with disease with credible data. sensitivity in comparison to HbA1c and S. Fructosamine; whom both sensitivities reflected their efficiency in detecting

expectation for elevated glycation, in which S. Fructosamine showed more specificity than HbA1c, mostly related to minimization of RBCs lifespan during disease, as shown in table 3.

Table 3: Receiver Operating Characteristic curve analysis (ROC) of glucose profile (RBS, HbA1c and Fructosamine) in acute phase during (1-3) weeks COVID-19 patients.

Variable (s)	Area	P-Value	Cut off	Sensitivity	Specificity
RBS (mg/dl)	.000	.000	>105.50	13.3%	100.0%
HbA1c (%)	.120	.000	>6.550	0.0%	43.3%
Fructosamine (µmol/L)	.121	.000	>264.50	0.0%	63.34%

Displays comparisons between males and females during the recovery phase (4-6 weeks) after COVID-19. The results show that males have significantly higher RBS and HbA1c levels than females, with males recording an average RBS of 189.11 mg/dl compared to females' 113.42 mg/dl. Similarly, the average HbA1c level for males is 7.8%, while for females it is 6.51%. Fructosamine levels, measured for both sexes, average 355.02 µmol/L. These differences are statistically significant, with p-values less than 0.01, indicating a high level of significance (P<0.01), shown table 4.

Table 4: Comparison the levels of glucose profile (RBS, HbA1c and S.fructosamine) between male and female in recovery phase after (4-6) weeks COVID-19 patients

Pancreatic	Sex	Mean ±Std.	t-test	P-Value
RBS (mg/dl)	Female	113.42±3.76	7.033	.000 (P<0.01 HS)
	Male	189.11±9.82		
HbA1c (%)	Female	6.51±0.10	6.111	.000 (P<0.01 HS)
	Male	7.8±0.22		
Fructosamine (µmol/L)	Both	355.02±100.13	6.503	.000 (P<0.01 HS)

Data of ROC declared importance about increased specificity for both HbA1c and S. Fructosamine; with bias to S. Fructosamine; especially for individuals who have no history in DM, making them in total risk of exposure for this disease, due to elevated values for these two tests. All analyses were with highly significant acceptance, (P<0.01 HS). This statistical table is special and owned for this study with no consideration to other studies or as showed in table 5.

Table 5: Receiver Operating Characteristic curve analysis (ROC) of glucose profile (RBS, HbA1c and Fructosamine) in recovery phase after (4-6) weeks COVID-19 patients

Variable (s)	Area	P-Value	Cut off	Sensitivity	Specificity
RBS (mg/dl)	.016	.000	>104.0	16.7%	93.3%
HbA1c (%)	.012	.000	>7.050	0.0%	66.7%
Fructosamine (µmol/L)	.071	.000	>281.50	0.0%	76.7%

The statistical computations for "Random Blood Sugar," "RBS," "Glycated Haemoglobin," "HbA1c," and "Fructosamine" in the first (1-3) weeks of infection, also known as "The Acute Phase," are displayed in Table 4. In this period, there was a highly significant increase in these tests' levels when compared to controls, who are healthy individuals without COVID-19 or any chronic illnesses; as a result, males were consistently elevated more than controls. Some, on the other hand, advocated the idea that menstruation on a monthly basis replaces bodily tissues and stimulates new organs, therefore producing a new generation of humans through childbearing and raising [16]. Males are much more impacted by COVID-19 than females in all pancreatic profile tests, with the exception of fructosamine, which showed increasing problems with pancreatic functioning, notably by rising RBS and HbA1c to the upper limits [11].

Glycometabolic Control Post-COVID-19: A study published in Nature examined glycometabolic control in COVID-19 patients, finding that 46% of hospitalized individuals experienced hyperglycemia, with abnormalities persisting even two months after recovery. This aligns with the current study's findings that indicate significant glucose dysregulation during the acute phase, suggesting that COVID-19 may lead to long-term metabolic alterations even in patients without a prior history of diabetes [17]. Metabolic Alterations and Severity: Another relevant study highlighted in Frontiers in Endocrinology conducted a meta-analysis that demonstrated a correlation between the severity of COVID-19 and increased blood glucose levels. The analysis showed that severe cases had significantly higher blood glucose levels compared to mild cases, reinforcing the notion that acute COVID-19 can exacerbate glycemic control issues, as seen in the current study's elevated RBS values [18]. Dexamethasone-Induced Hyperglycemia: Research focusing on patients receiving dexamethasone for COVID-19 found that nearly half of those without pre-existing diabetes experienced hyperglycemia. This highlights the complexity of managing glucose levels in COVID-19 patients, particularly when glucocorticoids are involved. The current study's findings on elevated HbA1c and fructosamine may also reflect similar mechanisms at play, as glucocorticoids are known to induce insulin resistance and alter glucose metabolism [19].

This statistical table is special & owned for this study; especially for S. Fructosamine; which is a novel study in Iraq according to collected information about other studies, with no consideration to other studies or researches. However, because of the disruption to pancreatic tissues caused by increased responsibilities during the acute phase of the illness and chronic mechanical reorganization following recovery, HbA1c and fructosamine levels persisted even after recovery. In contrast, table 5 displays data that indicates a fluctuation in blood glucose levels in the direction of decrease; this fluctuation is mostly connected to nutrition and the assurance of females to lose weight after acquiring a few kilograms as a result of remaining in

quarantine or having less mobility. According to an equation that some may rely on for rapid test result prediction, the correlation between HbA1c and fructosamine was incorrect. This was linked to haematological or renal abnormalities during infection. due to medications & act of COVID – 19 upon organs; such as loss of albumin or RBCs shorted lifespan [20].

Conclusions

The findings of this study suggest that compromised glucose regulation is prevalent and persistent in individuals who have met the definition of COVID-19, both during acute infection and recovery. In males, compared to females, blood RBS, HbA1c, and fructosamine were significantly higher in both periods, showing that men are more at risk for high blood glucose levels. Moreover, the glucose profile post-recovery remained persistently raised, with more pronounced elevation in males, rendering them susceptible to DM and other metabolic complications. Fructosamine demonstrated greater utility as a follow-up indicator of glycemic homeostasis in non-diabetic patients compared to HbA1c, indicating avenues for future diagnostic considerations to help address the metabolic dysregulation caused by COVID-19.

Limitation of the study

This study has a relatively small sample size, which may affect the generalizability of the findings, particularly in capturing the full spectrum of glucose dysregulation in COVID-19 patients. Additionally, the study's geographical confinement to Baghdad may limit its applicability to other populations with different demographic or environmental factors. The study's design is cross-sectional, capturing data at a single point in time during the acute and recovery phases. This approach limits the ability to assess changes over time and establish causal relationships between COVID-19 infection and glucose metabolism. Without longitudinal follow-up, it is difficult to determine the long-term implications of elevated glucose levels post-COVID-19 or how these levels might change as patients continue to recover.

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تحليل مقارن للمؤشرات الحيوية للجلوكوز أثناء المراحل الحادة والتعافي لدى مرضى كوفيد-19

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الخلاصة:

يؤثر مرض كوفيد-19، أو المرض الناجم عن فيروس سارس-كوف-2، على عملية التمثيل الغذائي للجلوكوز إلى حد كبير. أفادت دراسات حديثة أن ارتفاع سكر الدم واضطرابات التحكم في الجلوكوز بين مرضى كوفيد-19 يمكن أن تزيد من شدة العدوى، وخاصة لدى الأفراد الذين يعانون من حالات مزمنة سابقة غير مميتة بما في ذلك مرض السكري. تهدف هذه الدراسة إلى تقييم بعض المؤشرات الحيوية للجلوكوز مثل سكر الدم العشوائي (RBS) ومستويات الهيموجلوبين السكري (HbA1c) والفركتوزامين التي قد تكون مفيدة لمرضى كوفيد-19 أثناء المرحلة الحادة من العدوى والتعافي. شملت هذه الدراسة 150 مشاركًا: 100 مريض كوفيد-19 (50 ذكرًا و50 أنثى) و50 من الضوابط في بغداد من نوفمبر 2021 إلى يونيو 2022. تم جمع عينات الدم خلال المرحلة الحادة (1-3 أسابيع) ومرحلة التعافي (4-6 أسابيع) من العدوى. تم قياس مستويات سكر الدم العشوائي (RBS) والهيموجلوبين السكري (HbA1c)والفركتوزامين باستخدام محلل كيميائي حيوي آلي بالكامل (INTEGRA-400 plusمن Roche). أظهرت هذه الدراسة الاختلافات الجنسية المهمة في المؤشرات الحيوية للجلوكوز في المراحل الحادة والتعافي لمرضى كوفيد-19. في المرحلة الحادة، كانت مستويات سكر الدم العشوائي (RBS) مرتفعة بشكل ملحوظ لدى الذكور إلى 382.98 ± 160.37 مجم / ديسيلتر مقارنة بالإناث 207.96 ± 65.38 مجم / ديسيلتر بينما لوحظت اتجاهات مماثلة في مستوى HbA1c والفركتوزامين على التوالي.) خلال مرحلة التعافي، تستمر مستويات الجلوكوز المرتفعة لدى الذكور أيضًا مما يشير بوضوح إلى أن التأثير الأقوى لكوفيد-19 على عملية التمثيل الغذائي للجلوكوز قد يكون أكثر لدى الذكور. تسلط هذه النتائج الضوء على الحاجة إلى متابعة ملفات تعريف الجلوكوز لدى الأفراد المصابين بكوفيد-19، وخاصة لدى الرجال . كشفت الدراسة أن مرضى كوفيد-19 غالبًا ما يعانون من ضعف تنظيم الجلوكوز، وخاصة عند الذكور. وبالمقارنة مع الإناث، فإن الذكور لديهم مستويات أعلى من RBS وHbA1c والفركتوزامين في الدم، مما يجعلهم أكثر عرضة لمستويات عالية من الجلوكوز في الدم. بعد التعافي، تظل مستويات الجلوكوز مرتفعة، وخاصة عند الذكور، مما يجعلهم أكثر عرضة للإصابة بمرض السكري ومضاعفات التمثيل الغذائي الأخرى. الفركتوزامين أكثر فائدة كمؤشر متابعة.