Annals of Clinical Case Reports

Short Communication
Published: 20 Sep, 2022

The Increased Glucose Level in Sputum Sample of the COVID-19 Patients with Positive CT Scan: A New Method for Detection of the Lung Inflammation

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Abstract

An increase in the glucose level in the sputum sample of the COVID-19 patients was analyzed as a diagnostic factor for the presence of inflammation in the patients suspicious of COVID-19 disease. During the immunological phase of COVID-19, a cytokine storm causes the dilation of the vessels around the alveoli in the lung, and consequently, the blood is leaked into the air sacs. This inflammatory phase and the probability of lung involvement are currently detected using the chest CT scan. We have, for the first time, measured the glucose level in the sputum sample of the COVID-19 patients and compared it with the data of the CT scan. The results revealed a meaningful increase in the sputum glucose of the patients with positive CT compared to those in negative cases. We believe that the measurement of the sputum sample could offer a cheap, simple, and fast method of diagnostics for screening patients with inflammation, especially in medical centers without access to CT scan machines.

Keywords: Infectious Disease; Respiratory; COVID-19; Glucose; CT-Scan; Colorimetry

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Received Date: *06 Sep 2022*
Accepted Date: *14 Sep 2022*
Published Date: *20 Sep 2022*

Citation:
Ali Khayamian M, Ghaderinia M, Simaee H, Abadijoo H, Mojtaba Yazdanparast S, Hosseinpour P, et al. The Increased Glucose Level in Sputum Sample of the COVID-19 Patients with Positive CT Scan: A New Method for Detection of the Lung Inflammation. Ann Clin Case Rep. 2022; 7: 2308.
ISSN: 2474-1655.

Introduction

Previous reports revealed enhanced glucose concentrations in nasal secretions of pulmonary diseases patients [1-3]. Such an increment may be a hallmark of the presence or progress of acute respiratory dysfunctions. One of the most lethal respiratory diseases in recent two years was COVID-19 with a considerable ratio of involvement and early diagnostic requirement to prevent mortality [4,5]. RT-PCR and lung CT-Scan are two favorable methods to diagnose this disease [6,7].

The main reason for glucose accumulation in the respiratory ambient of COVID-19 patients is the presence of an inflammation that causes the leakage of the vessels and entrance of the blood contents into the lung ambient [8]. Such a mechanism is previously discussed in COPD patients [1]. In our point of view (Figure 1) after being invaded by Coronavirus, hyperactivation of lung epithelial and endothelial cells would result in glycolytic metabolism in cell mitochondria [9,10], and hence, host cells require more glucose for viral replications. On the other hand, in the inflammatory phase of COVID-19 disease, cytokine storm would result in accumulation and clonal expansion of T-cells in lung ambient [11,12]. Such expansion would require hyper glucose consumption. Moreover, neutrophils that attack cells (either normal or virus host cells) in lung ambient also require a higher level of glucose to activate ROS production and release [13,14]. So, glucose content may correlate with the presence and inflammatory phase of COVID-19.

We tested the sputum glucose levels in suspicious people and compared the results with RT-

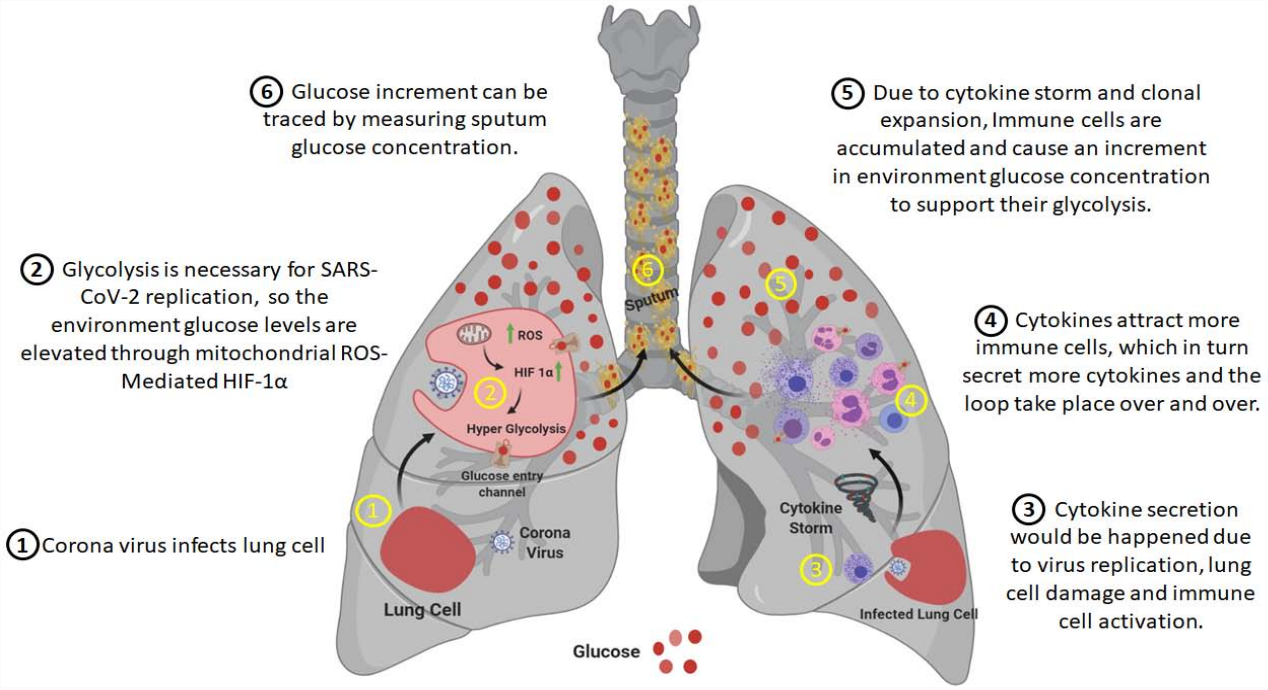

Figure 1: The mechanism of glucose increment in saliva due to lung inflammatory diseases like COVID-19.

PCR and CT-scan data. The effect of diabetes was also assessed to exclude the effect of diabetic blood glucose on the sputum. Sputum Glucose Levels (SGL) with similar volumes was measured by an enzymatic Spectrophotometric glucose detection kit (Figure 2A). The results reveal no correlation between the SGL and the RT-PCR while showing a significant relationship with the chest CT scan data. Therefore, SGL can be used as a complementary method to approve CT scan results of COVID-19 cases.

Figure 2B compares the data of SGL in 120 cases with negative and positive RT-PCR. The minimum and maximum SGL of negative cases was 5 and 78, and these values in positive cases were 10 and 75, respectively. Although the average SGL of the RT-PCR positive cases is 32 and is more than the value of 27 (recorded for negative cases), there is no meaningful difference between the results of RT-PCR and the SGL of the involved people to SARS-CoV-2.

Similarly, the results of SGL were compared with the CT scan data of studied cases. Contrary to the RT-PCR, a meaningful discrepancy between the SGL and CT scan diagnoses was observed. The minimum and maximum SGL of the cases with negative CT scan was 0 and 30, while these values in cases with positive SGL were 0 and 120, respectively. The average of the SGL value in negative cases is ~9, while for positive cases, it is ~49. This finding shows that a rationale threshold specification could be utilized as a diagnostic parameter for detecting lung inflammation in the COVID-19 patients with positive CT scans from their SGL.

To assess the possible effect of blood glucose on the SGL, we tested the Blood Sugar (BS) of the cases to distinguish diabetic from non-diabetic cases. Figure 2D displays the SGL *vs.* BS of the patients with positive CT scans. We have considered 140 mg/dl as the limit threshold for distinguishing between diabetic and non-diabetic cases. As could be deduced from Figure 2D, the BS of all of the CT positive patients spans in both diabetic and non-diabetic range without any meaningful difference (Figure 2E), but to unveil the effect of the BS on the SGL, we added two more cohorts to our study. The SGL from diabetic and non-diabetic donors with a clear CT scan was measured. A meaningful increase in the diabetic cases with an average of 37 mg/dl could be observed compared to the non-diabetic cases with an average of 5 mg/dl (Figure 2F). Also, the data in the diabetic cases are dispersed between 6 mg/dl to 120 mg/dl, while data variation in non-diabetic cases spans from 1 mg/dl to 14 mg/dl. Such a finding may be due to passive diffusion of the serum biomolecules (hormones and electrolytes) from blood capillaries to the salivary glands [15]. The diabetic cases should be excluded from the study.

By excluding the diabetic cases and plotting the ROC analysis, an AUC of 0.80 is obtained, and by considering the SGL of 10.5, the best sensitivity of ~81% and specificity of ~70% were reached (Figure 2G).

We recorded SGL of about 200 cases from COVID-19 and normal people with RT-PCR and CT scan results from diabetic and non-diabetic cohorts. A meaningful gap was observed between SGL levels and CT scan results, while no correlation was observed between RT-PCR and SGL.

This assay can sort the cases requiring a CT scan for better designation of their therapeutic procedure. Finally, we may observe a reduction in non-required CT-Scan. In summary, recording the glucose levels of sputum samples in non-diabetic cases by colorimetric kit as a fast sorting method showed a meaningful correlation with lung involvement in CT-Scan results (SGL >10.5 mg/dl). Such a low-cost method could be a fast and reliable method for medical centers where CT scan machines are not available.

Study design

This study aimed to investigate the correlation between glucose levels in the sputum sample of the COVID-19 patients and their lung inflammatory. In this regard, we gathered sputum samples out of 200 participants. All the participants were chosen from non-alcoholic and non-smoker people, and they were asked not to eat sugar-containing

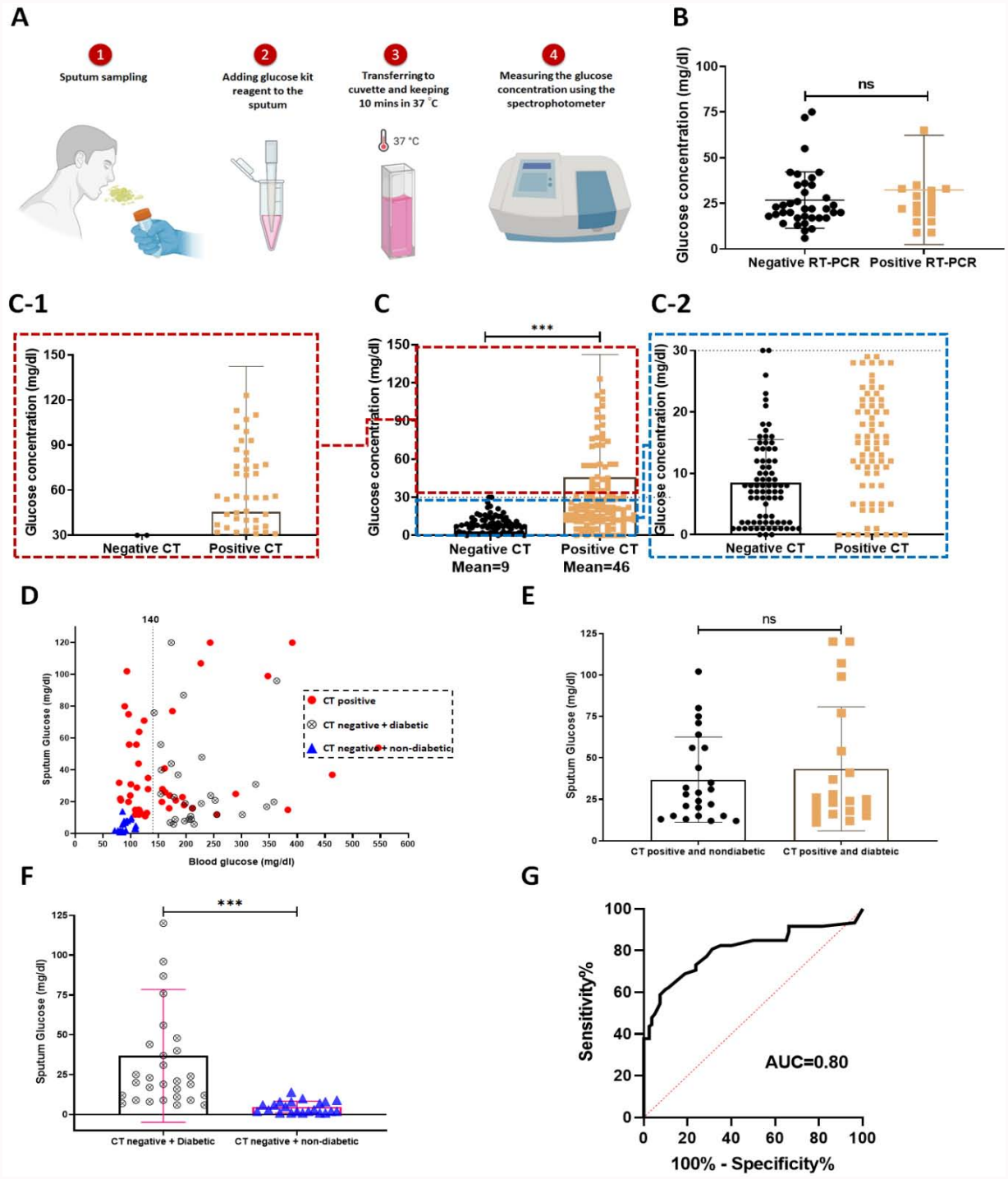

Figure 2: (A) Schematic diagram of the colorimetric detection of the glucose level in the sputum samples. (B) Glucose concentration between the suspicious COVID-19 cases with positive and negative RT-PCR. (C) Comparison of the results of glucose level in the COVID-19 patients with positive and negative lung CT scans. (D) Results of the Sputum *vs.* blood glucose of the patients with positive CT scan in the three cohorts of CT positive, CT negative and diabetic and CT negative and non-diabetic. (E) No meaningful difference between the blood glucose of all of the CT positive patients for both diabetic (BS>140 mg/dl) and non-diabetic cases (BS<140 mg/dl). (F) Significant increase in the sputum glucose levels of the diabetic patients with negative CT *vs.* non-diabetic cases. (G) ROC analysis for the current method after exclusion of the diabetic cases.

foods one hour prior to the test. CT-Scan results validated the presence of lung inflammation. Also, to evaluate the correlation between blood glucose and sputum glucose, some samples were gathered from diabetic patients with a high concentration of blood glucose while sampling. Prior to receiving samples, all participants provided written informed consent according to an ethically approved protocol by the institutional review board of Tehran University of Medical Science (IR.TUMS.VCR. REC.1399.230) at our central hospitals and assistant laboratories for the use of their samples.

Experimental setup

For measuring sputum glucose, we used spectroscopy, which is a

promising method to identify the highly specific vibrational modes of glucose molecules with very high sensitivity. In this regard, sputum samples were examined by an enzymatic, Spectrophotometric glucose detection kit (Biosystems S.A. Costa Brava30, Barcelona, Spain) with a detection range of at least 0.23 mg/dl in the SEPAS Pathology Laboratory to determine the amount of glucose. For this purpose, 10 µL of each sputum sample was diluted in 1000 µL of the reagent and stored in an incubator at 37°C for 10 min. Consequently, the absorption of concentrations was read by a spectrophotometer and the glucose concentration was measured.

Statistical analysis

The obtained data in this study was analyzed using the statistic software GraphPad Prism 8 and expressed as mean ± Standard Deviation (SD). Statically significant results were calculated using a student's t-test and reported when the P values were less than 0.05 for a specific experiment.

Diagnostic evaluation

To evaluate the proposed method, Receiving Operative Characteristic (ROC) curve was plotted. ROC is plotted based on different threshold values to find the best operating point based on the purpose. The area under the ROC curve (AUC) shows the ability of the proposed method to distinguish patients with lung inflammation.

Patient Consent Statement

Prior to receiving samples, all participants provided written informed consent according to an ethically approved protocol by the institutional review board of Tehran University of Medical Science (IR.TUMS.VCR. REC.1399.230) at our central hospitals and assistant laboratories for the use of their samples.

Funding

The funder of this project is "Nano Hesgarsazan Salamat Arya" company.

Acknowledgment

We thank Professor Saeed Sarkar and Mehdi Zeighami for their great support on this project and helpful collaboration.

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