

Impact of Diabetes Mellitus Medications in Some Biomarkers of COVID-19 Infected Patients

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ABSTRACT

COVID-19 pandemic has been the source of most health problems in the last two years with high mortality rates and fluctuation recovery rates, recorded in different countries. The diabetes mellitus (DM) is one of the multifactorial diseases that may be affected in the COVID-19 infected people. Present research was suggested to study the DM medications in some Biomarkers of COVID-19 infected patients. D-dimer and C-reactive protein (CRP) was used in the present work; the output of the distribution study subjects, according to DM patients shows there was 73% of infected COVID-19 is suffered from diabetes mellitus, and 27% was non-diabetes patients, the D-dimer levels were elevation in DM insignificant differences ($p < 0.004$). The CRP level was found in non-significant elevation in DM ($p < 0.203$). The DM patients enrolled in the present study were treated with three types of medications, metformin+ insulin, and insulin only. We found that in a group treated with insulin only have higher levels of d-dimer and lower levels in the group treated with metformin while the group that used both drugs, shows a high level but is lower than the group that used insulin only were significant ($p 0.012$). The CRP shows low levels in the group that used metformin only than others in non-significant differences ($p 0.037$). Also, our analysis of the relation between PCR results and DM-infected patients found that the positive results were high in the DM patients than non-DM patients in significant differences (Od 0.1037 CI95% 0.0116 to 0.9272 P 0.042). It can be concluded from finding that there was a strong association between DM and d-dimer, CRP, and these markers association with types of DM medications, and the DM cases should be careful to avoid COVID-19 infection, and the infection cases must be under hospital care.

Keywords: Biomarkers, COVID-19, CRP, D-dimer, Diabetes mellitus, Medications.

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INTRODUCTION

The COVID-19 is a new pandemic caused by SARS-CoV-2, which has different virulence effects on the human body, its causes severe acute respiratory syndrome with lethal complications,^{1,2} Variant mutated strains of COVID-19 strains were recorded in the world.³

Diabetes mellitus is a multifactorial disease that affects 422 million people in the world.⁴ Investigations show that DM patients have pre-disposition to microbial infections and the respiratory tract.⁵ Some processes contributed to this pre-disposition, like lazy leukocyte syndrome, which causes a decline in immunity that enhanced severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections.⁶ The microangiopathy impairs lung compliance with consequent affectation of the gaseous exchange. This is observed in some respiratory pathogens, including COVID-19.⁷ On the other

hand, several alterations in lung volumes and pulmonary diffusing capacity were observed in DM patients.⁸ The diabetic medication has a potential role in the glycemic balance in DM patients and protective activity against viral infections.⁹ Several protocols for COVID-19 medication have still been suggested like Ribonucleic acid (RNA) therapeutic strategies.¹¹⁻¹⁹ The present study deal with COVID-19 patients with and without diabetes mellitus have different medication protocol to detect some biomarkers used in COVID-19 severity evaluation.

METHODOLOGY

The present study includes COVID-19 infection patients with and without diabetes mellitus. A total of 37 infected patients were under hospital health care, data and markers were collected by the specialist physician. According to the ethical approval of World Health Organization (WHO) and the

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Ministry of Environment and health in Iraq, PCR, D-dimer, and CRP were implemented according to the manufacture leaflet of the test, and all patients were positive to CT scan test. Data were analyzed using an independent t-test and analysis of variance (ANOVA) one way, and data were represented by mean ± SD or SE at p<0.05.

RESULTS

The present work deal with DM and non-DM COVID-19 infected patients, Figure 1 show distribution study subjects according to DM patients and its shows that there was 73% of infected COVID-19 is suffering from diabetes mellitus, and 27% was non-diabetes patients.

The results of the present work represented by the effect of DM treatments in the D-dimer and CRP found that the DM causes an elevation in both biomarkers, the d-dimer levels were (653.00±240.64, and 411.11±237.00) for DM and non-DM group respectively in significant differences (p<0.004). The CRP level it can be found non-significant elevation (p<0.203) for study groups (45.40±21.03 and 35.25±21.16) with and without DM, respectively (Table 1).

The DM patients enrolled in the present study were treated with three types of medications 22.22% metformin, 22.22 metformin + insulin, and 55.56% insulin only, we found that the group treated with insulin only have a higher level of D-dimer (796.00±72.01)^b and lower level in the group treated with metformin (355.00±155.00)^a while the group used both drugs show high level but it lower than group used insulin only, these differences were significant differences (p 0.012).

The CRP shows low level in the group that used metformin only (21.50±11.50) than others (49.00±4.00 and 47.00±8.491) for Metformin+ insulin and insulin groups, respectively in non-significant differences (p 0.037) (Table 2).

Also, we analyze the relation between PCR results and DM infected patients, we found that the positive result was higher in the DM patients (87.5) than non-DM patients (48.27)

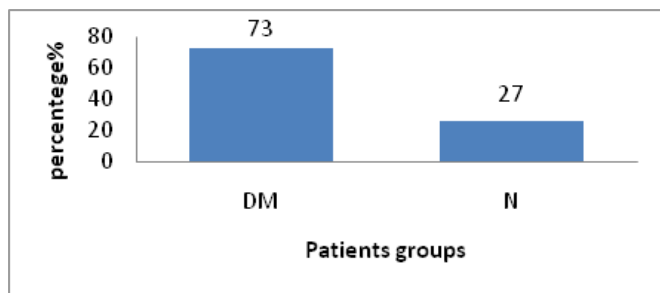


Figure 1: Study groups distribution according to diabetes mellitus infection

Table 1: The D-dimer and CRP levels in the study groups according to diabetes mellitus infection

Subjects	D-dimer	CRP
Infected patients without DM	411.11±237.00	35.2593±21.16
Infected patients with DM	653.000±240.64	45.400±21.03
T test	2.74	1.29
sig	0.004	0.203

in significant differences (Od 0.1037 CI95% 0.0116 to 0.9272 p 0.042) (Figure 2)

DISCUSSION

Diabetes mellitus patients are more pre-disposed to COVID-19 infection. In the present research, the percentage of DM was high than non-DM. This is also observed in other studies.^{12,13} different potential mechanisms in DM contributed to the COVID-19 infection including modulation in immune mechanisms like inflammatory cytokines,¹⁴ killer cells,¹⁵ and interferon production,¹⁶ the reactive oxygen species (ROS) generation,¹⁷ increased in insulin resistance, hyperglycemia¹⁸ and increases in the clotting components fibrinogen, and D-dimer leading to increases in blood viscosity.¹⁹ The effect of DM medication shows that the D-dimer and CRP was significantly lower in patients with metformin than other medication types. Nowadays, metformin is a first-line T2DM treatment agent.²⁰ These results were approved by Xueqi *et al.*, who found that pre-admitted metformin usage may benefit COVID-19 with pre-existed type 2 diabetes.²¹ The mechanism of metformin on COVID-19 might ascribe to pro-inflammatory decline and pro-fibrotic states and release acute lung injury by activating adenosine monophosphate-activated protein kinase.²² On the other hand, in-hospital metformin usage could have the risk incidence of acidosis increasing.²³ The usage of insulin shows elevation in CRP and D-dimer, a study implicated that using insulin causes an increased risk of mortality in confirmed COVID-19 cases in USA and China,^{24,25} notably the insulin usage was associated a greater rate of invasive ventilation thus led to an elevation in

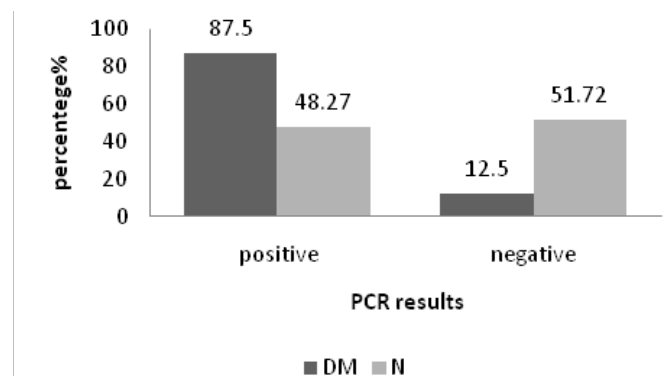


Figure 2: The percentages of PCR test in diabetes and non-diabetes patients in study groups.

Table 2: Effect of diabetes mellitus treatment in the D-dimer and CRP levels in study subjects

Type of treatment	D-dimer	CRP
Metformin	355.00 ± 155.00 ^a	21.50 ± 11.50
Metformin + insulin	505.00 ± 85.00 ^{ab}	49.0000 ± 4.000
Insulin	796.00 ± 72.01 ^b	47.000 ± 8.491
Non-diabetes patients	411.11 ± 45.61 ^a	35.25 ± 4.07
Normal value	Less than 0.50 ng/mL	Less than 10 mg/L
sig	0.012	0.373

ab; Different letters refer to significant differences among groups (ANOVA one way P less than 0.05)

deteriorated inflammation like high level of CRP and ESR.²³ The combination between insulin and metformin lowered CRP and-dimer that usage of insulin only, this types of DM medications may be an important in several cases of CIVID-19 infection to control on glucose homeostasis although of mortality risk, the present study concluded that the DM cases should be careful to avoiding COVID-19 infection and the infection cases must be under hospital care.

REFERENCES

- Poutanen SM. Etiologic agents of infectious diseases. In: Long SS, editor. Principles and practice of paediatric infectious diseases. 4th ed. 2012. p. 1547-1712.
- Bogoch A, Watts A, Thomas-Bachli C, Huber MUG, Kraemer K. Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel. *J Trav Med.* 2020;10:1093.
- Hossain M K, Hassanzadeganroudsari M, Apostolopoulos. The emergence of new strains of SARS-CoV-2. What does it mean for COVID-19 vaccines?. *Expert review of vaccines*, 2021;1-4. Advance online publication. <https://doi.org/10.1080/14760584.2021.1915140>.
- World Health Organisation [Online]. Diabetes Available from: <https://www.who.int/health-topics/diabetes> [Accessed 2020 May 30].
- Badawi A, Ryoo SG. Prevalence of diabetes in the 2009 influenza A (H1N1) and the Middle East respiratory syndrome coronavirus: a systematic review and meta-analysis. *J Public Health Res.* 2016;5(3):733-739.
- Muniyappa R, Gubbi S. COVID-19 pandemic, corona viruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab.* 2020;318(5):E736-E741.
- Ardigo D, Valtuena S, Zavaroni I, Baroni MC, Delsignor R. Pulmonary complications of diabetes mellitus: the role of glycemic control. *Curr Drug Targets Inflamm Allergy.* 2004;3(4):455-458.
- Fuso L, Pitocco D, Antonelli-Incalzi R. Diabetic lung, an underrated complication from restrictive functional pattern to pulmonary hypertension. *Diabetes Metab Res Rev.* 2019;35(6):e3159.
- Samuel S M, Varghese E, Büsselberg D, Therapeutic Potential of Metformin in COVID-19: Reasoning for Its Protective Role, *Trends in Microbiology*, 2021, In Press .
- Al-Terehi M N, Hasan R N, AL Jboory M J. An In Silico Antisense Rna Molecules Prediction For Sars-Cov 2 Spike Protein Inhibition, *PJAEE*, 2020;17(7).
- Al-Terehi MN, Alkaim AF, Yaro A. An in silico approach to design potential siRNA molecule of SARS-CoV-2 virus structural genes, a preliminary opinion for COVID-19 inhibition, *Ann Trop Med & Public Health*; 2020; 23(S11): SP23111.
- A. Remuzzi, G. Remuzzi COVID-19 and Italy: what next? *Lancet Lond. Engl.* 2020; 395 (10231),1225-1228,11.
- Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev.* 2020;31:e3319.
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 28;395(10229):1054-1062.
- Sestan M, Marinovi S, Kavazovi I, Cekinovi D, Wuest S, Turk W , Brizi I, Jonji S, Konrad D, Wensveen F M, Poli B. Virus-induced interferon- γ causes insulin resistance in skeletal muscle and derails glycemic control in obesity. *Immunity.* 2018;49:164–177.e6.
- Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. *Nat. Rev. Immunol.* 2020;20:389–391. doi: 10.1038/s41577-020-0343-0.
- Imai Y, Kuba K, Neely GG, Yaghubian-Malhami R, Perkmann T, van Loo G, Ermolaeva M, Veldhuizen R, Leung YH, Wang H, Liu H, Sun Y, Pasparakis M, Kopf M, Mech C, Bavari S, Peiris JS, Slutsky AS, Akira S, Hultqvist M, Holmdahl R, Nicholls J, Jiang C, Binder CJ, Penninger JM. Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell.* 2008; 18;133(2):235-249.
- Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR 3rd, Aguilar RB. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β -Cell-Centric Classification Schema. *Diabetes Care.* 2016 Feb;39(2): 179-186.
- Al-Jbouri, AMS., Abood, FM, Hindi, NKK, Alkaim, AF; Evaluation of antimicrobial activity of the aquatic extract against bacterial isolates from periodontitis in Babylon Province, Iraq ; *Biochemical and Cellular Archives*, (2018) 18; 1345-1350.
- Kadhim, MM, Kubba, RM. Theoretical investigation on reaction pathway, biological activity, toxicity and NLO properties of diclofenac drug and its ionic carriers. *Iraqi Journal of Science*, 2020;61(5):936-951.
- Al-Duhaidahawi, DL, Jabir, MS, Al-Amiery, AA, Moneim, AEA, Alkaim, AF, Kadhun, AAH; Novel antioxidants compounds derived from isatine *Biochemical and Cellular Archives*, (2018)18 (1); 709-713.
- Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: a possible role beyond diabetes *Diabetes Res. Clin. Pract.* 2020; 164.
- Cheng X, Liu YM, Li H, Zhang X, Lei F, Qin JJ, Chen Z, Deng KQ, Lin L, Chen MM, Song X, Xia M, Huang X, Liu W, Cai J, Zhang XJ, Zhou F, Zhang P, Wang Y, Ma X, Xu Q, Yang J, Ye P, Mao W, Huang X, Xia J, Zhang BH, Guo J, Zhu L, Lu Z, Yuan Y, Wei X, She ZG, Ji YX, Li H. Metformin Is Associated with Higher Incidence of Acidosis, but Not Mortality, in Individuals with COVID-19 and Pre-existing Type 2 Diabetes. *Cell Metab.* 2020; 6;32(4):537-547.e3.
- Agarwal S, Schechter C, Southern W, Crandall JP, Tomer Y. Preadmission Diabetes-Specific Risk Factors for Mortality in Hospitalized Patients With Diabetes and Coronavirus Disease 2019. *Diabetes Care.* 2020;43(10):2339-2344.
- Chen Y, Yang D, Cheng B, Chen J, Peng A, Yang C, Liu C, Xiong M, Deng A, Zhang Y, Zheng L, Huang K. Clinical Characteristics and Outcomes of Patients With Diabetes and COVID-19 in Association With Glucose-Lowering Medication. *Diabetes Care.* 2020;43(7):1399-1407.