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CREATINE KINASE ELEVATION IN COVID-19 PATIENTS ON STATIN Osamah AL-KILIDAR1 , Volkan EYUPOGLU 2 , Mahmood KHUDHAIR 3 1 The graduate school of natural and applied sciences, Department of Chemistry, Çankırı Karatekin University, Çankırı, Türkiye 2 The graduate school of natural and applied sciences, Department of Chemistry, Çankırı Karatekin University, Çankırı, Türkiye 3 Faculty of Medicine, Department of Chemistry, Al Nahrain University, Baghdad, Iraq Abstract Recent studies have related the safety of statin drugs in COVID-19 patients, and its anti-inflammatory effect could reduce the severity of the infection and accelerate the recovery; while some case reports refer to rhabdomyolysis occurrence in COVID-19 patients, it is interesting that some of them were on statin therapy, this serious symptom considered an advanced adverse effect of statin drugs, in this study, we investigate the statin effect on creatine kinase in140 patients, our cohort divided to four groups; 35 infected with Coronavirus on-statin, 35 infected not on statin, 35 not infected on- statin and 35 healthy Individuals as control,

abbreviated to (A, B, C, and D) respectively, to compare their outcomes with each other. As a result, we can imply that statin has a highly significant effect on the CK, the p-value at 0.002 and, in group A rhabdomyolysis was reported in two patients versus one case in group B. Keywords: Covid-19, Rhabdomyolysis, Statin, Creatine kinase. 1. Introduction Since the World Health Organization (WHO) announced that the novel Coronavirus (COVID-19) had become a pandemic that endangers the whole world, causing acute respiratory distress syndrome (ARDS) [1], studying the effect of the virus on the body's biochemistry has become a necessity, to know and determine the reasons that lead to exacerbation disease more accurately, especially the study of complications and consequences that lead to an increase in mortality that is not only related to ARDS but also because of the comorbidities, the study of the association of this virus with the diseases and the accompanying medications has become mandatory. Renal failure is among the severe consequences which restrict the medications required to relieve and treat the symptoms of viral infection, which puts therapists in a great challenge during the treatment period, particularly the COVID-19 severity seems to be related to older age and comorbidities; in particular, patients with pre- existing cardiovascular disease (CVD) are at high risk for adverse outcomes, and SARS-CoV2 infection is associated with common vascular and arrhythmic complications[1]. Thus, statins are considered one of the most important and best drugs that reduce cholesterol levels for primary or secondary prevention of cardiac disease[2]. On the other hand, this adverse effect may be accelerated with COVID-19 infection, particularly since many case reports have been published about myopathy and rhabdomyolysis during the infection period, which may be due to the penetration of the virus itself into skeletal muscle and hepatocytes, or it may be due to drug interactions that may occur during treatment also; these reports refer to patients admitted to the hospital with respiratory syndrome associated with COVID-19, their creatine kinase levels were exceeded upper limit of normal many times and developed Rhabdomyolysis, then they left after recovery with chronic kidney disease (CKD), noteworthy many of them were under statin therapy.[3,4] Muscle weakness and elevated creatine kinase levels were also common with the progenitors of the novel coronavirus (SARS-CoV1 and MERS)[5]. Therefore, prescribing or continuing these medications in patients with Covid is under suspicion, and it has become necessary to investigate whether they cause a deterioration in patients' health. This article aims to study the relation between Creatine Kinase (CK) and covid-19 by comparing CK levels in statin users with and without COVID-19 and studying the relation between rhabdomyolysis and statin treatment in covid-19 patients. 1 2. Materials and Methods Samples were collected from the sixteenth of March to the tenth of May 2022 from Al-Shifa specialized Crisis Center / Baghdad, where isolation and treatment of COVID-19 patients for moderate and advanced cases since the beginning of the pandemic. Patients were chosen after a study and review of 244 cases. A questionnaire was collected about; age, chronic diseases, muscle pain, statin use, exercise, smoking, and alcohol consumption. Cases that did not meet the obje- ctives of this study were excluded. Where applied, 104 individual calibrated exclusions depending on comorbi- dities, medications used, drug allergy, all hepatic diseases, metabolic syndrome, or statin-related allergies were excluded. Our cohort was divided into four groups as follows: A Covid patients on statins consist of 35 individuals, B covid patients not on statins consist of 35 individuals, C group represents 35 uninfected individuals on statins, and the D group contains 35 Individuals not infected nor using statins (healthy). 2.1. Study population Our cohort was divided into four groups as follows: A Covid patients on statins consist of 35 individuals, B covid patients not on statins consist of 35 individuals, C group represents 35 uninfected individuals on statins, and the D group contains 35

Individuals not infected nor using statins (healthy). 2.2. Apparatus RANDOX kit Creatine kinase N-acetyl-L-cysteine (CK-NAC) with serial number 487390 prepared and packaged in the United Kingdom (UK). CK is characterized by instability due to oxidation at the active site, specifically in sulphydryl groups, leading to incorrect test results. Therefore, the best solution is to reactivate the enzyme by adding thiol compounds as N-acetyl-L-cysteine (NAC); the test system also includes adenosine-5'- monophosphate (AMP) in addition to didanosine pentaphosphate which inhibits the activity of myokinase, the determination of test depending on creatine phosphate and ADP, that characterized with greater sensitivity, addition to the ability to use small samples without blanks. The reagents consist of Rla. which contains Imidazole buffer, glucose, Mg-acetate, and Ethylenediaminete- traacetic acid (EDTA). R1b. consist of ADP, AMP, Diadenosine pentaphosphate, NADP, HK, G-6-PDH, N-acetylcysteine, and Creatine phosphate. CK in the sample catalyzes the transforming of the phosphate group from creatine phosphate to ADP to forming creatine and ATP, which is catalyzed by hexokinase to react with glucose to form glucose-6- phosphate and ADP, then the glucose -6-phosphate reacts with NADP+ with the presence of glucose -6- phosphate dehydrogenase as a catalyst to forming glucose-6- phosphate and NADPH + H+, The technique used for the measurement is UV method. The instruments and tools are listed in Table1 below. Table 1 Instruments and tools used in the current study NO INSTRUMENT SERIAL NO. COMPANY ORIGIN 1 CHEM-S1\ clinical semi-automated instrument FL701534\ GENEX laboratories USA 2 Medical laboratory centrifugation 5000 rpm HIGHTOP China 3 Gel tube (2.5mL) AFCOVAC Jordan 4 Disposable syringes (5 mL) China 5 Micropipettes (20-200µL), (100-1000µL), and (1-10 mL) Slamed Germany 6 Water bath HH-2 China 7 Deep Freeze GFL Germany 8 Plain tube (5 mL) China 9 pipette tips (1, 0.1, 0.01 mL) China 2.3. Statistic Statistical calculations were applied through SPSS software ® 23.0. with P-value ≤ 0.05 was considered the change as significant. The one-way ANOVA test has been implemented to compare the means of variants between and within groups. A t-test was used for multiple comparison tests across the p-value, showing significance and probability. The median, Q1, and Q3 were calculated for each group and each group variable. Then all groups were studied by distributing their data in one chart for each variable to show the difference in results, the extent of change, and the effect of statins and COVID-19 on creatine kinase and liver enzyme. 3. Results and Discussion After our standards were applied, 70 / 244 COVID-19 patients were chosen, and their ages were between 40 and 83 years old. Their symptoms are almost the same ranging between cough, chest pain, myalgia, back pain, diarrhea, fatigue, and headache. Group A consisted of 35 individuals under statin therapy for at least three months before being infected with COVID-19, and most were not doing any exercise. Reasons behind the use of statin in this group were diabetes, CAD, hypercholesterolemia, hypertension, and obesity. Mechanical ventilation was needed for most of them during their treatment duration in the hospital. The most frequent medications were; Favipiravir, Azithromycin, acetaminophen, Corticosteroids, and vitamin C. Correspondingly, 35 individuals were not under any statin therapy, but they at the same condition as the first group; diabetes, hypercholesterolemia, hypertension, and obesity had a presence in this group as well; it is noteworthy that seven patients were under statin therapy and they discontinued due to muscles pain. And they considered group B. Whereas the third group, C (35 patients), were not infected with COVID-19 and had been vaccinated against novel coronavirus, they were under statin therapy for at least three months before enrolling in our cohort. The last group was the control (group D) which consisted of 35 healthy individuals, never been infected with COVID 19 or treated with statin. Characteristics of admitted cohort and classification into four groups

are shown in Table 2 next. 3.1. Creatine Kinase (CK) After analyzing data with ANOVA one-way test, as shown in Table 3, the results confirm a variance between groups. The alternative hypothesis is accepted due to the significant p-value of 0.0021. The F statistic is greater than F critical value (F crit). SS shows the sum of squares quantifies between and within groups, which quantifies the variability within and between groups of interest. Table 2 Characteristics and classification of the admitted cohort into four groups GROUP A GROUP B GROUP C N=35 N=35 N=35 Reang of age 40 - 83 43 - 82 45 - 75 Male 54% (n=19) 54% (n=19) 48% (n=17) Female 46% (n=16) 46% (n=16) 51% (n=18) ATORVASTATİN (ATV) 20mg 39% (n=14) Non 57% (n=20) Atorvastatin (ATV) 40mg 20% (n=7) Non 3% (n=1) ROSUVASTATİN (RTV) 20 mg 34% (n=12) Non 31% (n=11) Rosuvastatin (RTV) 40 mg 9% (n=3) Non 9% (n=3) Simvastatin (SVT) 80 mg. 3% (n=1) Non Non Diabetes 26% (n=9) 17% (n=6) 60% (n=21) Coronary artery disease (CAD) 14% (n=5) Non 26% (n=9) Hypercholesterolemia 63% (n=22) 35% (n=7) 83% (n=29) Hypertension 77% (n=27) 91% (n=32) 69% (n=24) GROUP D N=35 41 - 68 57% (n=20) 43% (n=15) Non Non Non Non Non Non Non Non Non Obesity 83% (n=29) 29% (n=10) 51% (n=18) 37% (n=13) Table 3 CK-ANOVA test results SOURCE OF SS df VARIATION Between Groups 778190.5 3 Within Groups 6847525 136 Total 7625716 139 MS F P-value F crit 259396.8 5.15193 0.0021 2.671178 50349.45 The variance shows the average of the squared differences from the mean, and it is greater in group A the average and Sum (total of values) as well; the count shows the number of data points in each group and is equal in all groups and as shown in Table 4 below. Table 4 CK-NOVA test summary GROUPS COUNT SUM AVERAGE VARIANCE A 35 10024 B 35 7843 C 35 5229 D 35 3122 286.4 121968.5 224 69592.37 149.4 7060.071 89.2 2776.871 Then the multiple comparisons test was applied to compare groups and determines the most affected group. The median shows a greater value at 149 in group A, and the p-value at 0.002 indicates the highest risk and is considered highly significant. Also, Q3 was 305 in group A, which means 75% of individuals had CK levels more minor than this value, which is compatible with Dashti-Khavidaki and Khalili [6] in their hypothesis that statin may induce myotoxicity in COVID-19 patients, also corresponding with Castiglione et al. [7] in their opinion that the use of statin with antiviral drugs could increase myotoxicity. The B group (COVID not on statin) also shows a significant p-value of 0.016. Q3 shows 307.5, as listed in Table 5 below. 31% (n=11) among group B had abnormal CK values, and 5.7% (n=2) had the greatest level of CK at 1180, 1054 U/L (up to 6 fold ULN); the therapists had to do dialysis on one of them because of the high levels of serum potassium, creatinine, and urinary albumin with a dark urine color, which indicates rhabdomyolysis occurrence, this is consistent with the outcomes of Haroun et al. [4] which showed that elevated CK and rhabdomyolysis they were common consequences among COVID-19 patients. The C group (statin) shows a significant p-value versus the D group at 0.02, where the greatest CK 397 U/L is 2.85% (n=1). Whereas A versus B and C show non-significant values, and B versus C cohort individuals are distributed among groups as shown in Figure 1 below. Table 5 Comparative CK results in all cohort CK A B C D Median 149 144 25% Q1 82 64.25 75% Q3 305 307.5 Multiple comparisons test P-Value A vs. B >0.999 A vs. C >0.999 A vs. D 0.002 B vs. C >0.999 B vs. D 0.016 C vs. D 0.020 128 97 177 72.5 44.25 134 Figure 1. Distribution of cohort groups according to CK results In group A, the CK results obtained for 35 patients were; a mild increase up to 325 U/l in 13.8% (n=5), three under AVT 20 mg/day, and two under AVT 40 mg/day. The moderate increase in 8.3% (n=3) of them (less than three times the ULN, up to 568 U/L), which considered statin-related myotoxicity (SRM) stage 2 due to their symptoms, and more than the ULN reached approximately seven times in 8.3% (n=3) patients (up to 1325 U/L)

which considered SRM at stage 3. All of them were treated with 40 mg/day (AVT and RVT) except for the three mentioned above with 20 mg/day statins. While it exceeded seven times the ULN (1435 U/L) in 2.7% (n=1) SRM 3 according to CK concentration, was on SVT 80 mg. Noteworthy classification of Alfirevic et al. [8] shows that the stages of SRM listed previously in table 2.2 were used due to the presence of statins in all individuals in group A and the appearance of symptoms of muscle injury. This use came to clarify the convergence and not to assert that statins are the only cause of muscle injury here. Furthermore, the rest of the group, 63.8% (n=23) within the normal range, were under statin 20 mg/day. The clinicians decided that two patients had to be transferred to the dialysis unit due to the appearance of renal failure symptoms, where elevating was reported in serum potassium, creatinine, and urinary albumin with a very dark urine color. However, urinary myoglobin was not examined, the previous biomarkers were sufficient to indicate that rhabdomyolysis already occurs, and that was confirmed by their CK levels (1325 U/l and 1435 U/l) which were not performed by the hospital and were conducted for the purpose of this study while the patients were already in the hospital. These two cases were related to males ages 72 and 81 years old who were admitted with cough, chest pain, and fever. Then they were diagnosed with SARS-CoV2 due to a positive rtPCR swab. After review of their data case in the hospital, the clinician's initial assessment; of diabetes type 2, atherosclerosis, and a cardiac catheterization had been done previously to one of them, and both were under treatment with ATV 40 mg, SVT 80 mg, metformin, metoprolol, and Plavix, the most effective medications described in-hospital are Favipiravir, Paracetamol, and Azithromycin. However, this outcome seems to be consistent with Chan et al. [9] in terms of the occurrence of rhabdomyolysis during the infection period and compatible with Suwanwongse and Shabarek [10] in rhabdomyolysis occurrence with a statin user. Also, these outcomes may correspond with the results of Hougaard Christensen et al. [11] due to the high possibility of drug interaction between azithromycin and statins, especially there is a high dose of simvastatin, which concentration rises to 5 times the ULN, and atorvastatin, rises to 4 times the ULN in the presence of azithromycin, in addition to the antiviral effect, where two types of CYP inhibitors are combined lead to inadequate metabolism of statins and an increase in their circulation concentration, which increases the statin exposure of skeletal muscles even after discontinuing statins, the half-life of some statins considered long, especially ATV, which lasts up to 80 hours. In the questionnaire presented to individuals in group A or their companions, 38% of them (n = 15) answered that fatigue and back pain were the first symptoms of the disease that they felt. The initial diagnosis of the therapists indicated that 25% (n = 9) who were admitted to the hospital had muscle pain, back pain, and general weakness, in addition to the common symptoms of COVID-19. Therefore, these results may reconcile with the report of Chan et al. [9] Regarding fatigue and elevated CK as one of the initial symptoms of infection. Compared with the B group (Covid not on statin), the p-value was non-significant and the C group (statins). However, when comparing these last two groups with the D group, it changed to significant, and this indicates that statins and COVID-19 cause elevation of CK, but in heterogeneous patterns and related to clinical and pharmacological factors, while the more elevated was partial with the A group (COVID with statin) significantly with patients whose treated with high doses of statins and that appear clearly in the patients' distribution which shown in figure 1. However, these findings differ from Castiglione et al. [7] hypothesis that statin use in hospitalized COVID-19 patients had a positive effect on symptom improvement and shorter recovery time through its anti-inflammatory effect by upregulation of angiotensin-converting enzyme 2, which is the main pathway of the virus, in

order to use statin as a low-cost drug in low-income countries, where our results showed the statin plays a role as an additional factor that accelerates the occurrence of muscle damage, especially with high doses that led to the consequences of renal injury. Myopathy and even rhabdomyolysis occurred with group B and at a higher frequency in numeral and severity in group A. These data indicate that these complications occur due to novel coronavirus disease and are exacerbated by the presence of statin, especially at higher doses. It may be due to mitochondrial dysfunction caused by statins; the impairment of energy transfer leads to accelerated muscle breakdown when viral infection depletes skeletal muscle energy. This is exacerbated by using drugs that increase the exposure of the skeletal muscles to statins by inhibiting CYP pathways and raising their concentration in blood circulation. Therefore, the use of statins with COVID-19 patients should be limited to the presence of the risk of heart attack, atherosclerotic cardiovascular disease, or diabetes, with monitoring of CK levels and avoiding high doses of statins, where the reconsideration of the benefits of using statins in coronavirus patients is required due to the consequences that may be occurred. 4.

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