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Changes in Liver and renal function of Subjects infected with corona Virus 19 (COVID 19) on Zinc and Vitamin C in a Health care facility in Southern Nigeria

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Abstract

Background: The COVID-19 outbreak by the new coronavirus strain was recognized as a pandemic by the World Health Organization (WHO)). Vitamin C is a water-soluble antioxidant vitamin. Zinc is crucial for many cellular processes, including the preservation of immune function and is an anti-inflammatory and antioxidant micronutrient. **Aim:** The aim of the study was to determine changes of some liver and renal parameter in patient with COVID 19 administered with Vitamin C and Zinc treatments. **Methodology:** Sixty three subjects who had symptoms and were admitted to the wards within the cottage hospital had their sample analysed for COVID-19, Total Protein, Albumin, alanine aminotransferase (ALT), aspartate aminotransferase(AST), alkaline phosphatase (Alk Phos) Total Bilirubin, Direct Bilirubin, Sodium, Potassium, Chloride, Bicarbonate, Urea and Creatinine using Biuret, Bromocresol green, Reitman and Frankel, Phenolphthalein Monophosphate, Jendrassik-Grof, ion selective electrode, Phosphoenol pyruvate carboxylase, Berthelots and Jaffe's methods respectively. The data were analyzed using t-test and ANOVA tools. **Results:** There was no significant difference ($P>0.05$) in Total protein (g/L) and albumin(g/L) concentrations of 82.60 ± 2.70 and 47.04 ± 1.63 at baseline and 103.30 ± 11.00 and 48.06 ± 2.13 at post treatment. There was a significant decrease ($P<0.05$) in ALKPHOS (U/L) from 159.97 ± 8.98 at baseline to 77.88 ± 10.14 at post treatment. Direct bilirubin showed significant increase ($P<0.05$) from 0.90 ± 0.12 at baseline to 1.55 ± 0.30 at post treatment.Bicarbonate (Mmol/l) and Creatinine (Umol/l) significantly increased from 16.17 ± 1.81 and 73.78 ± 2.03 at baseline to 38.40 ± 2.17 and 151.42 ± 15.98 at Post Treatment respectively while Urea (Mmo/l) significantly reduced ($P<0.05$) from 21.00 ± 3.97 at baseline to 10.62 ± 2.71 at Post Treatment. Other parameters had no significant difference ($p>0.05$) in the levels before and after treatment. **Conclusion:** The study showed that administration of Zinc and vitamin C to subjects with COVID 19 infection caused decrease alkaline phosphatase and urea levels with increase Direct Bilirubin, bicarbonate and creatinine in those patients.

Keywords*: COVID, Liver, Renal, Vitamin C, Zinc.*

Introduction

Throughout history, there have been a number of pandemic diseases; the most notable and recent pandemic of COVID-19 began in December 2019 in Wuhan, China. Although COVID-19 infection is self-limiting in approximately 80% of cases, male individuals, the elderly and those with comorbidities such as diabetes mellitus, hypertension, or underlying cardiorespiratory illness are at a higher risk of becoming severely ill [1] [2] [3]. COVID-19 infection is mainly characterized by respiratory illness with flu-like symptoms such as fever, cough and shortness of breath, whereas severe infection can cause death due to diffuse alveolar damage and progressive respiratory failure [5]. Angiotensin-converting enzyme 2 (ACE2), the human cell receptor of SARS-CoV-2, whose expression is dominant in alveolar type 2 cells, is also expressed in organs such as the liver, kidney, heart and brain; thus, SARS-CoV-2-infected patients are often observed to have systemic damage with widespread inflammation [6] [7] [8].

Vitamin C is a water-soluble antioxidant, has been reported to ameliorate the free radical induced damage by carbofuran [9] [10]. Since ascorbic acid is water soluble, it can work both inside and outside the cells to combat free radical damage [10]. There are several transport mechanisms to get it inside: Glucose-dependent transporters like GLUT1 and 3 as well as more specialized sodium-dependent transporters for ascorbic acid, SVCT1 and 2 [11]. Vitamin C can "donate electrons to free radicals such as hydroxyl and superoxide radicals and quench their reactivity" [12] [13]. Vitamin C reported to be an antioxidant [14], has been shown to mitigate lead induced oxidative stress toxicity [15]. Vitamin D, vitamin C, and the trace element zinc are known to support immune function [16]. Zinc is an essential trace element which plays a role in enhancing immune system. Deficiency of zinc can impact immunity because it maintains barriers and develops both innate and adaptive immune systems. Zinc deficiency leads to lack of formation, activation and maturation of lymphocytes, disturbs the intercellular communication via cytokines, and weakens the innate host defence [17] [18]. Zinc deficiency may impair phagocytosis of macrophages and neutrophils, NK cell activity, generation of the oxidative burst and complement activity [19]. Zinc deficiency also reduce lymphocyte proliferation, Th1 cytokines production (IL-2 and interferon-γ), and leads to a Th1/Th2 imbalance [20]. Not only having an effect on cell-mediated immunity, zinc is also an anti-inflammatory and antioxidant agent [21]. Zinc is also considered to be a second messenger in immune cells. Its role includes activating T cells by the T cell receptor and the cytokine interleukin IL-2, and antibody-binding receptors which are predominantly found on cells of the innate immune system [22]. The aim of the study is to determine changes of liver and renal parameters in patients with COVID 19 administered with Vitamin C and Zinc treatments.

Materials and Method

Study area

The study was carried out in a cottage hospital located in Port Harcourt, Southern Nigeria. The cottage hospital

Subjects

Subjects were randomly selected via simple random sampling method. Sixty-three subjects on who had symptoms and were admitted to the wards in the cottage hospital had their samples analysed for COVID-19 and liver and renal biomarkers before and after two weeks of treatment with Zinc and Vitamin C.

Reagents

The cholesterol, triglycerides, HDL and LDL precipitants, Urea, Creatinine, glucose, Total protein, albumin, AST and ALT reagents produced by Randox reagents UK were purchased in Port Harcourt while the Alkaline

Phosphatase reagent produced by QCA Spain was purchased for analysis.

Biochemical analysis

Determination of ALT and AST was done using Reitman, and Frankel method [23].

Alkaline Phosphatase activity was done by Phenolphthalein Monophosphate method .

The Serum Total Bilirubin Concentration was determined using Jendrassik-Grof method [24]. The serum total bilirubin concentration is determined in the presence of caffeine, which releases albumin bound bilirubin, by the reaction which diazotized sulphanillic acid [24] [25].

The Serum direct Bilirubin Concentration was determined using Jendrassik-Grof method [24]. The serum Direct/indirect bilirubins react with diazotized sulphanillic acid in alkaline medium to form a blue coloured complex [24] [25].

Total Protein concentration was carried out using Biuret method. [26].

Bromocresol green (BCG) method [27] was used for albumin estimation.

Estimation of Sodium, Potassium and Chloride was done using Ion selective electrode analyser method [28]. The analyser utilises Ion Selective Electrode (ISE) technology. ISE is a type of electrochemical sensor. It converts the ion activity to the electric potential of the electrode. The relation conforms to the NERST equation, that the logarithm of the ion actitvity has a linear relation with the electrode potential [29].

Creatinine estimation was done by Jaffe's colorimetric method [30].

Serum bicarbonate concentration was determined by the method [31] described as outlined in Teco Diagnostic Kit. The Phosphoenol pyruvate carboxylase (PEPC) catalyzes the reaction between phosphoenol pyruvate and biocarbonate ion to form oxaloacetate and phosphate ion. Oxaloacetate is subsequently reduced to malate with simultaneous oxidation of an equimolar amount of reduced nicotinamide adenine dinucleotide (NADH) to NAD. The reaction is catalyzed by malate dehydrogenase (MADH). This results in a decrease in the absorbance of the solution at 340nm that is directly proportional to CO_2 concentration in the sample.s

Statistical analysis

Data obtained were subjected to statistical analysis using Statistical Package for Social Science version 25 using statistical tools such as t-test and analysis of variance (ANOVA). Results were expressed as Mean ± Standard error of Mean (X±SEM). The values of $P<0.05$ were considered significant.

Results

There was no significant difference ($P>0.05$) in total protein (82.60±2.70 vs. 103.30±11.00 g/L), albumin (47.04±1.63 vs. 48.06±2.13 g/L), AST (2.77±0.14 vs. 2.14±0.13 U/L), ALT (6.71±3.23 vs. 9.10±3.89 U/L), and total bilirubin (5.90±0.60 vs. 6.90±1.60 µmol/L) between baseline and post-treatment. However, ALKPHOS significantly decreased ($P<0.05$) from 159.97±8.98 to 77.88±10.14 U/L, while direct bilirubin significantly increased ($P<0.05$) from 0.90±0.12 to 1.55±0.30 µmol/L.

Table 1. Effects of two weeks treatment with Vitamin C and Zinc on Liver function parameters of COVID 19 Subjects

	Total Protein (g/L)	Albumin (g/L)	AST (U/L)	ALT (U/L)	ALKPHOS (U/L)	Total Bilirubin (Umol/L)	Direct Bilirubin (Umol/L)
Baseline	82.60±2.70	47.04±1.63	2.77±0.14	2.14±0.13	159.97±8.98	5.90±0.60	0.90±0.12
Post Treatment	103.30±11.00	48.06±2.13	6.71±3.23	9.10±3.89	77.88±10.14	6.90±1.60	1.55±0.30
T-value	3.529	0.147	1.612	3.475	36.988	0.295	4.176
P-value	0.063	0.702	0.207	0.065	0.000	0.588	0.043

There were no significant changes (P>0.5) in sodium (147.69±3.16 vs. 144.93±3.82 mmol/L), potassium (5.27±0.21 vs. 5.83±0.29 mmol/L), and chloride (98.27±3.66 vs. 107.81±3.93 mmol/L) between baseline and post-treatment. However, bicarbonate significantly increased from 16.17±1.81 to 38.40±2.17 mmol/L, creatinine increased from 73.78±2.03 to 151.42±15.98 µmol/L, and urea significantly decreased from 21.00±3.97 to 10.62±2.71 mmol/L (P<0.05).

Table 2. Effects of two weeks treatment with Vitamin C and Zinc on some renal function parameters of COVID 19 Subjects

Group	Sodium (Mmol/l)	Potassium (Mmol/l)	Chloride (Mmol/l)	Bicarbonate (Mmol/l)	Urea (Mmo/l)	Creatinine (Umol/l)
Baseline	147.69±3.16	5.27±0.21	98.27±3.66	16.17±1.81	21.00±3.97	73.78±2.03
Post Treatment	144.93±3.82	5.83±0.29	107.81±3.93	38.40±2.17	10.62±2.71	151.42±15.98
t	0.314	2.404	3.160	62.923	4.510	25.197
P	0.576	0.124	0.078	0.000	0.036	0.000

There was no significant difference (P>0.05) in total protein, albumin, AST and ALT, total bilirubin and direct bilirubin levels across the groups but there was significant difference (P<0.05) in AKLPHOS across the groups.

Table 3. Effects of two weeks treatment with Vitamin C and Zinc on Liver function parameters of different gender of COVID 19 Subjects

Group	Total Protein (g/L)	Albumin (g/L)	AST (U/L)	ALT (U/L)	ALKPHOS (U/L)	Total Bilirubin (Umol/L)	Direct Bilirubin (Umol/L)
Male control	81.20±2.17	46.14±2.36	2.82±0.21	2.23±0.18	73.01±14.55	6.05±0.06	0.82±0.12
Female control	85.00±6.30	48.56±1.81	2.70±0.16	2.00±0.18	81.18±14.00	5.78±0.12	1.01±0.28
Male COVID 19 Subjects	96.40±12.57	49.46±2.74	6.47±4.23	5.97±3.18	142.74±9.35 [a,b]	8.07±0.23[b]	1.50±0.37
Female COVID 19 Subjects	113.30±20.35 [a,b]	45.98±3.43	7.08±5.14 [a,b]	13.73±8.45 [a,b]	170.13±12.99 [a,b]	5.09±0.21	1.63±0.50
F-value	1.549	0.443	0.535	1.826	13.074	0.583	1.451
P-value	0.206	0.722	0.659	0.146	0.000	0.627	0.232

a= significant when compared with Male control
b=significant when compared with Female control

There were no significant differences (P>0.05) in sodium, potassium, chloride, and urea levels among the groups. However, bicarbonate and creatinine levels showed significant difference (P<0.05 in their levels across the groups.

Table 4. Effects of two weeks treatment with Vitamin C and Zinc on some renal function parameters of different gender of COVID 19 Subjects

Group	Sodium (Mmol/l)	Potassium (Mmol/l)	Chloride (Mmol/l)	Bicarbonate (Mmol/l)	Urea (Mmo/l)	Creatinine (Umol/l)
Male control	146.33±4.00	3.03±0.23	101.93±3.53	17.52±2.45	2.50±0.53	74.02±2.49
Female control	145.00±5.22	3.68±0.43	92.05±7.81	13.90±2.57	1.68±0.58	73.38±3.57
Male COVID 19 Subjects	148.88±4.90	5.45±0.35 [a,b]	107.11±5.09	39.28±2.86 [a,b]	9.96±3.38 [a,b]	139.51±18.44 [a,b]
Female COVID 19 Subjects	139.09±6.03	6.41±0.49 [a,b]	108.84±6.31	37.09±3.30 [a,b]	11.61±4.55 [a,b]	169.03±28.87 [a,b]
F-value	0.802	2.475	1.615	21.175	1.811	8.936
P-value	0.495	0.065	0.190	0.000	0.149	0.000

a= significant when compared with Male control
b=significant when compared with Female control

Discussion

The study examined the effect of administration of Vitamin C and Zinc on subjects diagnosed with COVID 19. The result of this study showed significant increase (P<0.05) in bicarbonate, creatinine and direct bilirubin with significant decrease (P<0.05) in Alkaline Phosphate, and urea of the subjects diagnosed with COVID 19 at baseline compared with Post Treatment with Vitamin C and Zinc. This is contrary to the work of Eze [32], who reported that Co-administered vitamin C and Zinc 100 and 50 mg/kg respectively restored alanine aminotransferase and aspartate aminotransferase function in diabetes induced hepatotoxicity. This showed that vitamin C and Zinc may play an important role in the prevention of hepatocellular injury that may occur in diabetes. This is further supported by the findings of Hamden [33]. The hepatoprotective effect of vitamin C is said to be associated with it oxidative property. Vitamin C is a water-soluble antioxidant which decreases lipid peroxidation either directly or indirectly by regenerating vitamin E, the major lipid-soluble antioxidant [14]. Vitamin C was also reported to scavenge aqueous reactive oxygen species (ROS) by rapid electron transfer that inhibits lipid peroxidation [34]. Zinc-deficient individuals are prone to increased respiratory and diarrheal morbidities [35] [36]. Furthermore, it was found that zinc supplementation in children with zinc deficiency may reduce the morbidity and mortality related to lower respiratory tract infections caused by the measles virus [37]. Zinc administration is also associated with a 41% reduction in the prevalence of childhood pneumonia [38], a lower respiratory tract infection. Clinical studies have shown that zinc supplementation can also reduce, by up to 54%, the severity and duration of various cold symptoms, such as fever, cough, sore throat, muscle pain and nasal congestion [39] [40], which may also occur after SARS-CoV2 infection.

The Female COVID 19 Subjects had significant increase (P<0.05) in Potassium, Bicarbonate, Urea, creatinine total protein, AST, ALT and ALP compared with male and female controls. The male COVID 19 Subjects had significant increase (P<0.05) in Potassium, Bicarbonate, Urea, creatinine, Total bilirubin and ALP compared with male and female controls. In

this work it was observed that vitamin C may have hepatoprotective effect. This hepatoprotective effect tends to increase synergistically when co administered with Zinc. The synergistic effect of vitamin C and Zinc was evaluated in animals [41]. who stated that co-administration of vitamin C and Zinc during nickel intoxication reversed nickel induced oxidative stress in the liver of rats.

Supplementation with zinc was shown to be effective in the treatment of acute diarrhea, which may be due to viral infection [42]. Regarding zinc sources, it was found that supplementation with zinc amino acid chelate, compared with placebo and zinc sulfate, had a better effect in reducing the incidence of diarrhea and acute respiratory infection, in addition to resulting in a lower incidence of side effects, in preschool children [43]. An in vitro study found that zinc may have antiviral activity to inhibit SARS-CoV RNA polymerase. Therefore, zinc may have a beneficial effect on COVID-19 infection [44].

Conclusion

The study has shown that administration of Zinc and vitamin C to subjects with COVID 19 infection caused decrease alkaline

phosphatase and urea levels with increase Direct Bilirubin, bicarbonate and creatinine in those patients.

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