"THE VITAMIN D, IL-6 AND THE EGFR MARKERS A POSSIBLE WAY TO ELUCIDATE THE LUNG–HEART–KIDNEY CROSS-TALK IN COVID-19 DISEASE: A FOREGONE CONCLUSION"

Dott. Diego Tomassone M.D. Ph.D.

«Holos medica clinical and research»

Italy

2nd European Congress on

Chemistry and Applied Sciences (CPD accredited)

November 09-10, 2023

Millennium Hotel Paris Charles De Gaulle, Paris, France

CHEMISTRY CONGRESS 2023

ABSTRACT

Background: Based on recent findings, we speculated the existence of the lung, heart, and kidney axis as the main pathway for the COVID-19 disease progression.

Methods: Here we report an observational study conducted a team of researchers and doctors of the 118-Pre-Hospital and Emergency Department of SG Moscati of Taranto City in Italy. The study was conducted on a totality of 185 participants that were divided into three groups. The study group included COVID-19 affected patients (PP n = 80), the first control group included patients with different pathologies (non-COVID-19 NNp n = 62) of the SG Moscati Hospital, and the second control group included healthy individuals (NNh n = 43). The core of the current trial was focused on assessing the level of the vitamin D (serum 25(OH) D concentration), IL-6, and the renal glomerular filtrate (eGFR) in COVID-19 disease and non-COVID-19 patients in both groups.

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ABSTRACT

Results: It was observed that the majority of COVID-19-infected patients showed a progressive multi-organ involvement, especially in regard to the lung, kidney, and heart. The majority of the COVID-19 patients exhibited preexisting comorbidities which include cardiovascular, respiratory, and renal disorders accompanied by a severely low level of vitamin D, extremely high level of IL-6, and low glomerular filtration rate (eGFR). The significant overall damages exerted by the immune-mediated responses under the hyper-expression of proinflammatory cytokines and interleukins, such as IL-6, may be facilitated by either a decreased level of vitamin D or the ageing process. The reduced presence of vitamin D was often found together with a reduced functionality of renal activity, as revealed by the low eGFR, and both were seen to be concomitant with an increased mortality risk in patients with lung disorders and heart failure (HF), whether it is showed at baseline or it develops during manifestation of COVID-19.

Conclusions: Here we want to explain how a low level of vitamin D and advanced age can be indicative of systemic worsening in patients with COVID-19, with the aim of providing a wider context in which to visualize a better therapeutic approach.

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INTRODUCTION

In this observational study [1] we hypothesized the existence of the lung, heart and kidney axis as the main pathway for the progression of COVID-19 disease mainly on the basis of the existence of symmetrical abnormal markers, such as vitamin D, egfr and IL-6. The role of vitamin D or pro-hormone D in viral infection is a hot topic of growing interest. From an immunological point of view, the focus is on the involvement of D in the entire cascade of host responses to virus invasion. Recent findings have confirmed the immunomodulatory effects D and the induction of autophagy, apoptosis and even direct antiviral effects. There is considerable variation in the prevalence of vitamin D deficiency worldwide, mainly depending on age; in COVID-19, elderly people and patients with metabolic comorbidities were the highest with mortality rates and were also those with lower serum levels of 25OHD [2,3,4,5].

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SARS-COV-2 PATHOGENETIC HYPOTHESIS

The Seneca study revealed an average concentration of 25OHD of 10.4 ng/ml in elderly people aged 70-75 in Spain. In this regard, experimental evidence indicates that vitamin D can inhibit IL-6, IL-1, IL-17, TNF-α and IFN-γ by reducing the activation of P38 MAP kinase in human monocytes/macrophages (M1 and neutrophils), improving the activity of T-regulatory cells (T-regs), Th2, and IL-10 m2 [5,6,7,8,9]. Therefore, we hypothesized that the key pathogenetic mechanism for the successful growth of SARS-cov-2 could be facilitated by the low level of vitamin D, because of its role as a crucial mediator of Ang-II production within the RAS and ACE2/ACE2r mechanism. All the consequences of severe complications typical of COVID-19 disease begin through under-regulation of ACE2 and ACE2r expression, which is the main input for the virus to invade human cells, tissues, organs and systems.

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The resulting high accumulation of Ang-II leads to an uncontrolled hyper-inflammatory state that occurs under the over-expression of IL-6, a prerequisite for acute cardiac and renal failure observed especially in elderly people or patients with previous metabolic comorbidities. As is now known, the adverse effects of Ang-II can increase an uncontrolled accumulation of cholesterol plaques along the vessels and visceral glomerular epithelial cells (podocytes) which, in turn, aggravates systemic and glomerular hypertension, promoting the onset of renal lesions induced by ischemia, leading to renal or cardiovascular failure (Figure 1) [10,11,12].

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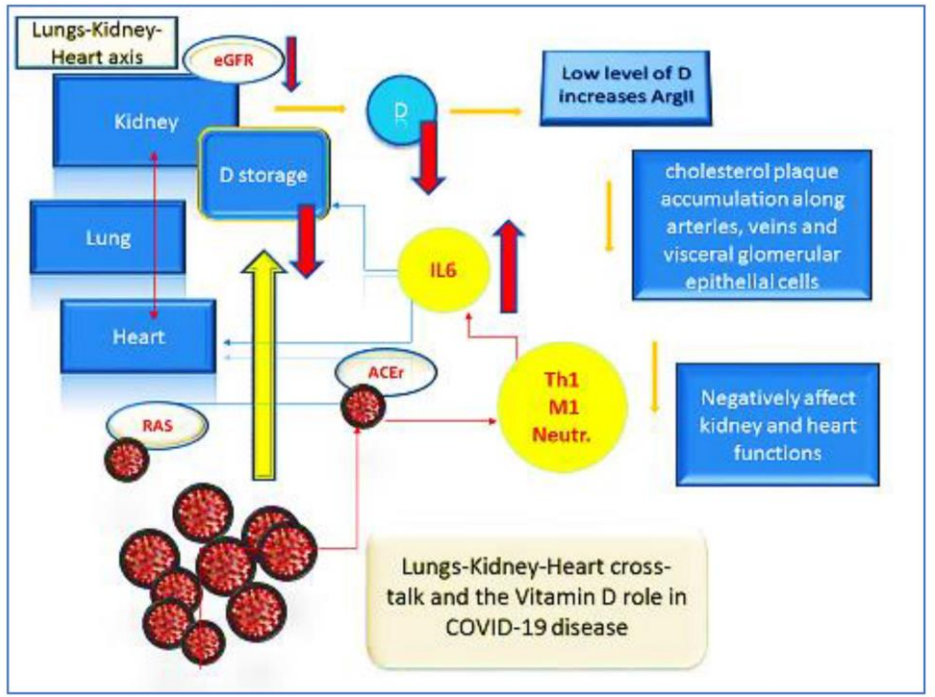

Figure 1. The regulation of the acid-base balance; modification of the partial pressure of the concentration of carbon dioxide, oxygen and bicarbonate; and control of blood pressure, Fluid homeostasis and systemic blood supply all depend closely on renal and cardiac lung activity.

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SARS-COV-2 PATHOGENETIC HYPOTHESIS

Figure 1. SARS-cov-2 spreads dangerously prevalently, due to the low level of vitamin D as a crucial mediator of Ang-II production within the RAS and angiotensin-converting enzyme receptor 2 (ACE2R) and the mechanism of the angiotensin 2 converting enzyme (ACE2/ACE2r). The entire sequence of complications related to COVID-19 begins through the underregulation of the expression of ACE2r as the main input of SARS-cov-2. The high accumulation of Ang-II induces uncontrolled hyper-inflammatory responses driven by the IL-scenario6 which has been seen as a prerogative cause of acute heart and kidney failure particularly observed in elderly people or in patients with pre-existing metabolic comorbidities. The set of adverse effects related to Ang-II facilitates the accumulation of cholesterol plaques along the vessels and visceral glomerular epithelial cells (podocytes) that cause systemic and glomerular hypertension or cause renal damage induced by ischemia, which results in renal and cardiovascular failure.

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SARS-COV-2 PATHOGENETIC HYPOTHESIS

Ang-II's contribution to the pathophysiology of heart and kidney failure is based primarily on the following observations: (1) Ang-II is produced within the myocardium and renal cortex, (2) Ang-II is activated within the hypertrophic heart in insufficiency and overproduced in the hypertrophic kidneys and (3) pharmacological inhibition of RAS and Ang-II in animal models or in patients with hypertrophic heart and damaged kidney showed high efficacy. In this perspective, few authors have proposed a low level of D production in the kidneys as a key factor of COVID-19 related super-inflammatory mode and organ failure [10,11,12,13,14,15].

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DISCUSSION RESULTS

Complete cessation of vitamin D synthesis would consequently increase an uncontrolled reaction on Ang-II accumulation which, in turn, disperses the high vitality of pro-inflammatory cytokines and interleukins, as IL-6, followed by a sudden regression of the functionality of the kidneys, heart and pulmonary axes (16).

We found that vitamin D deficiency, high level of IL-6 and low level of egfr were highly indicative in COVID-19 tropism, differences in average levels of vitamin D, IL-6 and egfr obtained by comparing the three groups were statistically significant. The data suggested that vitamin D was related to the type of COVID-19 disease or other typical inflammatory, acute or chronic diseases, since it was expressed by the PP and NNP groups, indicating its role in the acumination and pathogenesis of COVID-19 ($p > 0,05$).

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The mean values of vitamin D, IL-6 and egfr in the COVID-positive groups (PP), COVID-free (nnp) and Control group (NNh), together with the respective confidence intervals, are given in **Table 1**. Confidence intervals have been calculated with the 95% confidence level, using the Student t test, as shown in **Figure 2**. The mean values of IL-6 in the control group are normal. The level of IL-6 in the COVID-positive group is nine times higher than normal and the patients in nnp showed an extremely high level of IL-6, exceeding the normal level by eighteen times. The normal level of IL-6 < 7 pg/ml. The mean values of IL-6 and the respective confidence intervals are shown in **Figure 3**. The mean value of egfr in the control group (NNh) was normal, while the level of egfr in both PP and nnp groups was slightly lower than normal. The normal level of egfr is >90 ml/min. The mean values of egfr and the respective confidence intervals are shown in **Figure 4**.

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Table 1. Mean values of vitamin D, IL-6, and eGFR for three groups, together with their respective confidence intervals with the confidence level 95%.

	Groups	Mean	±δ	Confidence Interval	
Vitamin D (ng/mL)	PP Patients	18.0475	2.639475	15.40802	20.68698
	NNp	14.49355	1.871572	12.62198	16.36512
	NNh (Healthy)	44.0986	6.599012	37.49959	50.69762
IL-6 (pg/m)	PP Patients	64.10633	26.77383	37.3325	90.88016
	NNp	124.5258	68.18824	56.33757	192.714
	NNh (Healthy)	3.023256	0.337694	2.685562	3.36095
eGFR (mL/min)	PP Patients	71.71623	6.263475	65.45276	77.97971
	NNp	76.79361	68.18824	8.605366	144.9818
	NNh (Healthy)	112.9769	4.122511	108.8544	117.0994

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DISCUSSION RESULTS

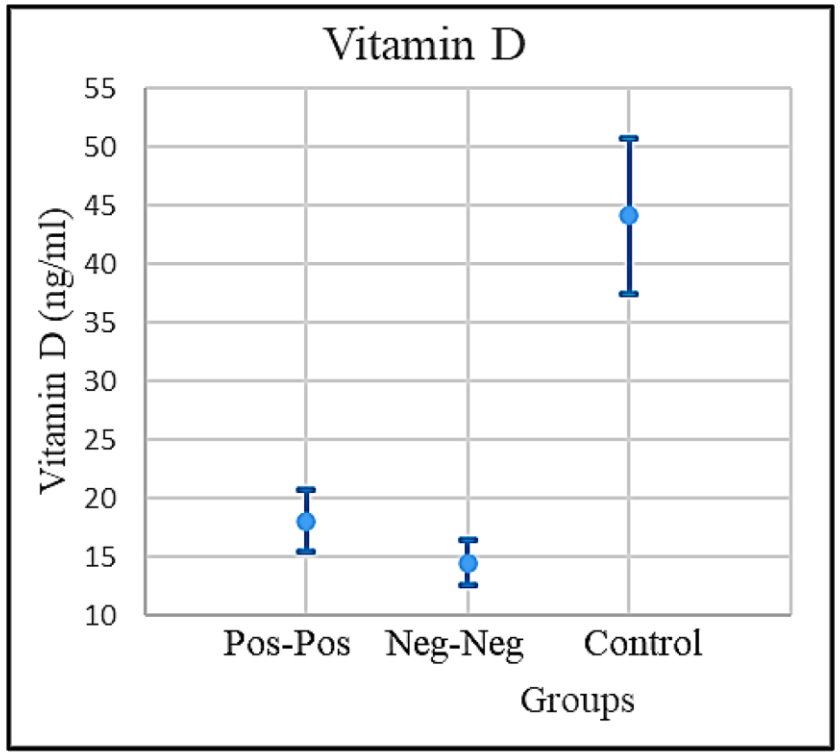

Figure 2. Average vitamin D levels and confidence intervals for COVID-positive, COVID-free and control groups.

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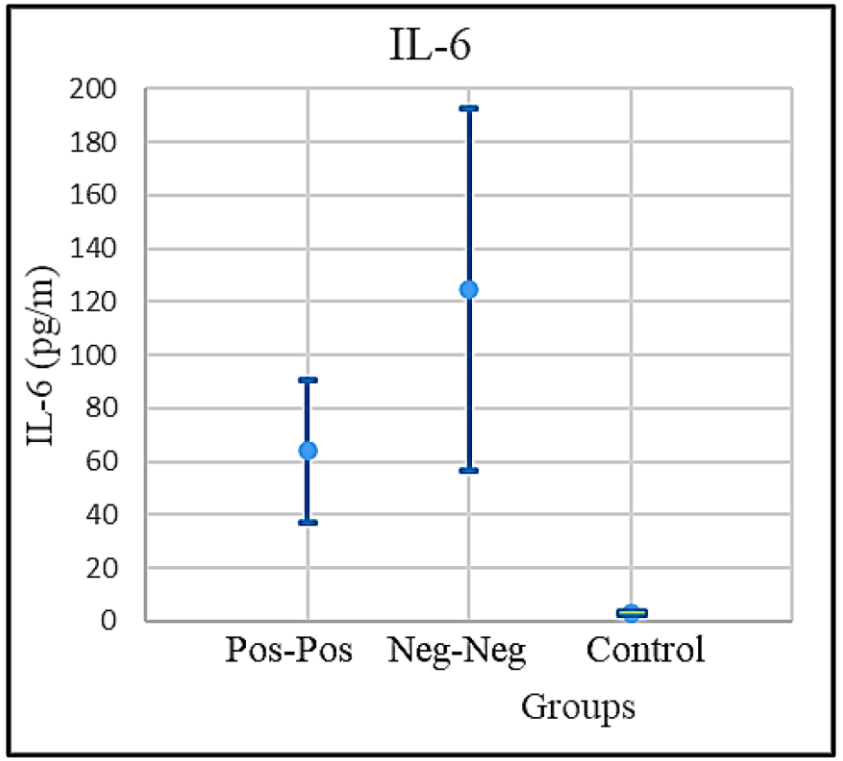

Figure 3. Average levels of IL-6 and confidence intervals for COVID-positive, COVID-free and control groups.

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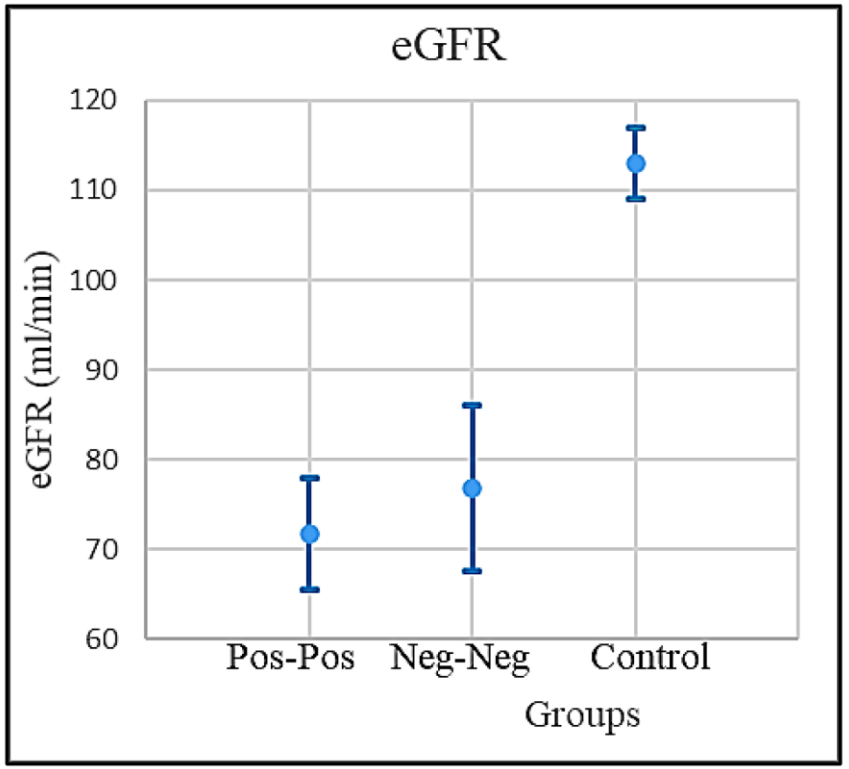

Figure 4. Average levels of egfr and confidence intervals for COVID-positive, COVID-free and control groups.

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Age eventually plays a key role in maintaining a proper and balanced immune response. The data clearly showed that levels of vitamin D, egfr and IL-6 are inversely related; the older the individual, the lower the vitamin D and the egfr and the higher the IL-6 (**Table 2**, **Table 3** and **Table 4**).

Table 2. The Student's *t*-test for differences of the vitamin D mean values in PP vs. NNp, PP vs. NNh, and PP vs. NNh groups; the differences of the mean levels of vitamin D in all three groups are statistically significant. The differences of the mean levels of vitamin D in all three groups are statistically significant.

Vitamin D (ng/mL)			
	PP	NNp	NNh
Diff of means =	3.55	26.05	29.61
Sp =	10.20	15.90	14.92
1/sqrt(np) =	0.17	0.19	0.20
df =	140	121	103
t-cr =	1.98	1.98	1.98
t-score =	2.06	8.67	10.00
Test is	Significant	Significant	Significant

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Table 3. The Student's *t*-test for differences of the IL-6 mean values in PP vs. NNp, PP vs. NNh, and NNp vs. NNh groups. The difference of the mean levels of IL-6 in COVID-positive (PP) NNp groups is statistically insignificant, but the difference of the mean values of IL-6 in the NNh group and the PP and NNp groups was statistically significant.

IL-6 (pg/m)			
	PP	NNp	NNh
Diff of means =	60.42	61.08	121.50
Sp =	198.93	97.24	206.60
1/sqrt(np) =	0.17	0.19	0.20
df =	140	121	103
t-cr =	1.98	1.98	1.98
t-score =	1.80	3.32	2.96
Test is	Insignificant	Significant	Significant

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DISCUSSION RESULTS

Table 4. The Student's *t*-test for differences of the eGFR mean values in PP vs. NNp, PP vs. NNh, and NNp vs. NNh groups. The difference of the mean levels of eGFR in PP, NNp, and NNh groups is statistically insignificant, but the difference of the mean values of eGFR in the NNh compared to both the PP and NNp groups was statistically significant.

eGFR (mL/min)			
	PP	NNp	NNh
Diff of means =	5.08	41.26	36.18
Sp =	32.27	24.09	29.69
1/sqrt(np) =	0.17	0.19	0.20
df =	140	121	103
t-cr =	1.98	1.98	1.98
t-score =	0.93	9.06	6.14
Test is	Insignificant	Significant	Significant

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THERAPEUTIC HYPOTHESIS

Therefore, an upcoming therapy would support the rational use of vitamin D. However, based on our clinical experience, we propose that this strategic approach includes a combined approach that allows us to act on the immune system, on the respiratory system and nervous system, contributing to better breathing through the centers of the brain stem and the phrenic nerve. For example, the use of vitamin D, vitamin K and erythropoietin (EPO) has been shown to modulate the ventilator response in the locus coeruleus to CO2 in rats, positively regulating hyperpnea induced by hypercapnia [12,17,18,19]. Vitamin D has been shown to mediate intracellular oxidative stress by increasing superoxide dismutase 1 and 2 (SOD1-2) (as seen in the hypoxic cancer microenvironment).

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EPO-mediated regulation of the central respiratory control, involving both MEK1/2 and PI3K, has been seen as crucial for phrenic motor facilitation, suggesting spinal plasticity in respiratory motor control under prolonged conditions of poor oxygen. On the other hand, vitamin K not only allows the activation of D through the hydroxylation mechanism, but also prevents cellular mitochondrial dysfunction, restores oxidative phosphorylation and aerobic glycolysis, and finally supports the hypoxic microenvironment of cleansing typical of the tissues analyzed in lung and cardiovascular tumors and necrosis due to massive thromboembolism [12,13,14,18,20,21,22,23,24,25] (**Figure 1**).

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CONCLUSIONS AND FUTURE PERSPECTIVES

To summarize, heart, lung and kidney functions are closely related, especially if you see the whole picture from the point of view of emergency medicine. The regulation of the acid-base balance; modification of the partial pressure of the concentration of carbon dioxide, oxygen and bicarbonate; and control of blood pressure, Fluid homeostasis and systemic blood supply all depend closely on renal and cardiac lung activity. It follows that the degree of severity of COVID-19 would depend on the age and pre-existing diseases, as well as an excessive consumption of vitamin D stored inside the body in response to the invasion of SARS-cov-2 through the RAS/acer mechanism. With this in mind, it follows that any therapeutic approach should include a flexible approach involving the use of multiple agents, especially in those at high risk, such as the elderly and patients with metabolic-chronic comorbidities [17,26,27,28,29,30].

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We are well aware that further studies with a larger sample are needed to confirm direct evidence of the effect of vitamin D on COVID-19 disease. In this work we in our small we have evidenced that the deficiency of vitamin D is positively associated to the increase of the IL-6 and the decrease of the egfr, especially in the group of study Covid-positive. In addition, this study weighed our proposed hypothesis indicating vitamin D, egfr and IL-6 as strong markers in the monitoring phase of COVID-19 disease; meanwhile, they were also signifying the concrete existence of a kidney, heart and lung axis.

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