UNDERSTANDING THE RELATIONSHIP BETWEEN COVID19, VITAMIN D LEVELS, CYTOCHROME P450 ENZYMES & PARATHYROID LEVELS

A Case for using High Loading Dose Vitamin D (600,000UI) in 26 patients

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When it comes to understanding the relationship between Vitamin D3 (Cholecalciferol) and the Cytokine Storm induced by COVID19 (SARS-COV2), it becomes more clear when we have a more in-depth understanding of liver and kidney metabolism. Before I get into the biochemistry and pathophysiology of this subject I must emphasize the importance of early detection and quick treatment of patients with COVID19 symptoms.

I have lost track of how many studies across the globe have demonstrated that ***80% of all COVID19 patients have vitamin D3 deficiency or insufficiency.*** Approximately 8 out of 10 patients in the ICU have vitamin D3 deficiency or insufficiency.

But today I would like to share a couple of words regarding the existing correlation between cytochrome P450 enzymes, specially CYP2R1, vitamin D, PTH levels and COVID19 patients.

Vitamin D Metabolism

As we know through basic biochemistry, vitamin D synthesis derives from the sun exposure (UVB rays), where 7-dehydroxicholesterol is converted into cholecalciferol.

Cholecalciferol through systemic circulation, reaches hepatic metabolism where a series of cytochrome P450 enzymes express CYP2R1 (25 hydroxylases).

This enzyme converts cholecalciferol into calcifediol. Once calcifediol enters systemic circulation it reaches the proximal convoluted tubules (PCT) found in the kidneys where 1 alfa 25 hydroxylase is expressed helping convert Calcifediol into vitamin D active form, ***calcitriol.***

*Many cofactors are all also necessary for an adequate Vitamin D metabolism such as magnesium, boron, vitamin E, vitamin B2, B3, B6, B9, B12, CoQ10 and vitamin K2 allow for adequate **phase I** hepatic metabolism of **cytochrome P450 enzymes**, but this is another topic for later discussion.*

When it comes to the innate and acquired immune system, we know that macrophages, T cells, and B cells are equipped with their own converting enzymes, allowing them to convert calcifediol into calcitriol. This means they don't require kidney conversion through 1 alfa hydroxylase.

Intracellular calcitriol upregulates protein transcription mediators which will allow the immune cells to make Cathelicidins and Beta-defensins helping fight off SARS-COV2.

Beta-defensins help penetrate the enveloped SARS-COV2 membrane creating pores that generate loss of viral genetic material and inhibiting viral replication.

It is very important recognizing that vitamin D reduces dramatically the levels of IFN alfa, gamma, IL-1, IL-6, IL-12, IL-33, TNF, CCL-2,3,5, CXCL-8.9, and 10. Basically, all of the inflammatory mediators found in the cytokine storm!.

When our immune system is confronted with the SARS-COV2, it is the innate immune system that gets the first hand of interaction. Eventually, the acquired immune system kicks in leading to the synthesis of specific neutralizing antibodies, IgM being the first and finally IgG granting immunity to the individual.

*When vitamin D levels are low **(<40ng/ml),** the maturation of naive T cells convert into Th1 cells that end up expressing IL-1 and Interferon-gamma. This activates the **proinflammatory pathway** that promotes the **cytokine storm.***

*Obviously, this is a very summarized version of what actually happens. But once the cytokine storm gains momentum, it starts causing damage to many other organs like the **lungs, heart, kidneys and liver.***

On the other hand when adequate levels of vitamin D **(>40ng/ml)** are circulating, naive T cells mature into Th2 cells which end up activating B Cells (acquired immune system) and promoting antibody synthesis (anti-inflammatory pathway) avoiding the cytokine storm.

High Loading Dose of Vitamin D

When the body finds itself under stress due to inflammation, CYP2R1 (25 hydroxylase) is upregulated at much higher rates, allowing the body to convert cholecalciferol into calcifediol faster. But when our body finds itself in a deficient state of vitamin D, this conversion does not take place, hence the importance of **NORMALIZING** quickly vitamin D levels by giving **HIGH LOADING DOSE** of vitamin D (600.000 UI of cholecalciferol for patients >50kg).

Patients must wait approximately 15 to 20 days in order to receive physiologic dose after HLD of vitamin D. This initial recommendation of normalizing vitamin D levels with a HLD was promoted by the Brazilian vitamin D expert, Dr. Cicero Coimbra since the beginning of the COVID19 pandemic. Other physicians around the world have also made this same claim.

Cytochrome P450 Enzymes & PTH

Measuring hepatic enzymes (liver function) can be **EXTREMELY** helpful in determining hepatic conversion capability of cholecalciferol into calcifediol during early COVID19 intervention. Measuring CYP450 phase I metabolic enzymes are good predictors of liver conversion capability via 25 hydroxylase activity. In its counterpart 24 hydroxylase breaks down calcitriol into its inactive form when its no longer needed.

Giving too much corticosteroids can be detrimental and actually breakdown the active form vitamin D (calcitriol) via upregulation of ***24-hydroxylase***. Glucocorticoids enhance 24-hydroxylase activity. They also inhibit intestinal calcium absorption and promote bone resorption and decrease bone formation, thereby decreasing bone mass and increase risk of fractures. This is where PTH levels can come in handy. Elevated PTH levels that exceed upper reference laboratory levels suggests excess corticosteroid usage which translates into the breaking down of calcitriol and lowering 25 OH vitamin D levels in COVID19 patients.

Calcifediol vs Cholecalciferol

The use of calcifediol (according to the study done in Cordoba-Spain) instead of cholecalciferol was a game-changer in COVID19 therapeutics. Calcifediol does not require hepatic conversion and helps downregulate the pro-inflammatory pathway halting it and upregulating the anti-inflammatory pathway with a gain of immunity through IgM / IgG production.

Unfortunately, Calcifediol is not readily available in all countries. But cholecalciferol is inexpensive, over the counter and is readily available around the world.

Vitamin D is a liposoluble molecule. If it is taken at a normal physiologic dose ***(200IU/kg/day),*** it will require approximately 3 months in order to achieve adequate protective levels ***(40-100 ng/ml).*** In contrast, calcifediol only requires ***(2-3)*** days in order to reach optimal protective levels.

Protective Functions of Vitamin D

It is always important to remember the many functions that vitamin D offers for patients with COVID19:

1. ***Reduces Acute Respiratory Distress Syndrome.***
2. ***Regulates Cytokine Storm.***
3. ***Adjusts the modulation and activity of neutrophils.***
4. ***Regulates the Renin Angiotensin System.***
5. ***Maintains the integrity of the pulmonary epithelial barrier***
6. ***Stimulates the repair of alveoli and blood vessels.***
7. ***It helps to reduce the state of hypercoagulability and thrombus formation.***

I was able to clinically and laboratory prove each of these items mentioned above in several of my patients in a period of just 24 to 48 hours!

Personal Experience:

In my personal experience of treating COVID19 patients, I have had a hand full. Many of them were ICU patients from Brazil and Bolivia. High loading dose (HLD) of cholecalciferol was given with family consent and in accordance with some ICU physicians. All of my patients **(26 in total)** had low levels of 25 OH vitamin D ***(<20ng/ml).*** A ***600.000 IU loading dose of cholecalciferol*** was compounded in 10 ml of olive oil and administered through the patient's nasogastric tube followed by a 20 ml flush of distilled water. All patients were either intubated or had a tracheostomy tube placed and received standard ICU treatment. Every single patient had elevated leukocyte count.

One of them was a ***16-year*** old male with the Brazilian P.1 variant. His WBC count was of 23.000 per microliter. After administering HLD of cholecalciferol we were able to see a significant reduction in his WBC ***(13.000 per microliter)*** in less than ***24 hours.***

Physicians were perplexed to see such a rapid response after a initial dose.

Liver enzymes were mildly elevated. Oxygen demand was initially 50% and decreased to 30% 3 days after HLD. Oxygen saturation increased to 98-99% and arterial blood gas measurements were normal.

Oxygen demand was initially 50% and decreased to 30% 3 days after HLD. Oxygen saturation increased to 98-99% and arterial blood gas measurements were normal. Sedation was discontinued 5 days after HLD of vitamin D and 1 week later the patient was discharged from the ICU.

Once again, I would like to reinstate the importance of early recognition of COVID19 symptoms. If the patient is left untreated in the first 3 days of the initial symptoms without giving a HLD of vitamin D, we are allowing organ (liver) damage to take place secondary to the cytokine storm. This in short term translates into loss of cytochrome p450 enzymes and CYP2R1 (25-hydroxylase) conversion capability.

Recommendations

1.) Measuring blood levels of 25 OH vitamin D in COVID19 patients should be a standarized screening practice amongst healthcare professionals. Having this additional laboratory parameter at hand, gives us a more in-depth scenario of the potential severity of COVID19 patients.

2.) Measuring phase I liver cytochrome P450 enzymes (CYP450) tells us a great deal about vitamin D conversion capability. This parameter would help identify what patient would benefit best with HLD of vitamin D and help reduce inflammatory mediators ***IFN alfa, gamma, IL-1, IL-6, IL-12, IL-33, TNF, CCL-2,3,5, CXCL-8.9, and 10.***

3.) Finally, since most ICU patients receive IV corticosteroids due to the cytokine storm, measuring PTH values will allow healthcare providers to avoid giving too much steroids causing excessive breakdown of calcitriol and lowering of 25 OH vitamin D levels. PTH levels can help guide providers with a more precise corticosteroid titration. Maintaining PTH levels just below the upper laboratory reference range, allows for more adequate vitamin D conversion (cholecalciferol to calcifediol). This in the long run offers COVID19 patients a better chance in upregulating their anti-inflammatory pathway that may lead them towards a better and faster recovery.

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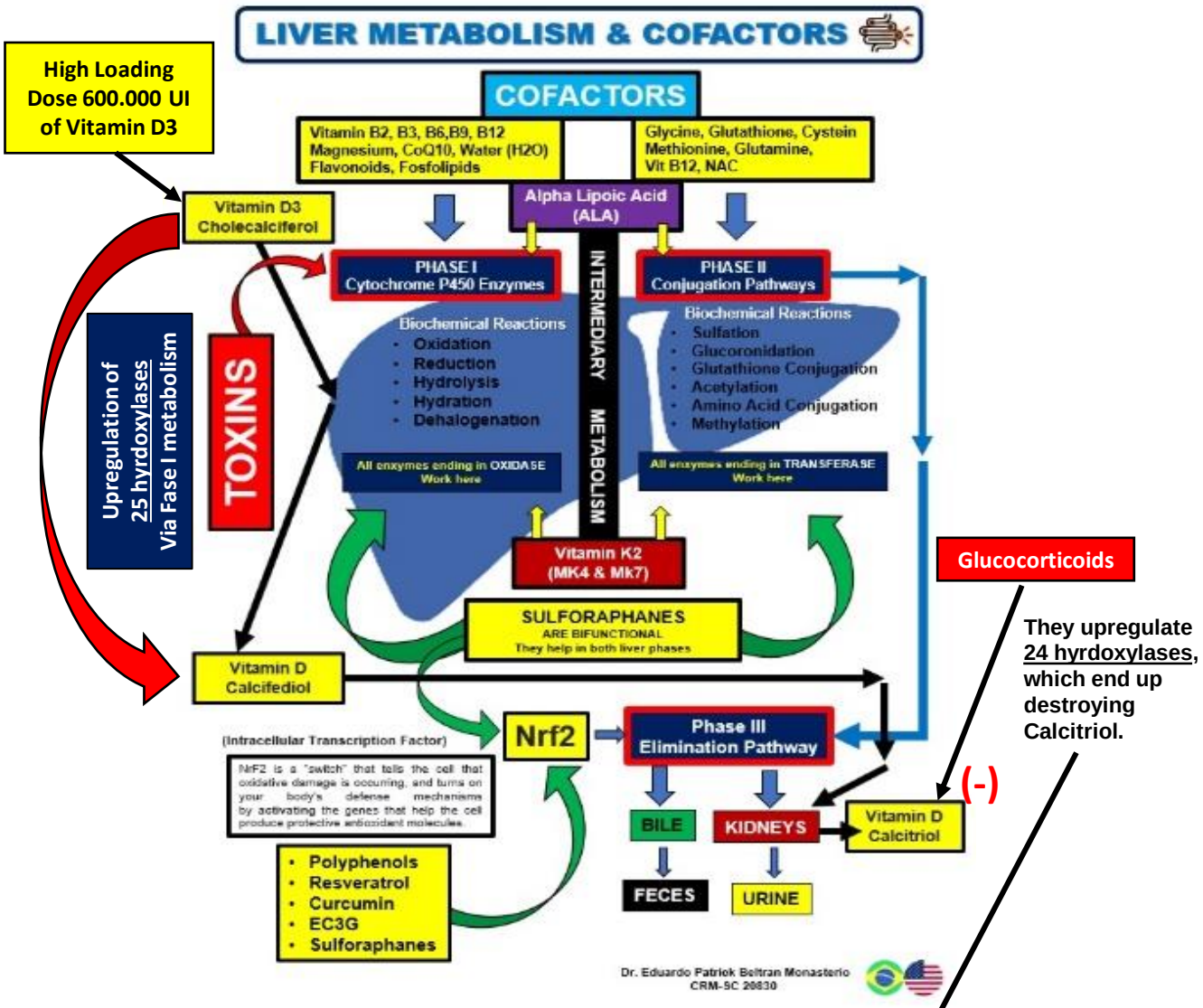
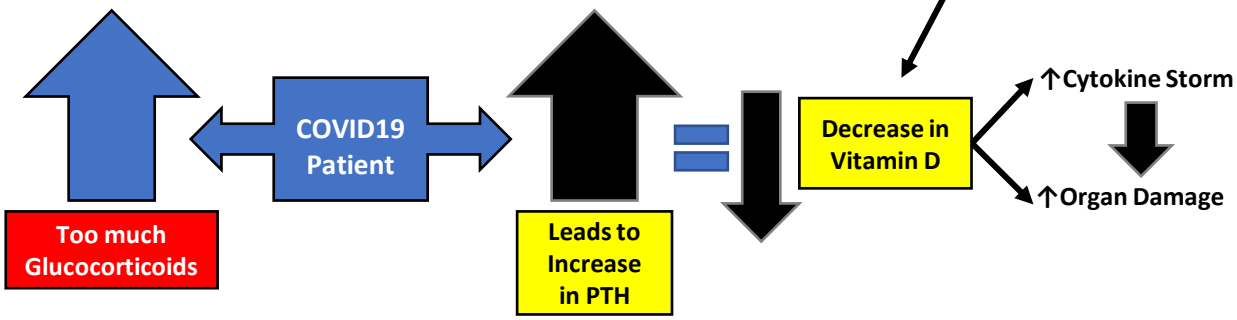
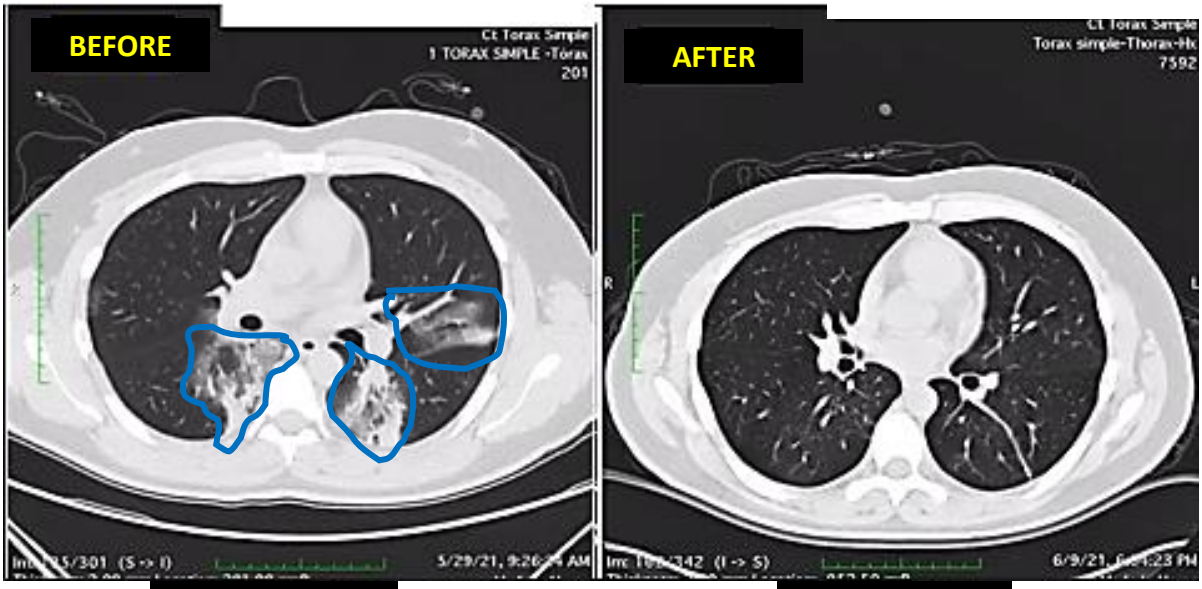


RELATIONSHIP BETWEEN PTH & GLUCOCORTICOIDS





May 29th,2021

June 9th ,2021

Laboratory Exams

ESTUDIO	RESULTADO	UNIDAD	VALOR DE REFERENCIA
HEMOGRAMA			
Hematies	5.950.000	/mm3	4.300.000 - 6.000.000
Caracteres Morfológicos	NORMOCITOS		
Hemoglobina	16,6	g/dL	13,5 - 17,8
Hematocrito	50,9	%	41 - 54
Recuento de Plaquetas	307.000	/mm3	140.000 - 400.000
Leucocitos	8.600	/mm3	4.300 - 11.100
Fórmula Leucocitaria			
Neutrofilos : Segmentados	66	%	40 - 78
Neutrofilos : Cayados	0	%	0 - 5
Linfocitos	29	%	20 - 40
Monocitos	4	%	2 - 10
Eosinófilos	1	%	1 - 5
Basófilos	0	%	0 - 2
Indices Hematimétricos			
VCM	86	fL	80 - 100
HCM	27,8	pg	27 - 33
CHCM	32,5	g/dL	32 - 36
VPM	6,4	fL	6,2 - 11,8

Muestra: Sangre con EDTA
Mi¿½todo : Contador Automatizado ELITE-5

ESTUDIO	RESULTADO	UNIDAD	VALOR DE REFERENCIA	
25-OH VITAMINA D3/D2	31,4	ng/ml	Suficiente	20 160
			Insuficiente	12 - 20
			Deficiente	<12

Muestra: Suero
Mi¿½todo : ORGENTEC ALEGRIA SMC300

ESTUDIO	RESULTADO	UNIDAD	VALOR DE REFERENCIA
PTH INTACTA	51,6	pg/ml	12 - 72

Muestra: Suero

ESTUDIO	RESULTADO	UNIDAD	VALOR DE REFERENCIA
PCR - PROTEINA C REACTIVA CUANTITATIVA - NEPHSTAR	0,70	mg/l	< 5,0

Muestra: Suero
Mi¿½todo : NEPHSTAR - NEFELOMETRIA AUTOMATIZADA

The patient received HLD of 600,000 IU of cholecalciferol on May 29, 2021. After 48 hours, the patient had less shortness of breath. Initial oximetry was 87% and rose to 92% within 48 hours. After 11 days, the patient underwent another chest tomography showing resolution of the picture by image. Laboratory parameters showed normalization of CBC, there was an increase in 25 OH vitamin D (Before 12 ng/dl), PTH below the upper reference limits (due to less use of corticosteroids) and normalization of C-Reactive Protein. Patient was discharged from hospital on June 10, 2021 with 98% saturation without oxygen.