

## Is urban malnutrition feeding cytokine storms in COVID-19 patients? Vitamin D insufficiency, a Hong Kong perspective

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The 5<sup>th</sup> Wave of SARS COVID-19, predominantly the Omicron variant, hit Hong Kong hard with unprecedented hospital admissions and mortality in the vulnerable. By mid-March 2022, 1,900 children were admitted with 2 yrs. and younger, being the highest proportion in PICU. Sudden complications, some fatal were reported with fainting, coma and convulsions. Over 6555 elderlies have succumbed.

Clinical presentations of COVID-19 include symptoms of viral infection and the life-threatening auto-immune response to the invasion. Termed 'Cytokine storm', this uninhibited release of inflammatory factors by the patient's immune system is comparable with a raging forest-fire destroying without precision. The T-cells becoming overactive have been implicated in excessive inflammatory cytokine release.<sup>9</sup>

### What role does malnutrition play in facilitating immune overreaction? In Hong Kong, a developed city, which undernutrition could be undermining the health of a population?

Vitamin D (VitD) facilitates innate and adaptive immunity. It has potential links to regulation of cytokine storms, coagulopathies, cardiac and nervous system morbidity.<sup>4</sup> Its presence in the body at normal levels (30ng/ml or 75nmol/L) supports the healthy maturation of the immune system. VitD enhances cellular immunity in young children, importantly the regulation and differentiation of T cells.<sup>13</sup> Healthy levels of VitD are known to support protection from viral infection and bronchial inflammation especially in children.<sup>14</sup> (Table 2)

A 2018 study had shown 22-60% of HK infants had severe VitD deficiency below 25 nmol/L (10ng/ml).<sup>5</sup> Recent data published by HKU for the HK paediatric population found evidence of a progressive decline in serum 25(OH)D levels since social distancing measures first began in 2020 COVID-19 pandemic. By Nov 2021, VitD Levels were found to be declining at the rate of 6.32nmol/L per month and this is from an already lower baseline. Pregnant and breast-feeding mothers would also have a lower VitD levels due to reduced sun exposure unless supplemented.<sup>17</sup> Seventy-two percent of Hong Kong young adults were VitD deficient in 2017.<sup>17</sup> Vitamin D receptor polymorphisms which may cause dysfunction and VitD deficiency have been reported at a higher incidence in Chinese ethnicity including in Hong Kong.<sup>10, 12</sup>

This unrecognized population wide Low VitD status may add to grave complications in acute infections such as COVID-19. Studies have shown that lower Serum VitD levels in COVID-19 patients are associated with higher pro-inflammatory cytokine levels, increased viral presence, a higher risk of hospitalization, ICU admission and death.<sup>3</sup> VitD deficient patients (<20 ng/mL) have a 14 time higher risk of critical disease compared to patients with healthy VitD levels (≥40 ng/mL)(p<0.001).<sup>8</sup> (Table 1)

Complications in lower VitD groups included dyspnea, 3-fold higher risk of arterial pO<sub>2</sub><60mmHg and higher CRP.<sup>1</sup> Multi-organ systemic inflammation with encephalitis were documented in VitD insufficient and deficient paediatric populations from Turkey and UK. The UK study specifically looked at ethnic minority including Asians and also documented higher incidence of VitD deficiency in the infected children vs uninfected.<sup>3, 7</sup>

### Urgent supplementation policy in vulnerable groups

Having present-day data of local deficiency, evidence from global studies and proof of healthy VitD levels in immune modulation, swift action is warranted to improve this easily modifiable factor in the war against COVID-19. The youngest age group and others, not eligible for COVID-19 vaccines are left further immunocompromised if VitD deficient. (Table 3)

Presently there is no known program of Vitamin D supplementation for the Hong Kong adult, elderly or paediatric population. As social distancing measures continue, urgent targeted therapeutic supplementation is needed to support immune regulation. Improvement of the VitD status of the Hong Kong population will be a cost-effective, ethical measure to support reduction of severe illness and hospitalizations during the COVID-19 pandemic and future viral illnesses.

A daily oral dose of VitD3 (Cholecalciferol) at 1000 IU (25µg) raises serum 25(OH)D levels by 15-25nmol/L over weeks/months without toxicity and is well within the range of safety.<sup>19, 20</sup> In critical care, a larger loading dose is required, while daily moderate doses are efficient to improve respiratory outcomes in vulnerable groups.<sup>19</sup>

For supplementation, infants would need further categorization as formula-fed or breast-fed with the latter at a higher-risk of lower VitD status. Cholecalciferol food fortification at a population level

would prevent recurrence of deficiency and potentially reduce viral complication load on the over stretched hospital system during the pandemic and annual flu season.

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**Table 1: VitD levels in relation to severe/critical COVID-19, moderate COVID-19 and healthy controls**

Population studied	Severe/Critical COVID-19	Moderate manifestation COVID-19	Healthy controls	p value
N= 1176 Galilee Medical Center (GMC) in Israel. <sup>8</sup>	87.4%<20 ng/mL	34.3%<20 ng/mL		<i>p</i> < 0.001
N= 149 Bagcilar Training and Research Hospital, Istanbul, Turkey. <sup>11</sup>	10.1 ± 6.2 ng/mL	26.3 ± 8.4 ng/mL		<i>p</i> < 0.001
n=75 Paediatric Kirikkale University Hospital Turkey. <sup>2</sup>	not tested	21.5 ± 10.0 ng/mL	28.0 ± 11.0 ng/mL	<i>p</i> < 0.001

**Table 2: Effect of serum 25(OH) D on immune modulation**

1. Induces differentiation of T-regulatory Cells and inhibits Th17 cell proliferation by upregulate PLC-γ1 expression.<sup>18</sup>
2. Promotes secretion of anti-inflammatory cytokine TGF-β121.<sup>18</sup>
3. Suppresses pro-inflammatory cytokines such as interleukin-17 (IL-17)<sup>18</sup>
4. Vitamin D signaling is essential in regulating pro-inflammatory signaling of Th1 (a Th1 skew is noted in Broncho-alveolar lavage fluid CD4<sup>+</sup> T cells of COVID-19 patients as seen in VitD deficiency)<sup>6</sup>

**Table 3: High-Risk population for VitD deficiency: conditions and medications known for lowering VitD levels.<sup>19</sup>**

Conditions	Medications
Kidney, Liver Heart failure esp. Transplant patients	Glucocorticoids
Inflammatory and bowel malabsorption disease	Antiretroviral medication
Granuloma- forming disease such as Sarcoidosis, tuberculosis	Antifungals
Hypo-Hyperparathyroidism	Anti-Seizure medication
Hospitalized and ICU patients	Rifampicin
Obese	Cholestyramine
Elderly	
Oncology patients	
Pregnant, Breast feeding	
COPD, Asthma, Cystic Fibrosis	