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SHORT COMMUNICATION

What chances do children have against COVID-19? Is the answer hidden within the thymus?

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Abstract

A new type of coronavirus named as SARS-CoV-2 pandemic has begun to threaten human health. As with other types of coronaviruses, SARS-CoV-2 affects children less frequently, and it has been observed that the disease is mild. In the pathogenesis of a standard viral infection, the pathogen's contact with the mucosa is initially followed by an innate immunity response. T cells are the primary decisive element in adaptive immunity capability. For this reason, the adaptive immune response mediated by the thymus is a process that regulates the immune response responsible for preventing invasive damage from a virus. Regulatory T cells (T-reg) are active during the early periods of life and have precise roles in immunomodulation. The thymus is highly active in the intrauterine and neonatal period; it begins to shrink after birth and continues its activity until adolescence. The loss of T-reg function by age results in difficulty with the control of the immune response, increased inflammation as shown in coronavirus disease (COVID-19) as an inflammatory storm. Also, the thymus is typically able to replace the T cells destroyed by apoptosis caused by the virus. Thymus and T cells are the key factors of pathogenesis of SARS-CoV-2 in children.

Conclusion: We speculated that thymus activity and T lymphocyte function in children protect them against the virus effects. Stimulating and preventing the inhibition of the thymus can be possible treatment components against COVID-19.

What is Known:
- *The SARS-CoV-2 infection does not often progress with an invasive clinic in children.*
- *Thymus activity and T lymphocyte functions are highly active in children.*

What is New:
- *Effective thymus activity and T lymphocyte function in children protect them against the invasive SARS-CoV-2 infection.*
- *Stimulating and preventing the inhibition of the thymus can be possible treatment components against COVID-19.*

Keywords Children · Coronavirus · COVID-19 · Immunosenescence · SARS-CoV-2 · Thymus

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Abbreviations

ACE2	Angiotensin-converting enzyme-2
CD 26	Cluster of differentiation 26
COVID-19	2019 coronavirus disease
GM-CSF	Granulocyte macrophage colony-stimulating factor
IL-7	Interleukin-7
MERS-CoV	Middle East respiratory syndrome
OSM	Oncostatin M
RNA	Ribonucleic acid
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGF	Transforming growth factor β
T-reg	Regulatory T cells

A new type of coronavirus named as SARS-CoV-2 has begun to threaten human health and marked its first appearance in December 2019 in the capital of China's Hubei Province, Wuhan. In just 2 months, the virus had spread to every continent (except Antarctica) and became the cause for a pandemic. The number of confirmed cases worldwide has 3,407,747 and including 238,198 deaths, reported to the World Health Organization by date 04 May [1].

Coronaviruses are enveloped, positive sense, single-stranded ribonucleic acid (RNA) viruses that measure 80–220 nm in size and are responsible for 15% of common cold cases in humans while also causing serious infections such as croup, bronchiolitis, and pneumonia. The coronaviruses have many types that cause endemic infections; with the addition of the 2003 SARS-associated coronavirus (SARS-CoV) and the 2012 Middle East respiratory syndrome (MERS-CoV), coronaviruses have been responsible for many deaths and continue to considerably impact public health [2]. While having a high mortality rate in adults, the SARS-CoV and MERS-CoV have not caused deaths in pediatric patients. Including the SARS-CoV-2, it has been shown that coronavirus infections in children present in mild forms [3]. Historically, outbreaks such as the Spanish flu, paralytic polio, and influenza have similarly been shown to have mild effects on children [4]. Scientists researched why children and young people were protected in the 3 recent coronavirus epidemics; they speculated that less outdoor activity, international travel, and lower angiotensin-converting enzyme-2 (ACE2) receptor expression in children were primarily responsible [4].

In the pathogenesis of a standard viral infection, the pathogen's contact with the mucosa is initially followed by an innate immunity response (e.g., macrophage, antigen presenting and natural killer cell) and the objective is to eliminate the pathogen in the initial stage. Subsequently, adaptive immunity comes into play and is responsible for the elimination of infected cells, activation of the antibody response, and production of memory T cells.

T cells are the primary decisive element in adaptive immunity capability. For this reason, the adaptive immune response mediated by the thymus is a process that regulates the immune response responsible for preventing invasive damage from a virus. Therefore, the thymus is the most influential organ in the transmission of viral disease [5]. The thymus is highly active in the intrauterine and neonatal period; it begins to shrink after birth and continues its activity until adolescence. The thymus decreases in both function and activity as the person ages [6]. Thymic involution and the gradual decrease in T cell count and ability with age are together termed as immunosenescence. With immunosenescence, the person becomes susceptible to autoimmune diseases, infections, and cancer [7, 8]. Regulatory T cells (T-reg) are active during the early periods of life and have precise roles in immunomodulation. It has been shown that T-reg activity decreases with immunosenescence [9]. The loss of T-reg function results in difficulty with the control of the immune response, increased inflammation, and a tendency to autoimmunity.

Clinic and pathological examination of coronavirus disease (COVID-19) cases showed a cytokine storm associated with a disregulated immune response, which ultimately resulted in extensive tissue damage. This tissue damage is caused by an out-of-control immune response induced by the virus [10]. The primary reason for the clinical picture being seen in this manner in patients of ages 50 and up may be due to a deficient, irregular, and uncontrollable antiviral response as a result of thymus involution and immunosenescence.

Important factors in achieving an adequate immune response are an increase in thymus activity and T cell action along with immune system coordination. Severe cases of COVID-19 consist of lymphopenia, especially T cell loss [11]. The primary mechanism responsible for lymphopenia is cluster of difference 26 (CD 26) marked T cells being targeted by the coronavirus, resulting in apoptosis of these cells and impairment of the immune system [12, 13]. The thymus is typically able to replace the T cells destroyed by apoptosis; however, this is not consistent in older patients. Greater thymus activity and T lymphocyte function in children protect them against autoimmune disease, viral infections, and cancer. Research has shown an increased rate of childhood mortality with reduced thymus size [14].

When examining the critical COVID-19 cases in the literature, the male gender seems to be more common; this is speculated to be due to greater tobacco use and angiotensin-

Table 1 Treatment options that can prevent thymic atrophy or stimulate thymus

Molecule/therapy option	Treatment	Effects
Zinc	Oral supplement	Lowers age-associated thymic atrophy with partial recovery of lymphocyte functions, as measured by mitogen responsiveness and NK cell activity on mice, and serves as a co-factor of thymulin which is associated with both intrathymic and extrathymic T cell differentiation
Antioxidants	Vitamin E, high-dose vitamin C and N-acetyl cysteine	Reduces thymic atrophy
IL-7	Recombinant human IL-7	Increased TCR diversity in clinical studies in humans, in vitro proliferation of peripheral T cells and increased thymic output in aged mice
Glucocorticoids	Inhibition of glucocorticoids	Glucocorticoids reduce thymic cell count during *Salmonella typhimurium* and *Francisella tularensis* infections in mice; therapies with thymopoeitic potential are known to reduce GCs.
Leptin		It reduces thymic atrophy, increases intrathymic IL-7, and decreases pro-inflammatory cytokine release in mice, but not all conditions are suitable for administration.
Keratinocyte growth factor		Increases thymic output and naive T cell pool in aged mice.
Ghrelin, an appetite-stimulant hormone		Improvement in thymocyte numbers, thymic output, and T cell activation in aged mice

converting enzyme-2 (ACE2) receptor expression [15]. The literature also shows that thymic involution is more apparent in males compared to females [16]. This difference in thymic involution indicates that males face a greater extent of immunosenescence. We believe this mechanism might be responsible for clinical worsening in males. We also believe that the reason females experience a relatively lower rate of thymic involution is due to their higher levels of leptin; some studies have shown that leptin protects the thymus from atrophy [6, 17].

In conclusion, stimulating and preventing the inhibition of the thymus can be possible treatment components against COVID-19 infections. In this context, potential thymus-stimulating cytokines include human interleukin-7 (IL-7), keratinocyte growth factor, thymic stromal lymphopoietin, keratinocyte growth factor, leptin, and molecules with antioxidant activity such as high-dose vitamin C, oral zinc supplements, luteinizing hormone-releasing hormone receptor antagonist, ghrelin, and systemic administration of a fusion product of granulocyte macrophage colony-stimulating factor (GM-CSF) (Table 1) [6, 18]. In addition, agents that inhibit thymus suppressing cytokines can also be used; these include transforming growth factor β (TGF), oncostatin M (OSM), and leukemia inhibitory factor [6].

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Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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