

The Enigmatic Functional Role of Thymus Gland in Fighting Against SARS-CoV- 2 and COVID- 19 - Literature Review

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Abstract: Background and Objective: Coronavirus disease 2019 (COVID- 19) caused a world pandemic, spreading rampantly throughout the world. Although people of all ages were infected, there was an obvious partiality in terms of the disease severity follow infection in children patients' group of age. Consequently, in order to achieve a better understanding of the discriminative behavior of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV- 2) aggressiveness throughout all different groups of age, thus, the main potential aims of this review were not only to give a new impetus toward the unintentional omission of the effective immune role of the thymus gland in children on tackling COVID- 19, but also to discuss the potential possibility of thymosin replacement therapy utilization in the form of thymosin alpha 1, as a key booster in fighting against COVID- 19.

Method: A literature search of COVID- 19 and SARS- CoV2 related published articles and literatures using science search engines encompassing PubMed, Medline and Google Scholar.

Results: The main result of this review had exhibited low possibility of SARS- CoV- 2 infection, far less reported lymphopenia as well as low exposure rate to opportunistic complications of COVID- 19 in children, compared to adults and elderly individuals. Therefore, this discrepancies in infection rates and laboratory findings may potentially indicate the paramount importance of fully functioned thymus gland in fighting against SARS- CoV- 2 infection in children.

Conclusion and Recommendations: COVID- 19 remains a global dilemma causing massive devastation on all aspects of social and economic life. Due to the discriminative behavior of SARS- CoV- 2 aggressiveness throughout all different groups of age detected through this literature review. Hence, more research and clinical trials on thymosin alpha- 1 efficacy are needed in order to understand the possible role of the thymus gland in protecting against SARS- CoV- 2 infection and minimizing COVID- 19 symptoms and complications.

Keywords: COVID- 19, SARS- CoV- 2, Lymphopenia, Thymus gland, Thymosin Alpha 1.

الدور الوظيفي الغامض للغدة التيموسية في مجابهة كل من كوفيد- 19 وسارس كوف- 2-
مراجعة أدبية

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ياسر جمالات

معهد قوانغتشو لطب الأطفال || مركز جوانزو الطبي للنساء والأطفال || قوانغتشو || الصين

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الملخص: الخلفية والأهداف: بات مرض فيروس كورونا 2019 (كوفيد-19) يشكل تهديداً متصاعداً على جميع الأصعدة المختلفة وذلك نظراً لسرعة انتشاره حول العالم. على الرغم من تسجيل حالات إصابة بالعدوى في جميع الفئات العمرية إلا أنه تم ملاحظة ارتفاع في نسبة احتمالية ظهور الأعراض الانتهازية لدى الفيروس عند البالغين وكبار السن دون الأطفال. لذلك هذه المراجعة الأدبية الموجزة وجدت لتقديم صورة أوسع حول تفسير سلوك فيروس كورونا المرتبط بالمتلازمة التنفسية الحادة الشديدة النوع 2 (سارس كوف-2) العدائي وتَحْيُزُهُ لفئات عمرية محددة دون الأخرى وكذلك لإبراز الدور الفعال للغدة الثايموسية في مجابهة عدوى كوفيد-19 عند الأطفال و الذي قد يهْمِشُهُ بشكل غير مقصود العاملون في المجال الصحي، بل أيضاً مناقشة إمكانية استخدام الثيموسين ألفا-1 كداعم رئيسي في مجابهة كوفيد-19.

الطرق والوسائل: مراجعة للأدبيات والدراسات المنشورة مؤخراً والمتعلقة بكوفيد-19 وفيروس سارس كوف-2 بواسطة كل من محركات البحث العلمية بيمد وميدلاين والباحث العلمي من جوجل.

النتائج: أظهرت النتيجة الرئيسية لهذه المراجعة احتمالاً منخفضاً للإصابة بعدوى سارس كوف-2 بالإضافة إلى انخفاض معدل التعرض للمضاعفات الانتهازية لدى الأطفال مقارنةً بالبالغين وكبار السن وكذلك أيضاً أشارت إلى أنَّ نتيجة الفحوصات المخبرية المتمثلة بقلة الليمفاويات لم تكن شائعة لدى الأطفال بعكس كبار السن والبالغين. لذلك قد يشير هذا التباين في نسب معدلات الإصابة والنتائج المخبرية إلى الأهمية القصوى للغدة الثايموسية التي تعمل بكامل طاقتها الوظيفية في مكافحة عدوى سارس كوف-2 عند الأطفال.

الخلاصة والتوصيات: لا يزال مرض كوفيد-19 يشكل معضلة عالمية تسبب دماراً هائلاً في جميع جوانب الحياة الاجتماعية والاقتصادية. ونظراً لعدم التوصل إلى علاج فعال في هذا الصدد، وبسبب السلوك العدواني المتحيز لسارس كوف-2 بين الفئات العمرية المختلفة الذي تم ملاحظته من خلال هذه المراجعة الأدبية؛ فإن الحاجة إلى المزيد من البحوث والتجارب السريرية لدراسة فعالية الثيموسين ألفا-1 تُشكّل أهمية قصوى من أجل فهم الدور المحتمل للغدة الثايموسية في الحماية من الإصابة بعدوى سارس كوف-2 وتخفيف أعراض ومضاعفات كوفيد-19.

الكلمات المفتاحية: كوفيد-19، سارس كوف-2، قلة الليمفاويات، الغدة الثايموسية، ثيموسين ألفا-1.

1. Introduction:

Coronavirus disease 2019 (COVID- 19) caused a world pandemic, spreading rampantly throughout the world(Hall, Laddu, Phillips, Lavie, & Arena, 2020). The disease first discovered in Wuhan city, the capital of central China's Hubei province late last year(Xu & Li, 2020). A novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS- CoV- 2) has been recognized as a causative organism. SARS- CoV- 2 belongs to coronaviruses (CoVs) family, which are a large group of viruses with a crown- like spikes. CoVs are enveloped, positive, and single- stranded RNA viruses, initially identified in the 1960s(Cui, Li, & Shi, 2019). They are considered to be zoonotic viruses targeting the respiratory and/or digestive tract of mammals, including humans, causing a vast array of illnesses ranging from mild common cold to severe disease(Kahn & McIntosh, 2005). They are divided into four main subgroups namely alpha,

beta, gamma, and delta coronavirus(Cui et al., 2019). The draft genome of SARS- CoV- 2 released on 10th of January 2020 showed that it is a Betacoronavirus that has 86.9% to 96% nucleotide sequence similarity to multiple strains of bat SARS- like coronaviruses(R. Lu et al., 2020; F. Wu et al., 2020; N. Zhu et al., 2020). Thus, It is assumed that SARS- CoV- 2 originated in bats, however, the intermediate animal reservoirs of the virus are still unknown(Shi et al., 2020; Zhou et al., 2020).

The current global cumulative total of COVID- 19 is 4.006.257 of confirmed cases with 278.892 deaths, until 11th of May 2020, and the number is drastically increasing(Data as received by WHO from national authorities by 11 May 2020"Coronavirus disease (COVID- 19) Situation Report – 112," 2020) <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>.

Although, people of all ages were infected, there was an obvious partiality in terms of the disease severity follow infection in children patients' group of age(L. Zhu et al., 2020). A certain number of studies, has been persistently reported a remarkable mild illness with no further sever complications in children patients after definitive infection with SARS- CoV- 2(X. Lu et al., 2020). The severity onset of COVID- 19 dramatically increased from children to adults, and elderly patients accordingly, along with the exclusion of patients with previous co- morbidities, has certainly left physicians and healthcare providers from all over the world puzzled. Consequently, the main design of this brief review is to objectify the possible biological reasons beyond the discriminative behavior of SARS- CoV- 2 aggressiveness, moreover, to clarify the correlation between thymus gland age- related physiological atrophy versus severity of SARS- CoV- 2 infection .

2. Objective:

The main purpose of this review is to achieve a better understanding of the discriminative behavior of SARS- CoV- 2 aggressiveness throughout all different groups of age. Thus, the predominant aims are to give a new impetus toward the unintentional omission of the effective immune role of the thymus gland in children on tackling COVID- 19. Also to discuss the potential possibility of thymosin replacement therapy utilization in the form of thymosin alpha 1, as a key booster in fighting against COVID- 19.

3. Method:

A literature review of recently published articles and literatures regarding COVID- 19 and SARS- CoV2 using science search engines including PubMed, Medline and Google Scholar.

4. Review of the Literature:

4.1 Anatomy and Physiology of The Thymus Gland

Throughout the long history of medicine, thymus gland has consistently remained as a mysterious human body organ(Liu & Ellis, 2016; Nishino et al., 2006). Thymus gland is a vital component of our

immune system, as it is the primary lymph node organ that serves as the initial place of development of T lymphocytes immune maturation. However, thymus gland is the last organ in the human body to fully understand its different mechanisms (Bodey, Bodey, Siegel, & Kaiser, 1997; Csaba, 2016; Domínguez-Gerpe & Rey- Méndez, 2003).

The thymus gland is a softly encapsulated bilobed organ located in the upper mediastinum and the upper part of the lower mediastinum close to the pericardium and deep to the sternum (Cooper, 1832; Safieddine & Keshavjee, 2011). Moreover, it is of dual embryonic origin. Thymic epithelium develops from the ventral diverticular epithelium of the third pharyngeal pouch, together with thyroid and parathyroid gland, during the sixth week of gestation (Anastasiadis & Ratnatunga, 2014). The thymus produces several polypeptides which cause differentiation of the lymphocytes. A few of these polypeptides have been chemically categorized and precisely three of them have been decoded and synthesized including thymosin alpha- 1, thymopoietin and the serum thymic factor (Fabien, Auger, & Monier, 1988). Lately, fully defined synthetic thymic hormones have been developed. Thus, it is no longer a question of deciding whether thymic hormones exist, but rather of clarifying their biological significance and possible clinical applications.

4.2 Thymosin Alpha- 1 and Its Clinical Applications

Thymosin alpha is a peptide biologically composed of twenty eight of amino acid residues. It has high hydrophilic and acidic properties, which more likely to be uncommon. Surprisingly, this protein does not have any hydrophobic regions, which definitely make its passive transport via lipid membranes quite impossible (Xue et al., 2013). It can also be referred to as thymosin alpha- 1, which virtually means that it is the first remnant of the precursor protein prothymosin- alpha.

Thymosin alpha- 1 (ZADAXIN[®]) has been launched onto the market for the treatment of number of diseases (Elizondo- Riojas, Chamow, Tuthill, Gorenstein, & Volk, 2011; J. Wu et al., 2013; Zhang, Chen, Yang, Duan, & Tang, 2009). Thymosin alpha- 1 functions in myeloid and plasmacytoid dendritic cells through TLR2 and TLR9 (Toll- like receptors) to activate and differentiate dendritic cells and T lymphocytes and to induce cytokines such as interleukin- 2 and interferon- gamma. Moreover, multiple studies (Ahmed et al., 1979; Peng et al., 2008; Yao et al., 2007) have been carried out to determine the immunoregulatory role of thymosin alpha- 1. Subsequently, results have shown that thymosin alpha- 1 cannot only enhance T lymphocytes maturation efficiency but also stimulate differentiation of stem cells into CD4⁺/CD8⁺ T lymphocytes and balanced CD3⁺/CD4⁺/CD8⁺ T lymphocytes of peripheral blood mononuclear cells. Therefore, thymosin alpha- 1 enable to eliminate and kill virally infected cell directly by stimulating natural killer cells (NK) and cytotoxic lymphocytes (CD8⁺ T cell) (Rustgi, 2005).

4.3 The Infection of SARS- CoV- 2 Among Children Patients

Many confirmed cases of SARS- CoV- 2 infection has been consistently reported among children and infant patients, since December 2019 (Stower, 2020). Nonetheless, the extreme combativeness of

SARS- CoV- 2 in adult and elderly patients, excluding patients with previous co- morbidities, which lead to a distinctive sever complications with a great risk of mortality. It tends to be more mild with no further sever complications among children patients, hence, the mortality rate in this group of age is remarkably low(Dong et al., 2020).

Li Zhu et al.(L. Zhu et al., 2020), had documented the main clinical characteristics and laboratory findings in a number of ten patients with age ≤ 18 years old. Clinical findings, exhibited that 40% of those patients endured fever, while 30% experienced cough as typical symptoms. Surprisingly, laboratory findings showed nether leucopenia nor lymphopenia. Indicating more comprehensive immune system in this age group ≤ 18 years old individuals, which might be due to the existence of the fully functioned thymus gland. However, the study reported no significant complications or serious illness among those individuals.

Another study(X. Lu et al., 2020), had investigated the spectrum of COVID- 19 disease, described the range of infection caused by SARS- CoV- 2 in children. The ultimate outcome of the report revealed that, unlike infected adults, the majority of infected children appear to have a milder clinical trajectory. Therefore, children are considered to be less vulnerable to COVID- 19, than any other individual group.

4.4 The Paramount Importance of Thymus Gland as a Biological Shelter Against SARS- Cov- 2 in Children

Thymus gland is considered to be an extremely crucial organ, when it comes into defending against general viral infections. It is a potential part of the lymphatic system in which T lymphocytes develop and multiply(Zdrojewicz, Pachura, & Pachura, 2016). The thymus gland generates progenitor cells that mature into T- cells, so called "thymus- derived cells".

Thymus gland is an age- related organ(Francis, Glazer, Bookstein, & Gross, 1985), thus, its mass gradually get smaller in size within ageing(Rezzani, Nardo, Favero, Peroni, & Rodella, 2014). Therefore, thymus gland is definitely unique in the way that it is larger in children, while much smaller in adults, and merely a remnant fatty tissue in elderly population(Francis et al., 1985). Hence, unlike children, adults and elderly population are more vulnerable to SARS- CoV- 2 infection and prone to develop further sever complications caused by COVID- 19.

On the other hand, lymphopenia was a less documented laboratory finding in children(Tan et al., 2020; L. Zhu et al., 2020). In contrast, it was a well- recognized finding among adults and elderly individuals. The reason beyond the reported paradox might be due to the functionally wrecked aged thymus gland in other individuals than children . For that reason, efficacy of the thymus gland function should be evolved into consideration, whenever providing the initial healthcare to COVID- 19 patients.

4.5 Invigoration and Regeneration of Thymus Gland Might be The Key Booster in Tackling COVID-19

There are a certain number of hormones produced by the thymus gland encompassing thymosin, which is incredibly important in stimulating both T- cells' production and development in order to shape the ultimate human immune system (Moretti, Oikonomou, Garaci, & Romani, 2015). Furthermore, thymosin dose also play a major role in antibodies formation by ameliorating the necessary development of B- cells. Therefore, thymosin replacement therapy in the form of thymosin alpha 1, in adult and elderly patients with COVID- 19 (King & Tuthill, 2016). This could be the hidden game changer in controlling the sever complications caused by COVID- 19, along with, eliminating the pathological and clinical progress of COVID- 19 and bring it to a halt.

5. Results:

The ultimate results of this review had exhibited low possibility of SARS- CoV- 2 infection as well as low exposure rate to opportunistic complications of COVID- 19 among children, compared to adults and elderly individuals. Moreover, unlike adults and elderly patients infected with SARS- CoV- 2 lymphopenia was a less reported laboratory finding in children. Therefore, this discrepancies in infection rates and laboratory results may potentially indicate the paramount importance of fully functioned thymus gland in fighting against SARS- CoV- 2 infection in children.

6. Conclusion and Recommendations:

COVID- 19 remains a global dilemma causing massive devastation on all aspects of social life. As no significant cure has been reached in this regard, and due to the discriminative behavior of SARS- CoV- 2 aggressiveness throughout all different groups of age detected through this literature review. Hence, more research and clinical trials on thymosin alpha- 1 efficacy are needed in order to understand the possible role of the thymus gland in protecting against SARS- CoV- 2 infection and minimizing COVID- 19 symptoms and complications. This may help to take a step forward in the development of more effective precaution methods and an ideal therapeutic paradigm.

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