Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Obesity Medicine 19 (2020) 100283

Contents lists available at ScienceDirect

Obesity Medicine

journal homepage: www.elsevier.com/locate/obmed

Association of high level gene expression of ACE2 in adipose tissue with mortality of COVID-19 infection in obese patients

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ARTICLE INFO

Keywords:
Adipose tissue
Angiotensin converting enzyme 2 receptor
Coronavirus
Severe acute respiratory syndrome coronavirus 2
COVID-19

ABSTRACT

Introduction: Obese patients have an increased risk of COVID-19 critical illness leading to ICU admission or death compared to normal weight individuals. SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) receptor is a critical step mediate virus entry into target cells. Articles have alluded that the level of ACE2 gene expression in adipose tissue is higher than lung tissue, but a PubMed search found no results in articles to demonstrate this. The aim of this study was to investigate ACE2 gene expression in adipose tissue and lung tissue using a public database.

Material and methods: A search of a public gene expression database to investigate ACE2 gene expression in human tissues.

Results: ACE2 gene expression was present in both visceral and subcutaneous adipose tissues. The gene expression profile demonstrated that ACE2 gene expression was higher in human visceral and subcutaneous adipose tissues than human lung tissue.

Conclusion: This study demonstrates that ACE2 gene expression is higher in visceral and subcutaneous adipose tissue than that in lung tissue, a major target tissue affected by SARS-CoV-2 infection. This suggests a mechanism by which excess adiposity may drive greater infection severity in patients with COVID-19.

1. Introduction

There is pressing urgency to understand the pathogenesis of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes Coronavirus disease 2019 (COVID-19) (Al-Benna, 2020a; Al-Benna and Gohritz, 2020a, 2020b). As of July 9, 2020, this global pandemic and public health emergency has caused 12,180,154 accumulated cases and 552,380 deaths, with an overall mortality rate of about 1% (Worldometer, 2020). Obese patients have an increased risk of COVID-19 critical illness leading to ICU admission or death compared to normal weight individuals (Hajifathalian et al., 2020; Onder et al., 2020). The complications of obesity are complex, and a number of other factors may affect COVID-19 severity (Edler et al., 2020; Englmeier, 2020; Korakas et al., 2020; Moriconi et al., 2020; Pinheiro et al., 2020). More than 500 million individuals are obese (body mass index $\geq$ 30 kg/m^2) globally, and thus understanding the mechanisms by which excess adiposity drives greater infection severity is critical for solving this global public health threat (World Health Organization, 2020).

Angiotensin-converting enzyme 2 (ACE2) facilitates cellular entry of SARS-CoV-2 (Ziegler et al., 2020). ACE2 is expressed in many human tissues including the lungs, serving as the doorway by which the virus can enter and spread (Ziegler et al., 2020). During infection, ACE2-expressing tissues become direct targets, resulting in serious pathological changes and progressive multiple organ failure or even death in severe cases (Ziegler et al., 2020). Evidence has been accumulating that besides lung injury, SARS-CoV-2 also damages the human heart, kidneys, liver, nervous system and skin (Edler et al., 2020). In addition, the influence of SARS-CoV-2 infection on adipose tissue needs further investigation (Korakas et al., 2020). Articles have alluded that the level of ACE-2 expression in adipose tissue is higher when compared to that in the lung tissue (Belančić et al., 2020). A PubMed search found no articles to support this. The aim of this article was to search a gene expression database to find ACE2 gene expression in human adipose tissue and human lung tissue.

Abbreviations: ACE, angiotensin converting enzyme; ACE2, angiotensin converting enzyme-2; AT1, angiotensin 1; AT2, angiotensin 2; AT(1–7), angiotensin (1–7); COVID-19, Coronavirus disease 2019; SARS CoV, severe acute respiratory syndrome coronavirus; SARS CoV-2, severe acute respiratory syndrome coronavirus-2.

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https://doi.org/10.1016/j.obmed.2020.100283
Received 9 July 2020; Received in revised form 13 July 2020; Accepted 14 July 2020
Available online 18 July 2020

2. Material and Methods

A search of the HCCDB gene expression database (http://lifeome.net/database/hccdb/home.html) for ACE2 expression in human adipose tissue and lung tissue (Lifeome, 2020). All data is publicly available online.

3. Results

The gene expression database included ACE2 expression profile. The gene expression profile demonstrated that ACE2 gene expression was present in human subcutaneous adipose tissue and human visceral adipose tissue (Fig. 1).

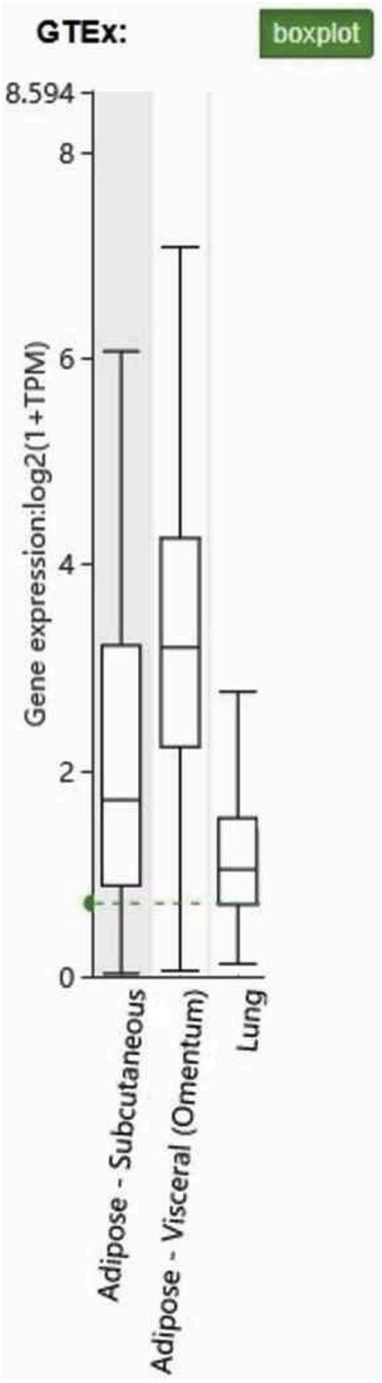

Fig. 1. ACE2 gene expression in human subcutaneous adipose tissue, human visceral adipose tissue and human lung tissue.

The gene expression profile demonstrated that ACE2 gene expression was higher in human subcutaneous adipose tissue and human visceral adipose tissue than in human lung tissue. (Fig. 1).

4. Discussion

ACE2 is recognised as the receptor for the entry of SARS-CoV-2 into host cells (Zhou et al., 2020; Ziegler et al., 2020). High expression of ACE2 (e.g. in bronchial airway epithelium) has been demonstrated to contribute to COVID-19 morbidity and severity patterns but limited studies have not looked at adipose tissue (Edler et al., 2020). This study demonstrates that ACE2 expression in adipose tissue is higher than that in lung tissue, a major target tissue affected by SARS-CoV-2 infection. Although, ACE2 up-regulation may be detrimental for COVID-19 in obese patients, this alone may not explain the severity of COVID-19 among obese patients. Interestingly, a study reported no difference in ACE2 expression between adipose tissues of eutrophic patients and obese patients (Pinheiro et al., 2020). In addition, there is no difference in the expression of ACE2 protein by adipocytes and adipose progenitor cells between individuals with obesity and those without (Radzikowska et al., 2020). While obesity does not appear to have an effect on ACE2 expression, obese patients have more adipose tissue and consequently an increased number of ACE2-expressing cells and subsequently a larger amount of ACE2 proteins.

Excessive adipose tissue in obesity secretes angiotensin 2 (AT2), which is a hormone with inflammatory properties and is generated in the renin–angiotensin system (RAS) pathway. Obesity and insulin resistance are strongly linked with RAS activity. Furthermore, oxidative stress and inflammatory response along with mitochondrial dysfunction modulate the function of RAS (Imafidon and Akomolafe, 2019; Nijhawan et al., 2019). Once RAS function is compromised, it causes widespread dysfunction in most tissues, through the aforementioned deleterious processes (Patel and Verma, 2020). At the cellular level, renin forms angiotensin I (ATI) from angiotensinogen. Angiotensin converting enzyme (ACE) cleaves AT1 forming angiotensin 2 (AT2) (Patel and Verma, 2020). AT2 acts at cell surface type I G protein-coupled receptors, AT1Rs then promote a pathological cascade including insulin resistance, oxidative stress, inflammation and vasoconstriction (Patel and Verma, 2020). Reduction of the phosphoinositol-3 kinase activity due to elevated free fatty acid levels is potentiated by AT2 and consequently insulin-stimulated glucose uptake is increased by RAS inhibition. Blockade of the AT1R has been shown to stimulate the differentiation of adipocytes that store free fatty acids, of which leads to reduced plasma free fatty acid levels and decreased insulin resistance (Singh and Rai, 2019). RAS activity can also be upregulated by insulin resistance. This can in turn promote a series of linked pathophysiological issues such as inflammatory diseases, as well as the metabolic disorders associated with obesity (Mediouni et al., 2020). In fact, the major effects of AT2 are mediated by AT1R and angiotensin 2 type 2 receptor (AT2R). Overexpression of angiotensinogen increases adiposity, which is seen through hypertrophy of adipocytes, inflammation and increased resistance to insulin. RAS inhibition can improve and even reverse these obesity related alterations in adipose tissue (Meng et al., 2020). The decrease in glucose-mediated insulin secretion is related with lower pancreatic insulin content and upregulated AT1R protein expression in obesity. In principal, β-cell dysfunction is strongly associated with AT1R upregulation, which accelerates glucose intolerance and insulin resistance, via a decrease in plasma glucagon-like peptide-1. In contrast, RAS blockade induces improvement in β-cell function and insulin sensitivity (Meng et al., 2020). The general progression of atherosclerotic disease is also influenced by RAS, as well as its primary mediator AT2. The mechanisms of this process include inflammation, disruption of fibrinolytic balance and endothelial dysfunction. The inhibitors of RAS such as ACE inhibitors (ACEI) and angiotensin receptor blockers act either by depleting the generation of

AT2 or by blocking the binding of AT2 to its receptors (Meng et al., 2020). The expression of ACE2 is substantially increased in patients with type 2 diabetes, who are treated with ACEI and ARBs (Meng et al., 2020). Similarly, treatment of hypertension with ACEIs and ARBs, results in an upregulation of ACE2 (Meng et al., 2020). Therefore, the increased expression of ACE2 would facilitate COVID-19 due to spreading of SARS-CoV-2. As the ACE2 protein is the receptor that facilitates SARS-CoV-2 entry into cells, the idea that treatment with RAS blockers might increase the risk of developing a severe acute lung injury and fatal acute respiratory distress syndrome in COVID-19 infection has been promoted but not proven.

'Cytokine storm', that is, one of the mechanisms responsible for the severity of COVID-19, is the hyperactivation of the immune system. It is promoted by the activation of $CD14^+$ and $CD16^+$ inflammatory monocytes producing an increased level of interleukin-6 (IL-6), interferon-γ and other pro-inflammatory cytokines (Abbas et al., 2020; Belančić et al., 2020; Kim and Cho, 2019; Mattioli et al., 2020). In those with obesity, increased inflammatory activity in the liver and visceral fat is independently correlated with increased levels of IL-6, which might have an additive/synergistic role in promoting greater severity of COVID-19. Taking the abovementioned facts into account, the adipose tissue synthesizes several pro-inflammatory adipokines and cytokines which can diminish the immune response and, thus, could constitute the link between obesity and the severity of COVID-19. In addition, a number of adipokines secreted by the adipose tissue are associated, mainly negatively, with pulmonary function (Xu and Pan, 2020).

Endothelial dysfunction is present in obesity and is indeed a final common pathway of a cluster of comorbidities, such as hypertension, diabetes, and dyslipidemia (Hamilton et al., 2002, 2004; Al-Benna et al., 2006). In obesity, the severity of endothelial dysfunction correlates with the degree of visceral adiposity, and studies have indicated the roles of pro-inflammatory factors and oxidative stress (Nijhawan et al., 2019). In addition to that chronic scenario, acute endothelial damage occurs, induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) endothelial tropism, which binds to the transmembrane angiotensin-converting enzyme II receptor (Ziegler et al., 2020). Vascular endothelial cell apoptosis ensues and, in conjunction with the aforementioned acute "cytokine storm," promotes the settings for lung microvascular dysfunction, vascular leakage, alveolar oedema, and ultimately hypoxia. Pro-inflammatory cytokines also increase the expression of adhesion molecules, resulting in endothelial activation and pro-coagulant changes, worsening microvascular flow and tissue perfusion (Belančić et al., 2020). The obesity-driven chronic inflammation and impaired fibrinolysis contribute to increase the risk of developing thrombosis, which currently seems to be one of the mechanisms potentially involved in worsening lung damage and in death Abbas and Kamel (2020).

5. Conclusions

Human ACE2 gene expression is higher in both human subcutaneous adipose tissue and human visceral adipose tissue than human lung tissue. This critical discovery implies that adipose tissue is susceptible to SARS-Cov-2 infection via the ACE2 receptor. Future research including nucleic acid detection and pathological diagnosis for adipose tissue can determine if SARS-Cov-2 can infect adipose tissue and establish the mechanisms involved. Patients with obesity haver a higher risk of COVID-19 and a poorer prognosis than those without obesity (Hajifathalian et al., 2020; Onder et al., 2020). Given the higher death rates, it is important that obese patients pay great attention to protection from SARS-Cov-2 infection, and close monitoring and treatment should be delivered to these obese patients in the early stages of COVID-19 (Al-Benna, 2020b, 2020c). As obesity is such a major risk factor for a negative clinical prognosis, weight loss *per se* is a viable strategy (Rahmati-Ahmadabad and Hosseini, 2020).

Funding

None.

Ethics approval

Ethics approval was not required. The study exclusively used publicly available data.

Consent to participate

Not required.

Patient consent for publication

Not required.

Availability of data and material

All data is publicly available.

Authors' contributions

S Al-Benna: protocol/project development; data collection and management; data analysis; manuscript writing/editing.

Declaration of competing interest

None.

CRediT authorship contribution statement

Sammy Al-Benna: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing.

Acknowledgements

None.

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