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.

Archives of Medical Research 53 (2022) 228–230

OPINION PAPER

Obesity and Severe COVID-19 in the Young: Is Downregulation of miR-126 a Piece of the SARS-COV2 Pathogenicity Puzzle?

Obesity has recently been identified as a risk factor for worse clinical outcomes from novel Severe Acute Respiratory Syndrome Coronavirus-2(SARS-CoV2) infection, known as Coronavirus Disease 19 (COVID-19) (1,2). Visceral fat (VAT) has been proposed as a marker of increased COVID-19 susceptibility and severity (2). The severity of COVID-19 appears to rise in the obese young[3]. It has been suggested that in populations with a high prevalence of obesity, COVID-19 will affect younger individuals more than previously reported (3). The mechanisms linking obesity to higher COVID-19 severity in the young are not yet well defined although several different mechanisms have been suggested (1,2). COVID-19 represents a highly contagious condition that can cause deadly comorbidities such as acute respiratory distress syndrome (ARDS), hyper-inflammatory condition and thrombogenicity (4,5). ARDS represents a life-threatening condition of seriously ill patients, characterized by disruption of the alveolar-capillary barrier (6). Severe acute respiratory failure is considered as the more likely cause of death among patients with COVID-19 (4). Alveolar epithelial cell type II represents the main target of SARS-CoV-2 virus leading to COVID-19 related ARDSb (4). It has been detected that the need for advanced respiratory support is significantly higher in obese patients than in non-obese ones (1,2). COVID-19 patients also appear to have a higher rate of thrombosis (5). People with COVID-19 have been demonstrated to be at increased risk of developing coagulopathy associated with poor clinical outcomes (4,5). SARS-CoV2 infection has been proved to cause the release of tissue factor (TF)-positive extracellular vesicles (EVs) into the circulation (5). TF-positive EVs appear to be likely to drive thrombosis in patients with COVID-19 (5). Interestingly, increased activity of circulating TF-positive EVs has been correlated to higher severity and mortality in COVID-19 patients (7). Furthermore, SARS-CoV-2 infection has been recognized to cause a hyperinflammatory reaction through the excessive release of cytokines, a condition known as "cytokine storm" that consists of an unrestrained secretion of several pro-inflammatory cytokines including IL-6 (8). Besides adipocytes, adipose tissue has also been demonstrated to contain mesenchymal stem cells (9). Adipose tissue has been documented to be an important source of stem cells, called adipose-derived stem cells, that release crucial active molecules for wound healing, control the immune system, reduce inflammation, and home in on damaged tissues (9,10). Adipose-derived stem cells have been proved to utilize membrane-derived small vesicles, named as cell-derived extracellular vesicles (EVs), to repair injured tissues (9,10). EVs, including exosomes (Exos), have been shown to release a few microRNAs (mRNAs), including MicroRNA-126 (miR-126), in both physiological and pathological conditions (9,10). In obesity, visceral fat accumulation has been shown to cause adipocyte and adipose tissue function abnormalities (9). It has been verified that obesity reduces the pro-angiogenic potential of adipose tissue stem cell-derived EVs, by impairing miR-126 content (5). miR-126 levels appear to be considerably lower in obese EVs patients than in normal EVs ones (9). Endothelial progenitor cells (EPCs)-Exos have been revealed to hamper pulmonary inflammation and injury (11,12). Exos derived from EPCs have been detected to improve acute lung injury by transferring miR-126 (11). Both MiRNA-126-3p and miRNA-126-5p have been indicated to maintain the lung alveolar epithelial barrier integrity (6). miR-126-3p and miR-126-5p represent the two mature miRNAs that the miR-126 gene gives rise (12). Transfer of miRNA-126 has been described as a novel mechanism by which exosomes can restore damaged alveolar epithelium (11). Modification of EPCs through miR-126 knockdown has been noted to reduce their Exos function in vitro implying that the potential of EPC-Exos to protect lung is inherited by the horizontal shuttled miR-126 (6,12,13). Concordantly, Exos with low levels of miRNA-126 do not exert their beneficial effect (10). Obesity relates to chronic low-grade inflammation with dysfunctional hypertrophic adipocytes producing an excessive amount of pro-inflammatory cytokines such as Interleukin-6 (IL-6) (8). Interestingly, miR-126 has been stated to counteract inflammation by reducing several pro-inflammatory cytokines including IL-6, while miR126 inhibitors have been found to produce opposite results (14). Remarkably, circulating miR-126 has been revealed to reduce blood thrombogenicity via regulating post-

☆ In memory of my Dad Sossio Mormile

https://doi.org/10.1016/j.arcmed.2021.08.003

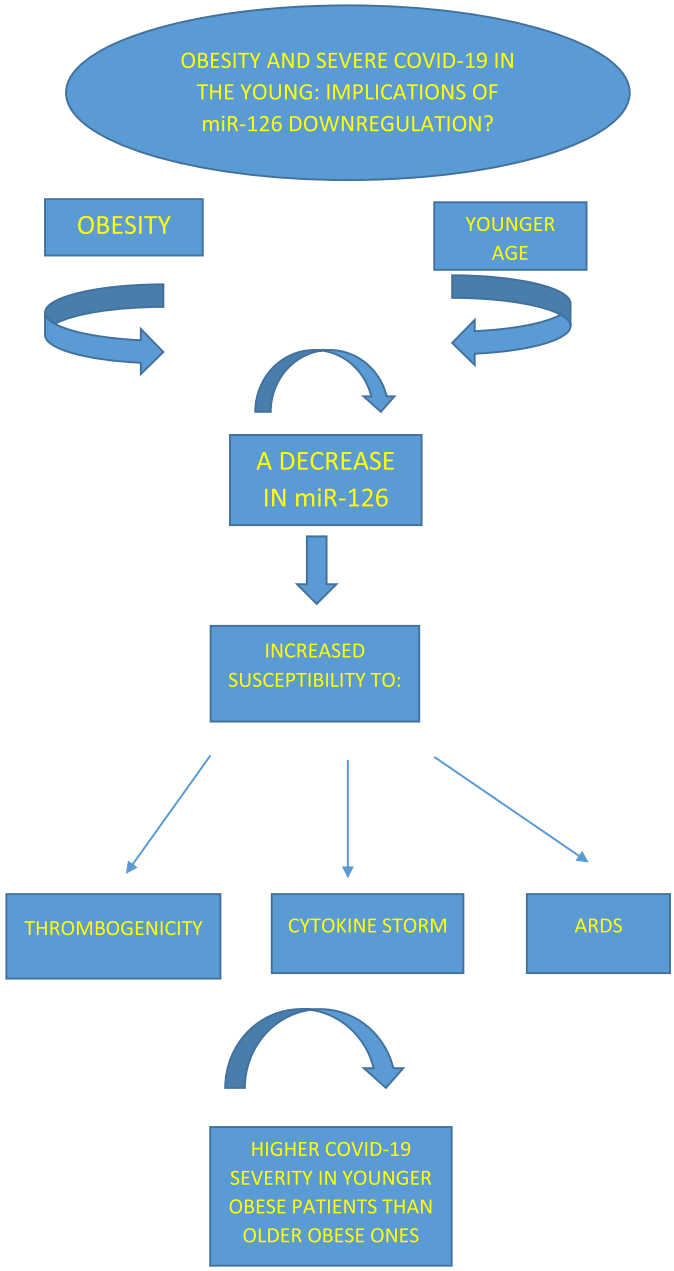

Figure 1. Representative scheme of the impact of obesity and younger age on miR-126 down-regulation leading to increased susceptibility to thrombogenicity, cytokine storm and ARDS resulting in higher COVID-19 severity in younger obese patients than older obese ones.
NAME FOR TOP OF PAGES: Mormile/*Archives of Medical Research* 53 (2022) x–x

transcriptional TF expression (12). On the contrary, it has been described that low miR-126 levels are linked to significantly increased levels of TF protein and TF-mediated thrombogenicity (7). Notably, it has been recognized that there is an aging/senescence-associated miR-126-3p upregulation (15). miR-126-3p is considered an aging biomarker (15). An important age-associated increase in plasma miR-126-3p levels has been documented in healthy individuals (15). miR-126-3p synthesis and release appear to be significantly increased in senescent cells in comparison to younger ones (15). It has been suggested that plasma miR-126-3p is significantly higher in the oldest than in the youngest as a related compensatory mechanism (15). With respect to the above, I suppose that (Figure 1) younger obese patients may be at higher risk for severe illness from COVID-19 than older obese ones because of ageing-related miR-126-3p down-regulation considering that miR126 may counteract deadly comorbidities that contribute to the increased severity of COVID-19 including ARDS, blood thrombogenicity and the cytokine storm.

I hypothesize that the condition of age-related lower circulating miR-126 levels may become increasingly strident in obese young subjects when compared to obese older individuals contributing to the severity of COVID-19 in this category of patients. Research studies are required to verify whether therapeutic strategies aimed at increasing or restoring miR-126 activity may improve outcome among critically ill patients hospitalized with COVID-19 notwithstanding the importance of implementing interventions aimed to reduce or prevent obesity at any age.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgments

None

References

1. Zhang F, Xiong Y, Wei Y, et al. Obesity predisposes to the risk of higher mortality in young CO VID-19 patients. J Med Virol 2020;92:2536–2542.
2. Watanabe M, Caruso D, Tuccinardi D, et al. Metabolism 2020;11:154319.
3. Kass DA, Duggal P, Cingolani O. Obesity could shift severe COVID-19 disease to younger ages. Lancet 2020;395:1544–1545. doi:10.1016/S0140-6736(20)31024-2.
4. Li X, Ma X. Acute respiratory failure in COVID-19: is it "typical" ARDS? Crit Care 2020;24:198.
5. Eljilany I, Elzouki AN. D-Dimer, Fibrinogen, and IL-6 in COVID-19 Patients with Suspected Venous Thromboembolism: A Narrative Review. Vasc Health Risk Manag 2020;16:455–462.
6. Mizuta Y, Akahoshi T, Guo J, et al. Exosomes from adipose tissue-derived mesenchymal stem cells ameliorate histone-induced acute lung injury by activating the PI3K/Akt pathway in endothelial cells. Stem Cell Res Ther 2020;11:508.
7. Rosell A, Havervall S, von Meijenfeldt F, et al. Patients with COVID-19 Have Elevated Levels of Circulating Extracellular Vesicle Tissue Factor Activity That Is Associated with Severity and Mortality. Arterioscler Thromb Vasc Biol 2020;41:878–882. doi:10.1161/ATVBAHA.120.315547.
8. Korakas E, Ikonomidis I, Kousathana F, et al. Obesity and COVID-19: immune and metabolic derangement as a possible link to adverse clinical outcomes. Am J Physiol Endocrinol Metab 2020;319:E105–E109.
9. Kokai LE, Marra K, Rubin JP. Adipose stem cells: biology and clinical applications for tissue repair and regeneration. Transl Res 2014;163:399–408 Epub 2013 Dec 4. PMID: 24361334. doi:10.1016/j.trsl.2013.11.009.
10. Togliatto G, Dentelli P, Gili M, et al. Obesity reduces the pro-angiogenic potential of adipose tissue stem cell-derived extracellular vesicles (EVs) by impairing miR-126 content: impact on clinical applications. Int J Obes (Lond) 2016;40:102–111.
11. Zhou Y, Li P, Goodwin AJ, et al. Exosomes from endothelial progenitor cells improve outcomes of the lipopolysaccharide-induced acute lung injury. Crit Care 2019;23:44. doi:10.1186/s13054-019-2339-3.
12. Witkowski M, Weithauser A, Tabaraie T, et al. Micro-RNA-126 Reduces the Blood Thrombogenicity in Diabetes Mellitus via Targeting of Tissue Factor. Arterioscler Thromb Vasc Biol 2016;36:1263–1271.
13. Wu X, Liu Z, Hu L, et al. Exosomes derived from endothelial progenitor cells ameliorate acute lung injury by transferring miR-126. Exp Cell Res 2018;370:13–23. doi:10.1016/j.yexcr.2018.06.003.
14. Yang HH, Chen Y, Gao CY, et al. Protective Effects of MicroRNA-126 on Human Cardiac Microvascular Endothelial Cells Against Hypoxia/Reoxygenation-Induced Injury and Inflammatory Response by Activating PI3K/Akt/eNOS Signaling Pathway. Cell Physiol Biochem 2017;42:506–518.
15. Olivieri F, Bonafè M, Spazzafumo L, et al. Age- and glycemia-related miR-126-3p levels in plasma and endothelial cells. Aging (Albany NY) 2014;6:771–787.

RAFFAELLA MORMILE

Division of Pediatrics and Neonatology, Moscati Hospital, Aversa, Italy

Address reprint requets to: Raffaella Mormile, Division of Pediatrics and Neonatology, Moscati Hospital, Via A. Gramsci 81031, Aversa-Italy; Phone: (+39) 3392045468; FAX: (+39) 0815001503

E-mail address: raffaellamormile@alice.it

Revised July 28, 2021

Received for publication June 5, 2021; accepted August 5, 2021 (ARCMED-D-21-00747).