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Journal of Endocrinology Research
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ARTICLE

SARS-CoV-2-the Unforeseen Peril of David Winning Against Goliath: the Immune Giant Collapsing Under Its Own Rampaging Cytokine Storm

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ARTICLE INFO

Article history
Received: 12 November 2020
Accepted: 27 November 2020
Published Online: 30 December 2020

Keywords:
SARS-CoV-2
Covid-19
Cytokine Storm
ACE2
Skeletal Muscle Mass
Visceral Fat
Triglycerides
CRP
Cortisol
Remdesivir
Leptin
Ghrelin
Free T3
IGF-1
HDL
TMPRSS2
ADAM17
Angiotensin
nsp12

ABSTRACT

We examined SARS-CoV-2 (Covid-19) available treatments and prophylactic methods that included interventions associated with inhibiting the "type II transmembrane serine protease" (TMPRSS2) to limit the fusion between the Covid-19 Spike proteins and ACE2 receptors, or newly developed therapeutics like Remdesivir that interferes with the viral RNA replication. We explored the dilemma of ACE2 receptors that have a protective function against high blood pressure associated disorders, yet, they serve as the viral points of entry, elevating the probability of infection. Human tissues' analysis reveals a higher ACE2 expression in adipose tissue, placing obesity-related conditions in the eye of the pandemic storm. It primarily exposes males due to the surge of ACE2 receptors in the testes along with other tissues. Males manifest a relatively higher positive ACE2 correlations with certain immune cells in the lungs, thyroid, adrenals, liver and colon, while females evidence higher ACE2 correlations with immune cells in the heart. The remaining tissues' ACE2/immunity expressions are equivalent in both sexes, indicating that despite its preference for males, the threat of Covid-19 can easily target females. Recent reports indicate that Covid-19 is empowered by hindering the critical process of viral recognition during the adaptive immune response leading to the "cytokine storm", the aggravated immune response that indiscriminately perseveres, rampaging the host's vital organs. Sedentary lifestyle, age-related hormonal imbalance, and adiposity induced inflammation predispose the body to the immune collapse following Covid-19 invasion, spotlighting the detrimental aftermath of metabolic dysfunction, and excess food consumption provoked by elevated cortisol and dysregulated appetite hormones. ACE 2 expression is suppressed in the skeletal muscle, rendering fitness and weight management an effective Covid-19 preventive intervention, along with social distancing, hygiene, and facial coverings. Physical activity, or exercise alternative methods have recently demonstrated statistically significant reductions of the inflammatory marker C-Reactive Protein (CRP), triglycerides, visceral fat, cortisol and the orexigenic hormone ghrelin, juxtaposed by optimal increases of IGF-1, skeletal muscle mass, Free T3, HDL, and the anorexic hormone leptin.

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DOI: https://doi.org/10.30564/jer.v2i1.2517

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) related to the Coronavirus disease 2019 (Covid-19) is currently recognized as a global health crisis. In a way, it resembles the initially unforeseen results of the David and Goliath battle, the virus against all our medical advances, ultimately leading to devastating consequences that range from lockdowns and economic disruption to family and personal tragedies with over a million deaths worldwide.

The purpose of this review was to analyse the six primary strategies currently available in the prevention and treatment of SARS-CoV-2: (1) Inhibit the "type II transmembrane serine protease" (TMPRSS2) that primes both ACE2 receptors and the Covid's Spike (S1, S2) glycoproteins to facilitate their fusion. (2) Increase shedding of the ACE2 receptors, induced by "A Disintegrin And Metalloprotease 17" (ADAM17) that may potentially restrict the spread of the disease. (3) Obstruct the action of the Nucleocaspic (N) protein involved in the replication of the viral DNA. (4) Prophylactic measures or techniques to harness the rampaging inflammatory response leading to the "cytokine storm" that promotes high mortality rates. (5) Protect against infection with increased hygiene, face coverings and social distancing. (6) Capitalize on wellbeing via a lifestyle that promotes optimal weight, fitness and hormonal balance to prevent and/or defend against infection.

2. The Dilemma of Ang II and ACE2 Receptors

The imminent fusion between Covid-19 Spike (S) proteins and angiotensin enzyme-2 (ACE2) receptors preludes the viral entry into human cells, placing the focus on the hierarchic multi-dimensional activity of the renin angiotensin system (RAS) [1]. Angiotensin enzyme (ACE) cleaves Ang II from Ang I, hence increasing Ang II , which can be then transformed into Ang III and IV. Angiotensins are vasoconstrictor hormones that increase blood pressure. ACE2 catalyses Ang II, generating Ang (1-7), a vasodilator agent that features antioxidant and anti-inflammatory effects; ACE2 metabolizes Ang I into Ang (1-9) which performs a protective function on the heart, the vessels, and possibly the kidneys; while ACE, which actually determines the Ang II production results in the degradation of Ang (1-7) [2,3,5,6]. Based on this simultaneous mosaic of processes, ACE inhibitors decrease the production of Ang II, and increase the Ang (1-7) in the system. With regards to Covid-19, as ACE inhibitors compromise the levels of Ang II, they reduce the concentrations of "A Disintegrin And Metalloprotease 17" (ADAM17) which is normally promoted by Ang II. ADAM17 can cleave ACE2 from the cellular membrane, shedding it into body fluids, thus restricting the viral S proteins' fusion with ACE2 receptors, consequently, limiting infection [6,7]. The ADAM17 cleavage of ACE2 that can be potentially beneficial to suppressing the entrance and spread of the virus, is an antagonist to the "type II transmembrane serine protease" (TMPRSS2) which cleaves both the ACE2 receptor and the viral S proteins, preparing them to fit into each other, hence facilitating the ominous proliferation of Covid-19 [8]. This priming action of TMPRSS2 is necessary for the S/ACE2 fusion that commences the viral advancement into the body.

Ang II is functional in upregulating ADAM17 that is involved in the ACE2 shedding thus restricting Covid-19 access into the cell; however, Ang II increases inflammation, oxidative stress and has been associated with atherosclerosis [9]; ACE2 catalyses Ang II, acting as a protective mechanism against the blood pressure increase induced by Ang II that would otherwise be deleterious to diseases such as hypertension, diabetes, and cardiovascular illness [10]. ACE2 receptors protect the lungs from pulmonary vasoconstriction and remodelling, they prevent myocardial hypertrophy and high blood pressure; yet, by the same token, they serve as a Covid-19 gateway, exposing the body to the deleterious effects of the virus. Ang II increases pulmonary edema and vascular permeability that can result in ARDS; it induces atherosclerosis, hypertension and possible heart failure; yet it is involved in the shedding of ACE2 receptors via ADAM17 which ultimately reduces the chances of viral entry. The lethal effects of SARS-COV-2 are more pronounced in pre-existing cardiac and pulmonary disorders, spotlighting the dualistic function of both Angiotensin II and ACE2 receptors that can be both an advantage and a disadvantage, rendering treatment insurmountable when SARS-CoV-2 is combined with dysfunctional vital organs.

3. The Complex Testimony of Human Tissues

SARS-CoV-2 affects the upper respiratory track with flu-like symptoms, and the lower respiratory system by symptoms including difficulty breathing that may evolve into pneumonia or the Acute Respiratory Distress Syndrome (ARDS). Counterintuitively, the lungs do not encapsulate the greatest multitude of ACE2 receptors. The analysis of 31 normal human tissues revealed that adipose tissue, heart, testes, kidneys and small intestines had the highest ACE2 expression, rendering these organs the primary Covid-19 targets, representing the most vulnerable points of viral entry. The lungs, adrenal gland, bladder, liver and colon manifest a moderate ACE2 expression, while the muscle, the brain, blood vessels, spleen and bone marrow

 DOI: https://doi.org/10.30564/jer.v2i1.2517

evince the lowest ACE2 expression [11,12]. These investigators also explored male, female, young and old immune cells including (1) B cells, lymphocytes that develop into plasma cells producing antibodies; (2) natural killer cells (NK); (3) CD8+ cells which include cytotoxic T cells that specifically target viral infections; and (4) interferons, that represent proteins designed to inhibit viral replication, as well as T cells' suppressors, designed to restrain an overreactive immune system. Males' ACE2 expression in the lungs, thyroid, liver, colon, kidney, stomach and pancreas was linked with increased levels of B, NK, CD8+ T cells and interferons. On the other hand, females' ACE2 expression in the lungs and thyroid was associated with decreased levels of B, NK, CD8+ T cells. Increased ACE2 expression in the female heart tissues was accompanied by increased B, NK, CE8+ T cells and Interferons, unlike male heart tissues, where ACE2 receptors and immune cells featured a negative correlation. ACE2 receptors in the kidneys, skin, stomach, and adipose tissue were associated with increased levels of immune cells in both sexes. ACE2 receptors were positively correlated with the lung tissues of older individuals over 45 years and negatively correlated with the lung tissues of younger individuals under 45 years of age. These results reflect a male vulnerability in terms of the positive ACE2/immune cells' correlation with the lungs and thyroid tissues, and a disadvantage for females regarding the positive ACE2/immune cells correlations with the heart tissues. The remaining tissues' ACE2/immunity correlations appeared to be similar in both sexes. The positive ACE2/immunity may signify the eventual mushrooming of the overstated immune response, preluding the lethal consequences of the cytokine storm, a process during which lymphocytes, leukocytes, interferons and NK cells spin out of control in an overly aggressive attack against the virus that causes injury to the vital organs. The positive ACE2/immunity correlations in male lungs, testes and thyroid tissues, and older individuals' lung tissues when compared to females and younger people respectively, may explain the higher SARS-COV-2 mortality rates among males and the eldest [11,12,13]. However, the higher correlation between ACE2 receptors and immune cells in female heart tissues, as well as the fact that such positive correlations are equivalent in both males' and females' kidneys, skin, stomach, and adipose tissue, warns against reaching the conclusion that women are indiscriminately less susceptible to the disease. Therefore, a thorough medical evaluation of all vital organs is necessary in evaluating female prognosis to Covid-19. More research focused on human tissues' analysis from SARS-COV-2 patients may be necessary to further elucidate the molecular interactions between ACE2 receptors and the complex network of immune activity.

4. The Mechanics of the Cytokine Storm

Cytokine storm reflects a persistent immune response, defensively propelled to annihilate the virus, that blindly perseveres, rampaging the infected vital organs with lethal consequences [14,15].

Cytokines are pleiotropic, multifunctional bio-communication agents composed by diverse, yet interconnected entities, including: 1. Interferons (INFs) which regulate immune activity and are classified into I, II, and II subtypes; INFs type I (IFN-αs, IFN-β, IFN-ω, IFN-κ, and IFN-τ) are crucial in eliciting immune responses against viral infections [16,17]. 2. Interleukins (IL) which are vital in stimulating the immune system; they are involved in the proliferation, differentiation and survival of leukocytes, otherwise known as white blood cells (WBCs). Interleukin-2 (IL-2) is a signalling molecule that has been used to treat cancer, while Interleukin-3 (IL-3) has a protective function regarding the survival of macrophages and mast cells, and a preventive one against cellular apoptosis [18]. Interleukins have both pro- and anti-inflammatory properties. Interleukins-1a and 1b (IL-1a and IL-1b) are proinflammatory. IL-6 is both a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-8 in involved in elevating inflammation [19]. IL-10 is largely accepted as an anti-inflammatory cytokine [20]. 3/ Chemokines which are mostly pro-inflammatory, recruit leukocytes and other immune cells, like neutrophils and monocytes/macrophages to attack viral entities; leukocytes demonstrate a positive chemotaxis - a Greek work that reflects a chemically driven movement towards a stimulus. Leukocytes shift from blood vessels towards, and into bodily tissues initiating inflammation. Chemokines are primarily classified into CXC, CC, C, and CX_3C subtypes [21]. 4. Colony-stimulating factors (CSFs) activate the genesis of hematopoietic progenitor cells (HPCs), and are closely associated to inflammation via an intertwined network that features IL-1 and the tumour necrosis factors (TNF) [22]. 5. Tumour Necrosis Factor (TNF) stimulates cytotoxic T lymphocytes (CTL), or otherwise known as T-killer cells, or CD8+ T-cells. TNF is a protagonist in the emergence of the cytokine storm and has been associated with chronic inflammation [23,24].

IL-1b is one of the central cytokines driving the lungs' proinflammatory processes [25]. The lungs' inflammatory condition provokes renal epithelial cell apoptosis and eventual renal dysfunction [26]. This happens as inflammation overflows from the lungs into the circulation, igniting systemic sepsis where TNF, IL-1b and IL-8 are eventually accompanied by a more substantial increase of IL-6,

DOI: https://doi.org/10.30564/jer.v2i1.2517

followed by the anti-inflammatory cytokine IL-10. This sequence suggests that IL-6 is stimulated by TNF and IL-1b which are manifested during the earlier stage of the infection [27,28]. The clinical manifestations of the cytokine storm appear to resemble a sepsis syndrome, or a Systemic Inflammatory Response Syndrome (SIRS), induced by the host's dysregulated response to infection. This may be partly genetically determined [29], while a sedentary lifestyle that accumulates adiposity and instigates inflammation, may be a major contributor to immune aberration evoking the cytokine storm. Interleukins (IL-1, IL-2, IL-6, IL-8) and TNF, along with the inflammatory marker C-Reactive Protein (CRP) are prominent in both subcutaneous and visceral adipose tissue, increasing the probability of Covid-19 infection, due to the abundance of ACE2 receptors in adipose tissue, while exposing the organism to the cytokine storm, due to the pre-existing elevated inflammatory condition [30-37].

Health is based on immune homeostasis which depends on a balance between proinflammatory cytokines and their inhibitors. For example, TNFR1 is the inhibitor of TNF, and IL-1RA is the inhibitor of IL-1b [38]. The disturbance of this balance is followed by the flaring of the cytokine storm. It is unclear if the immune cells can no longer distinguish between the virus and the infected tissues, or whether immune efficiency has deteriorated. Autopsies reveal minimal lymphocytes and neutrophils, yet a relatively larger number of macrophages, whose primary function is to engulf foreign substances and cellular debris [39]. However, an autopsy depicts a biological landscape after the war against the virus is over, and may not represent the processes occurring during the battle. Possibly, the excessive effort to overcome the virus depletes energy in the form of Adenosine Triphosphate (ATP), promoting lymphocytes' and neutrophils' apoptosis [40]. Energy depletion, however, does not accurately describe the entire process of why and how the immune activity turns against itself during the cytokine storm.

Initially, cytokines regulate an innate or non-specific line of immune defence. This evolves into the adaptive immune response that focuses on the specific virus, a critical switch largely controlled by cytokines and chemokines. The cytokine storm is either the result of a) a deficient initial response; b) an inadequate switch between the innate and adaptive defences, hence compromising viral identification; or c) a series of errors during the adaptive stage, obscuring immune ability to distinguish between self and non-self, attacking and rampaging the vital organs of the host. A number of investigators have postulated that insufficient production of Interferon (INF) type I can impair immune innate action [41,42,43]. A recent review suggests that coronavirus is designed to hinder the critical process of viral recognition, and suppress the production of IFN type I, ultimately inhibiting the emergence of the adaptive immune response [44]. IFN type I was reportedly lower in a patient with poor prognosis and outcome [45].

The Interferon-induced proteins 2 and 10 chemokines (CXCL2 and CCL10) appear to be associated with disease severity, and there is evidence that patients with elevated CXCL10 have a larger number of fatalities [46,47]. Additionally, there is evidence that severely ill patients are deficient in the human leukocyte antigen (HLA) system of proteins which are recorded by the major histocompatibility complex (HMC) gene. Additionally, they present defects related to the Immunoglobulin (IG) gene that regulates antigen receptors of the B cells. B cells secrete antibodies which target both bacteria and viruses, unlike T cells that can only recognize viral antigens [48]. HMC genes that encode many proteins involved in T cells antigens that are active during the adaptive response, are upregulated in recovered patients but not in deteriorated ones. HMC genes are essential for the adaptive immune response, therefore, possibly the transition from the innate to the adaptive immune response may be flawed. As a result the immune target remains non-specific, with compromised recognition of the actual virus, resulting in an indiscriminate general attack that involves the tissues of vital organs with inevitable deleterious circumstances [49,50].

5. Methods to Inhibit Viral DNA Replication

As previously stated Nucleocaspic (N) proteins are instrumental in the viral RNA replication and transcription that is facilitated by the RNA-dependent RNA polymerase 12 (RdRp), or otherwise known as non-structural protein 12 (nsp12) in collaboration with the non-structural proteins nsp7 and nsp8. Nsp12 is the primary target of Remdesivir, a nucleotide analogue (NA) antiviral inhibitor that has recently gained popularity in the treatment of SARS-CoV-2 by inhibiting viral RNA replication [51-57]. Clinical research found a statistically significant advantage of Covid-19 patients receiving a 5-day Remdesivir course vs standard care, but no difference between the 5- and 10-day Remdesivir courses [58]. However, a data analysis shows only a small clinical improvement between the 5-day / 10-day Remdesivir groups when juxtaposed against the standard care group. From the 193 patients who received a 10-day Remdesivir course, 2 died and one required invasive mechanical ventilation, while 0 needed non-invasive ventilations. From the 191 patients who received a 5-day Remdesivir course, 0 died or required invasive mechanical ventilation, while 5 needed non-invasive ventilation. From the 200 standard care patients, 4 died, 4 required

 DOI: https://doi.org/10.30564/jer.v2i1.2517

invasive mechanical ventilation, and 7 required non-invasive ventilation. Subsequent evidence with 1,300 participants revealed that Remdesivir may speed up clinical improvement and reduce fatalities in severely ill patients. Overall, most current research provides low certainty, and a weak recommendation for Remdesivir in the treatment of Covid-19 [59-62].

6. Protective Methods

The extensive person-to-person transmission of Covid-19 by asymptomatic individuals or those at the initial stages of the disease has driven the World Health Organization (WHO) to reverse their original recommendation that did not require face coverings [63-68]. Wearing masks can protect the public from those who have already contracted the virus, while being a successful prophylactic measure in reducing the viral load when one is near infected individuals [69,70,71]. Social models emerging from Taiwan, China and Hong Kong where a large part of the population wears masks have demonstrated both a lower infection and mortality rate, unlike countries like the USA where not wearing a mask is considered as a right to personal freedom [72,73,74]. Hygiene and social distancing are globally accepted as additional protective methods against Covid-19.

7. Capitalize on Wellbeing

A retrospective clinical trial on 150 Covid-19 patients demonstrated that Visceral adiposity ($p=0.032$ $p<0.05$), age ($p=0.009$ $p<0.01$) and inflammation measured by C-reactive protein (CRP - $p<0.0001$), were positively correlated with poor prognosis and elevated mortality rates [75]. Another clinical study used computer tomography (CT) to determine the presence of Visceral Adipose Tissue (VAT) in Covid-19 infected patients. BMI did not distinguish between patients in the normal ward and Intensive Care Unit (ICU) with or without mechanical ventilation. In fact the ICU patients without mechanical ventilation had a slightly higher BMI. ICU patients that did not required mechanical ventilation manifested larger amounts of subcutaneous fat; however, the most severely ill ICU patients that required mechanical ventilation were distinguished by their accumulated VAT. These investigators concluded that VAT may be a possible predictor of exacerbated symptomatology and poor prognosis after contracting Covid-19 [76]. These results were confirmed by another CT study examining hepatic steatosis associated with visceral fat, as well as epicardial adipose tissue (EAT) in younger Covid-19 patients under 40 years of age, that classified VAT as one of the primary risk factors of viral vulnerability and disease severity [77].

VAT has a higher expression of ACE2 receptors, which, as previously noted, represent the entry points of Covid-19, in contrast to muscle tissue that has the lowest expression of ACE2 receptors. Therefore, any method that reduces VAT, utilizing it as an energy source to increase muscle, can serve as a protective and preventive method to safeguard health during this pandemic. VAT generates more fatty acids, angiotensinogen, and interleukin-6 that can act as a proinflammatory cytokine, than subcutaneous adipose tissue (SAT) [78]. Glucose and fatty acids metabolism provide the energy both for the basal metabolic processes that sustain life during rest, and the increased demand for energy during exercise, where myokines like Insulin Growth Factor-1 (IGF-1), Fibroblast Growth Factor2 (FGF2), interleukins-6 (IL-6) and IL-7 are involved in muscle hypertrophy [79,80]. Experiments where artificially elevated free fatty acids were added during sustained physical activity found that the metabolic process initially used carbohydrates in the first 15 minutes, decreasing glycogen by 50%, and increasing fat oxidation by 15% after 30 minutes [81,82]. Fat metabolism reflects a complex process that commences with the release of free fatty acids (FFA) from the adipose tissue, which are transferred across the membranes of muscle cells, where they bind with protein receptors in the cytoplasm, with the mitochondria being the final destination, where the oxidation process, i.e. burning fat via oxygen takes place; this results in the release of electrons, which in turn push protons to mobilize the energy production process by spinning the ATPace synthase anabolic enzyme clockwise, to add a phosphate to Adenosine Diphosphate (ADP), via the transmembrane proton gradient, to compose Adenosine Triphosphate molecules of energy [83-88].

Growth Hormone (GH) appears to be instrumental in reducing visceral fat on the basis of a 12 month computed tomography (CT) clinical trials that administered recombinant human GH to 40 postmenopausal women, demonstrating reduced visceral fat tissue upon completion [89]. Relatively to SAT, VAT secretes less anorexic hormone leptin. Although a clinical trial in Europe demonstrated a high correlation between leptin and VAT [90], other studies with Asian men and African American women indicated that leptin is associated with overall fat rather than VAT specifically. VAT appears to be a reliable predictor of insulin sensitivity, elevated levels of triglycerides and inhibited high density lipoproteins (HDL) [91,92]. VAT is also associated with triiodothyronine (T3) and the identifier of atherosclerosis, pulse wave velocity (PWV) [93].

Weight management solutions including lasers and RF primarily address subcutaneous fat reduction with no evidence of increased fitness; additionally, there are several

DOI: https://doi.org/10.30564/jer.v2i1.2517

reports of eventual escalated inflammation following some of these procedures [94-99]. Pre-existing inflammation can potentially exacerbate the deleterious immune response termed "cytokine storm" that is detected in Covid-19 severe cases; therefore, inflammation inducing procedures may be counterproductive and conceivably dangerous. Physical fitness has been deemed a health enhancing solution by a number of research projects [100-108]. On the other hand, there is evidence that exercise may induce asthma that usually exacerbates Covid-19 symptomatology, or provoke an inverse cortisol/testosterone relationship, while supressing the anorexic hormone leptin, thus increasing food consumption [109-114]. Recent studies report an advantage with an exercise alternative method invented in London University that results in hormonal balance, and enhanced wellbeing as measured by statistically significant decreases of visceral fat, inflammation, CRP, BMI and Triglycerides, juxtaposed by optimal increases of skeletal muscle mass, Free T3, IGF-1 and HDL [115-125]. We combined some of the data presented in these studies and analysed the results with ANOVA for repeated measures.

8. Data Results Analysis

The visceral fat decrease and skeletal mass increase of 29 patients, 20 females and 9 males with an average BMI of 29.9 are shown on Table 1. Table 2 reflects the results of the same patients indicating a statistically significant increase in the anorexic hormone leptin contrasted by an op-

Table 1. Results of 29 Subjects on BMI, Visceral Adipose Tissue and Skeletal Muscle Mass

GENDER / AGE	MEDICAL HISTORY	BMI PRE	BMI POST	BMI DECREASE	VISCERAL FAT PRE	VISCERAL FAT POST	VISCERAL FAT % Decrease	SKELETAL MUSCLE MASS (SMM) PRE	SKELETAL MUSCLE MASS (SMM) POST	SMM % Increase
F/ 48	Diabetes Hyperphagia	31.2	29.3	6.1%	142.65	119.42	-16.28%	12.74	14.66	+15.07%
F/ 54	Diabetes Hyperphagia	30.4	28.6	5.9%	138.54	112.30	-18.94%	11.45	12.95	+13.10%
F/ 56	Prediabetes Hyperphagia	31.6	29.9	5.37%	144.23	121.12	-23.11%	12.66	14.76	+6.58%
F/ 47	Hyperphagia	28.7	26.7	6.9%	123.55	96.48	-21.91%	16.86	19.45	+15.36%
F/ 52	Prediabetes Hypertension Hyperphagia	26.8	24.9	7.1%	104.38	89.23	-14.51%	11.99	14.27	+19.01%
F/ 49	Hyperphagia	27.1	24.6	9.2%	108.93	87.44	-19.73%	12.67	16.59	+30.93%
F/ 58	Prediabetes Hypertension Hyperphagia	29.5	25.9	12.2%	119.67	98.66	-17.55%	11.32	12.60	+11.30%
F/ 50	Hyperphagia	27.3	25.3	7.3%	117.80	95.64	-18.81%	11.04	13.96	+26.45%
F/ 55	Prediabetes Hyperphagia	27.1	24.8	8.5%	98.77	81.32	-17.66%	12.30	13.94	+13.33%
F/ 49	Hyperphagia	29.5	26.3	11.5%	121.63	105.24	-13.47%	12.15	13.93	+14.65%
M / 39	Hyperphagia	33.8	29.4	14.9%	139.30	93.80	-32.66%	36.40	43.80	+20.3%
M / 40	Hyperphagia	29.6	25.7	13.2%	102.20	69.30	-32.19%	30.30	38.60	+27.39%
F / 39		26.1	23.2	11.1%	93.50	58.30	-37.64%	18.40	27.00	+46.79%
F / 41		25.9	22.7	12.4%	85.50	61.40	-28.30%	17.00	26.80	+57.64%
M / 40		24.8	22.4	9.7%	76.40	48.80	-36.12%	37.80	44.80	+18.5%
M / 42	Hyperphagia	28.6	24.7	13.6%	118.60	89.30	-24.70%	29.40	38.30	+30.27%
F / 48		27.33	23.8	12.9%	98.80	70.60	-28.54%	17.20	26.80	+55.81%
F / 43	Hyperphagia	29.4	26.2	10.9%	102.70	77.30	-24.73%	19.80	28.80	+45.45%
M / 39	Hyperphagia	33.2	30.5	8.1%	145.30	104.34	-28.18%	29.80	37.22	+25.89%
F / 42		28.9	24.7	14.5%	109.80	74.67	-31.99%	17.95	26.63	+48.35%
F / 42		29.7	25.7	13.5%	128.97	113.14	-12.27%	27.65	30.87	+11.64%
M / 36	Hyperphagia	33.3	26.9	20.1%	131.20	98.53	-24.9%	33.30	39.60	+18.91%
M / 39	Hyperphagia	34.2	27.3	20.2%	119.67	96.62	-19.26%	36.40	39.80	+9.34%
M / 43	Hyperphagia	32.8	26.4	19.5%	99.56	79.34	-20.22%	27.13	31.95	+17.75%
M / 35		29.6	25.9	14.2%	121.68	104.29	-14.29%	17.57	23.32	+32.72%
F / 42	Hyperphagia	35.2	27.4	22.2%	129.73	109.28	-15.76%	20.16	24.53	+21.67%
F / 45	Hyperphagia	33.8	26.1	22.8%	109.63	95.85	-12.56%	16.89	22.85	+35.28%
F / 49	Hyperphagia	32.6	27.8	14.7%	122.66	87.85	-28.38%	20.73	25.52	+23.11%
F / 38		28.9	24.5	15.2%	134.64	112.80	-16.22%	16.83	23.18	+37.73%
	BMI DECREASE	29.9	26.1	12.70%	Mean Average Visceral Fat % Decrease		-22.44%	Mean Average SMM % Increase		+25.87%

 DOI: https://doi.org/10.30564/jer.v2i1.2517

Table 2. Blood Plasma Results of 29 Subjects with an average BMI of 29.9 on Leptin (Reference Ranges of Leptin Levels According to Body Mass Index, Gender and Development Stage [Table 3]. Blood Plasma Results on Ghrelin for overweight individuals: 340-450 pg/mL. Ghrelin normal range for normal weight individuals: 520-700 pg/mL

GENDER/ AGE	MEDICAL HISTORY	BMI	LEPTIN PRE (ng/mL)	LEPTIN POST (ng/mL)	Normal Range (ng/mL)	% Increase (ng/mL)	GHRELIN PRE (pg/mL)	GHRELIN POST (pg/mL)	Normal Range (pg/mL)	% Decrease (pg/mL)
F/ 48	Diabetes Hyperphagia	31.2	21.45	27.44	12.2-67.5	+27.92%	483	414	340-450	-14.28%
F/ 54	Diabetes Hyperphagia	30.4	14.63	18.08	10.6-58.3	+23.58%	488	463	340-450	-5.13%
F/ 56	Prediabetes Hyperphagia	31.6	10.67	13.66	12.2-67.5	+28.02%	462	398	340-450	-13.85%
F/ 47	Hyperphagia	28.7	7.09	11.33	7.9-43.5	+59.80%	345	376	340-450	-8.98%
F/ 52	Prediabetes Hypertension Hyperphagia	26.8	12.34	15.12	5.9-32.4	+22.53%	498	453	340-450	-9.03%
F/ 49	Hyperphagia	27.1	10.65	12.39	6.8-37.5	+16.33%	357	313	340-450	-12.32%
F/ 58	Prediabetes Hypertension Hyperphagia	29.5	20.66	21.45	9.1-50.4	+3.82%	387	364	340-450	-5.94%
F/ 50	Hyperphagia	27.3	11.65	15.43	6.8-37.5	+3.82%	401	389	340-450	-2.99%
F/ 55	Prediabetes Hyperphagia	27.1	15.24	18.56	6.8-37.5	+21.78%	465	432	340-450	-7.09%
F/ 49	Hyperphagia	29.5	18.54	19.82	9.1-50.4	+6.90%	474	439	340-450	-7.38%
M / 39	Hyperphagia	33.8	7.38	7.84	**14.1-78.2**	+6.2%	683	614	340-450	-10.1%
M / 40	Hyperphagia	29.6	6.25	7.03	9.1-50.4	+12.48%	588	576	340-450	-2%
F / 39		26.1	12.43	13.22	**5.9-32.4**	+6.35%	612	584	340-450	-4.5%
F / 41		25.9	11.98	12.09	**5.1-28.0**	+0.9%	599	543	520-700	-9.34%
M / 40		24.8	5.53	5.94	**4.4-24.2**	+7.41%	602	553	520-700	-8.13%
M / 42	Hyperphagia	28.6	6.42	6.97	**7.9-43.5**	+8.56%	603	576	340-450	-4.47%
F / 48		27.33	10.87	11.84	**6.8-37.5**	+8.92%	687	612	340-450	-10.9%
F / 43		29.4	9.89	10.54	9.1-50.4	+3.53%	623	565	520-700	-9.30%
M / 39	Hyperphagia	33.2	5.47	6.01	**16.4-90.5**	+4.1%	589	532	340-450	-9.71%
F / 42		28.9	9.99	10.83	**7.9-43.5**	+6.4%	634	513	340-450	-19.08%
M / 36		29.7	3.69	3.98	**9.1-50.4**	+7.86%	687	602	340-450	-12.37%
M / 39	Hyperphagia	33.3	4.43	4.98	**16.4-90.5**	+9.78%	695	634	340-450	-8.77%
M / 43	Hyperphagia	34.2	5.62	6.22	**19.0-105.**	+10.68%	598	552	340-450	-7.69%
M / 35	Hyperphagia	32.8	6.15	6.83	**14.1-78.2**	+11.05%	629	587	340-450	-6.68%
F / 42		29.6	9.16	9.74	**9.1-50.4**	+6.33%	577	542	340-450	-6.06%
F / 45	Hyperphagia	35.2	5.23	6.09	**22.-121**	+16.44%	659	613	340-450	-6.99%
F / 49	Hyperphagia	33.8	7.22	8.17	**16.4-90.5**	**+13.15%**	644	617	340-450	-4.19%
F / 38	Hyperphagia	32.6	12.34	13.22	**14.1-78.2**	+7.13%	569	536	340-450	-5.79%
F / 37		28.9	11.38	13.08	**7.9-43.5**	+14.93%	499	461	340-450	-7.62%
Average BMI		29.9	Mean Average Leptin % Increase			+12.99%	Mean Average Ghrelin % Decrease			-8.30%

Table 3. Leptin Ranges by Body Mass Index ng/mL

BMI	Range			BMI	Range	
11	0.7	-	3.6	24	4.4	-24.2
12	0.8	-	4.2	25	5.1	-28.0
13	0.9	-	4.8	26	5.9	-32.4
14	1.0	-	5.6	27	6.8	-37.5
15	1.2	-	6.5	28	7.9	-43.5
16	1.4	-	7.5	29	9.1	-50.4
17	1.6	-	8.7	30	10.6	-58.3
18	1.8	-	10.0	31	12.2	-67.5
19	2.1	-	11.6	32	14.1	-78.2
20	2.4	-	13.4	33	16.4	-90.5
21	2.8	-	15.6	34	19.0	- 105.0
22	3.3	-	18.0	35	22.0	- 121.0
23	3.8	-	20.9	36	25.4	- 141.0

DOI: https://doi.org/10.30564/jer.v2i1.2517

timal decrease in the orexigenic hormone ghrelin. Table 3 depicts leptin ranges in relation to body mass index. Table 4 shows the inflammation reduction as measured by CRP and the cortisol decrease of 10 females with an average BMI of 32.91 and at least one medical condition.

Table 5 reflects the results of 30 subjects, 22 females and 8 males with an average BMI of 32.96 on HDL and Triglycerides. Thirteen out of these subjects were diabetics and thirteen were prediabetics.

Table 6 reflects the results of 20 subjects, 15 females and 5 males on Free T3 and IGF-1.

Table 7 shows the significance values for all variables after the data was analysed with ANOVA for repeated

Table 4. Blood Test Results on 10 Female Subjects with an average BMI of 32.9 for C-reactive protein (CRP) and Cortisol

Gender	Age	Medical History	BMI PRE	CRP PRE mg/dL	CRP POST mg/dL	Normal Range mg/dL	Cortisol Total, Serum µg /dL, PRE	Cortisol Total, Serum µg/dL, POST	Normal Range µg/dL
Female	56	Diabetes Fatty Liver	32.6	1.56	1.02	<1.00	18.44	15.66	3.09-25.0
Female	52	Prediabetes Fatty Liver	36.5	1.09	1.06	<1.00	21.89	20.12	3.09-25.0
Female	49	Hypertension Hypothyroidism	28.6	2.31	1.15	<1.00	24.98	18.47	3.09-25.0
Female	63	Hypertension Fatty Liver	34.9	1.93	1.06	<1.00	23.43	21.98	3.09-25.0
Female	51	Prediabetes Hypertension Hypothyroidism	34.2	1.43	1.22	<1.00	18.46	15.34	3.09-25.0
Female	55	Prediabetes Fatty Liver Hypothyroidism	35.4	1.64	1.01	<1.00	19.33	14.75	3.09-25.0
Female	48	Prediabetes Fatty Liver Hypothyroidism	30.9	1.04	0.86	<1.00	9.67	8.23	3.09-25.0
Female	61	Hypertension Fatty Liver	32.7	1.08	0.74	<1.00	14.76	10.65	3.09-25.0
Female	46	Heart Disease	29.5	1.84	0.98	<1.00	17.22	13.95 and	3.09-25.0
Female	58	Prediabetes Fatty Liver Hypothyroidism	33.8	2.11	1.03	<1.00	21.28	17.24	3.09-25.0
Mean Average CRP % Decrease					**-36.87 mg/dL**	**Mean Average Cortisol % Decrease**		**-17.47%** µg/dL	

Notes: CRP: <1.0 mg/dL. Low cardiovascular risk according to AHA/CDC

CRP: 1.0-3.0 mg/dL Average cardiovascular risk according to AHA/CDC

CRP: >3.0-10.0 mg/dL High cardiovascular risk according to AHA/CDC

Table 5. Blood Test Results on 30 subjects

Gender/ Age	BMI	Medical History	HDL PRE mg/dL	HDL POST mg/dL	HDL Normal Range mg/dL	Trigly cerides PRE mg/dL	Trigly cerides POST mg/dL	Trigly cerides Normal Range mg/dL
F/56	32.6	Diabetes Fatty Liver	53	61	>60	144	137	<150
F/52	36.5	Prediabetes Fatty Liver	39	57	>60	169	146	<150
F/49	28.6	Hypertension Hypothyroidism	61	79	>60	129	114	<150
F/63	34.9	Hypertension Fatty Liver	46	64	>60	163	152	<150
F/51	34.2	Prediabetes Hypertension Hypothyroidism	41	55	>60	159	150	<150
F/55	35.4	Prediabetes Fatty Liver Hypothyroidism	43	51	>60	173	159	<150

 DOI: https://doi.org/10.30564/jer.v2i1.2517

Gender/ Age	BMI	Medical History	HDL PRE mg/dL	HDL POST mg/dL	HDL Normal Range mg/dL	Trigly cerides PRE mg/dL	Trigly cerides POST mg/dL	Trigly cerides Normal Range mg/dL
F/48	30.9	Prediabetes Fatty Liver Hypothyroidism	63	76	>60	153	139	<150
F/61	32.7	Hypertension Fatty Liver	52	71	>60	175	148	<150
F/46	29.5	Heart Disease	59	68	>60	136	129	<150
F/58	33.8	Prediabetes Fatty Liver Hypothyroidism	38	52	>60	182	157	<150
F/45	34.4	Diabetes	32	39	>60	203	158	<150
M/69	28.5	Diabetes	35	47	>60	215	128	<150
M/46	35.3	Diabetes	28	37	>60	230	153	<150
F/50	38	Diabetes	49.6	53	>60	86.7	84.3	<150
F/49	40.5	Diabetes	34.5	38	>60	103	88	<150
F/46	36.2	Diabetes	32	39	>60	287	176	<150
M/48	38.5	Diabetes	29	41	>60	266	147	<150
F/44	38.2	Diabetes	30	35	>60	283	189	<150
F/43	27.7	Prediabetes	36	42	>60	294	197	<150
F/27	35.4	Prediabetes	36	48	>60	192	126	<150
F/63	30.7	Prediabetes	45	47	>60	155	117	<150
F/24	33.9	Prediabetes	45	52	>60	88	86	<150
F/30	32.0	Prediabetes	37	46	>60	156	124	<150
F/45	30.1	Diabetes	33	40	>60	225	179	<150
F/47	25.1	Diabetes	31	41	>60	237	188	<150
M/45	29.4	Diabetes	41	45	>60	112	105	<150
M/82	34.5	Diabetes	26	38	>60	97	94	<150
M/15	31.8	Prediabetes	36	42	>60	187	132	<150
M/58	28.9	Prediabetes	43.1	46.8	>60	141	136	<150
M/46	30.6	Prediabetes	52.3	56	>60	262	158	<150
BMI Average	32.96		40.88	50.22	22.84% Increase	180.09	139.25	40.84% Decrease

Note: High-Density Lipoprotein (HDL) Normal Range: Men > 60 mg/dL; Women > 60 mg/dL High-Density Lipoprotein (HDL) At Risk: Men: <40 mg/dL; Women < 50 mg/dL

Table 6. Blood Test Results on 20 Subject IGF-1 and Free T3 for each subject

Gender /Age	Medical History	IGF-1 PRE (nmol/L)	IGF-1 POST (nmol/L)	Normal Range (nmol/L)	IFG-1 % Increase	FREE T3 PRE (pmol/L)	FREE T3 POST (pmol/L)	Normal Range (pmol/L)	% Increase (pmol/L)
M/32	None known	25.97	30.35	15.08-32.5	+16.86%	2.98	4.22	2.63-5.7	+41%
M/35	None known	23.98	31.12	15.08-32.5	+29.77%	3.69	4.98	2.63-5.7	+34.95%
F/36	None known	16.33	20.75	11.25-28.8	+27.06%	4.77	5.37	2.63-5.7	+12.5%
F/35	None known	15.14	19.21	11.25-28.8	+26.88%	4.56	5.31	2.63-5.7	+16.44%
M/37	None known	22.27	28.11	15.08-32.5	+26.22%	4.15	5.47	2.63-5.7	+31.80%
M/39	None known	26.98	30.52	15.08-32.5	+11.80%	3.29	4.86	2.63-5.7	+47.7%
F/39	None known	15.86	21.08	11.25-28.8	+32.91%	4.36	5.64	2.63-5.7	+29.35%
F/32	None known	18.55	23.50	11.25-28.8	+26.68%	3.66	4.79	2.63-5.7	+30.87%
M/36	None known	24.56	31.34	15.08-32.5	+27.60%	3.19	4.12	2.63-5.7	+29.15%
F/33	None known	19.34	25.66	11.25-28.8	+32.67%	4.09	5.12	2.63-5.7	+25.18%

DOI: https://doi.org/10.30564/jer.v2i1.2517

Gender /Age	Medical History	IGF-1 PRE (nmol/L)	IGF-1 POST (nmol/L)	Normal Range (nmol/L)	IFG-1 % Increase	FREE T3 PRE (pmol/L)	FREE T3 POST (pmol/L)	Normal Range (pmol/L)	% Increase (pmol/L)
F/ 48	Diabetes Hyperphagia	12.23	14.17	11.25-28.8	+14.86%	2.19	2.88	2.63-5.7	+31.50%
F/ 54	Diabetes Hyperphagia	11.65	12.33	11.25-28.8	+5.83%	2.34	2.76	2.63-5.7	+34.95%
F/ 56	Prediabetes Hyperphagia	11.17	12.79	11.25-28.8	+14.50%	1.98	2.64	2.63-5.7	+33.33%
F/ 47	Hyperphagia	13.94	17.21	11.25-28.8	+23.45%	2.67	2.93	2.63-5.7	+9.73%
F/ 52	Prediabetes Hypertension Hyperphagia	12.27	14.32	11.25-28.8	+7.65%	2.32	2.89	2.63-5.7	+21.98%
F/ 49	Hyperphagia	12.18	14.72	11.25-28.8	+20.85%	2.89	3.05	2.63-5.7	+5.53%
F/ 58	Prediabetes Hypertension Hyperphagia	10.21	11.99	11.25-28.8	+17.43%	2.29	2.78	2.63-5.7	+21.39%
F/ 50	Hyperphagia	12.87	14.36	11.25-28.8	+11.57%	2.68	3.29	2.63-5.7	+22.76%
F/ 55	Prediabetes Hyperphagia	11.43	12.85	11.25-28.8	+12.42%	2.16	2.59	2.63-5.7	+19.91%
F/ 49	Hyperphagia	13.82	15.26	11.25-28.8	+10.41%	2.86	3.11	2.63-5.7	+8.74%
		16.97	20.75	Total IGF-1 % Increase	+20.81%	2.33	4.06	Total Free T3 % Increase	+27%

Table 7. Analysis of Variance Statistical Significance Results on all variable

	SS	df	MS	F-Ratio Value	p-Value	Significance Level
Visceral Fat and Skeletal Muscle Mass with respect to BMI	BT: 200125.5873 WT:23548.7737 E:14365.2314	BT:3 WT:112 Error:84	BT: 66708.5291 WT: 210.2569 E: 171.0147	***F* = 390.074**	<0.00001	P<0.00001
Leptin & Ghrelin with respect to BMI	BT: 7973224.9161 WT526895.232 E: 286246.947	BT:3 WT:112 E:84	BT: 2657741.6387 WT: 4704.4217 E: 3407.7017	***F* = 779.92202**	<0.00001	P<0.00001
CRP & Cortisol with respect to BMI	BT: 2611.4641 WT: 334.1695 E: 158.7755	BT:3 WT:36 E:27	BT: 870.488 WT: 9.2825 E: 5.8806	***F* = 148.02771**	<0.00001	P<0.00001
HDL & Triglycerides with respect to BMI	BT: 418381.4549 WT: 137444.281 E: 88582.5476	BT:3 WT:116 E:87	BT: 139460.485 WT:1184.8645 E: 1184.8645	***F* = 136.96899**	<0.00001	P<0.00001
IGF-1 & Free T3	BT: 4489.9666 WT: 1570.9796 E: 652.5712	BT:3 WT:76 E:57	BT: 1496.6555 WT: 20.6708 E: 11.4486	***F* = 130.72807**	<0.00001	P<0.00001

Abbreviations: BT: Between Treatments / WT: Within Treatments / E: Error

measures. Results yielded highly statistically significant results. Visceral fat decrease was accompanied with increased skeletal muscle mass. IGF-1, Free T3 and Leptin increased within the normal range, while cortisol and ghrelin decreased but without descending into abnormality. These results demonstrated a centralized tendency towards hormonal balance and optimal appetite regulation resulting by a healthy proportional interaction between the anorexic hormone leptin, juxtaposed by the relatively suppressed concentrations of the orexigenic hormone ghrelin, combined with reduced cortisol that is known to provoke stress-eating behaviours. Elevated HDL was accompanied by diminished triglycerides.

9. Discussion

The immune collapse during the cytokine storm following Covid-19 invasion that has infected over forty-three million individuals worldwide, resulting in over a million deaths, brings to mind the unpredictable defeat of the giant during the David and Goliath battle.

The virus enters the system via ACE2 receptors which catalyze Angiotensin II (Ang II). Excess Ang II increases blood pressure that is deleterious to diseases such as hypertension, diabetes, and cardiovascular illness, which represent the pre-existing conditions with elevated Covid-19 mortality rates. On the other hand, Ang II

 DOI: https://doi.org/10.30564/jer.v2i1.2517

increases concentrations of "A Disintegrin And Metalloprotease 17" (ADAM17) that can cleave ACE2 from the cellular membrane, shedding it into body fluids, thus restricting viral access.

Human tissues' research has revealed a multitude of ACE2 receptors in adipose tissue, heart, kidneys, thyroid, testes and small intestines with relatively less ACE2 expression in the muscle, brain, spleen and blood vessels. Lungs, liver, adrenal gland, bladder and colon seem to be somewhere in between. Investigation of B, NK, CE8+ T cells and Interferons in males, females, young and old, has shown a greater susceptibility among older individuals evidenced by a multitude of immune cells in the lungs. Higher ACE2 expression in the testes in addition to other tissues increase male vulnerability that is marked by the elevated number of certain immune cells in the lungs, thyroid, adrenals, liver and colon. In contrast, females present a higher positive correlation between immune cells and the heart; all other tissues manifest equivalent levels of immune cells in both sexes. In other words, there may be a Covid-19 preference for males and older individuals, but without a safety guarantee for females that may be equally susceptible in certain cases.

A literature review of the immune overreaction during the cytokine storm suggests a possible imbalance between pro-inflammatory cytokines and their inhibitors, a deficient immune response due to insufficient production of INF type I, or a dysregulated transition from the non-specific / innate to the adaptive immunity, that is designed to recognize and attack the particular threat, represented in this case by Covid-19. Hence, the frenzied immune overreaction aimlessly persevering, unable to distinguish self from non-self that rampages and injures the body.

New pharmaceuticals designed to interfere with viral RNA replication like Remdesivir that targets the non-structural protein 12 (nsp12) in collaboration with the non-structural proteins nsp7 and nsp8, have had modest to moderate clinical outcomes, providing a weak recommendation for Remdesivir in the treatment of Covid-19.

Protective techniques including, face coverings, social distancing and thorough hygiene, as well as prevention via fitness, health enhancement and weight management are currently the most reliable methods of limiting the spread of the pandemic. Visceral adipose tissue (VAT) is strongly linked to Covid-19 severely ill patients in ICU needing mechanical ventilation, irrespective of BMI which does not distinguish between patients in normal wards and ICU. VAT has a higher expression of ACE2 receptors that represent the portals for Covid-19 entry. VAT generates more fatty acids, angiotensinogen, and the pro-inflammatory interleukin-6 (IL-6). Any method that reduces VAT, utilizing it as an energy source to increase muscle which features the least ACE2 receptors, therefore limiting Covid-19 entry, can serve as a protective and preventive measure in safeguarding health during this health crisis. Lasers and RF primarily address subcutaneous fat reduction with no evidence of increased fitness Additionally, a number of studies report escalated inflammation following some of these procedures. Physical activity has universally accepted benefits, but also a downside by provoking an inverse cortisol/testosterone relationship, while supressing the anorexic hormone leptin, thus increasing food consumption. Recent research on an effortless exercise intervention presents statistically significant VAT and inflammation reduction, juxtaposed by skeletal muscle mass increase, along with reduced lipids, cortisol and the orexigenic hormone ghrelin; importantly, it also elevates Free T3, IGF-1 and the anorexic hormone leptin within the normal range, offering an optimal alternative to fast efficient fitness. These clinical trials, however, are mostly based on small samples, in the absence of imaging techniques that can substantiate their results, warranting the need for additional research.

Acknowledgement

The author would like to thank all the patients that supplied their records for the metanalysis included in this review.

Conflict of Interest

The author declares no conflict of interests. This study was conducted by independent operators that were not employed or contracted by the author.

Funding

No funding was received by a third party or institution.

References

[1] Bourgonje AR, Abdulle AE, Timens W, Hillebrands JL, Navis GJ, Gordijn SJ, Bolling MC, Dijkstra G, Voors AA, Osterhaus AD, van der Voort PH, Mulder DJ, van Goor H. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol., 2020, 251(3): 228-248.
DOI: 10.1002/path.5471 Epub 2020 Jun 10. PMID: 32418199; PMCID: PMC7276767

[2] Ferrario, C.M., Trask, A.J., Jessup, J.A. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1-7) in regulation of cardiovascular function. American Journal of

DOI: https://doi.org/10.30564/jer.v2i1.2517

Physiology-Heart and Circulatory Physiology, 2005, 289(6): H2281-H2290. https://doi.org/10.1152/ajpheart.00618.2005

[3] Benter, I.F., Yousif, M.H., Dhaunsi, G.S., Kaur, J., Chappell, M.C., Diz, D.I. Angiotensin-(1-7) prevents activation of NADPH oxidase and renal vascular dysfunction in diabetic hypertensive rats. American journal of nephrology, 2008, 28(1): 25-33. https://doi.org/10.1159/000108758

[4] El-Hashim, A.Z., Renno, W.M., Raghupathy, R., Abduo, H.T., Akhtar, S., Benter, I.F. Angiotensin-(1-7) inhibits allergic inflammation, via the MAS1 receptor, through suppression of ERK1/2-and NF-κB-dependent pathways. British journal of pharmacology, 2012, 166(6): 1964-1976. https://doi.org/10.1111/j.1476-5381.2012.01905.x

[5] Ocaranza, M.P., Jalil, J.E.. Protective role of the ACE2/Ang-(1-9) axis in cardiovascular remodeling. International journal of hypertension, 2012. DOI: 10.1155/2012/594361 PMCID: PMC3270559. PMID: 22315665

[6] Danser, A.J., Epstein, M. and Batlle, D. Renin-angiotensin system blockers and the COVID-19 pandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension, 2020, 75(6): 1382-1385. https://doi.org/10.1161/HYPERTENSIONAHA.120.15082

[7] Xia H, Sriramula S, Chhabra KH, Lazartigues E. Brain angiotensin-converting enzyme type 2 shedding contributes to the development of neurogenic hypertension.Circ Res., 2013, 113: 1087-1096. DOI: https://doi.org/10.1161/CIRCRESAHA.113.301811

[8] Heurich A, Hofmann-Winkler H, Gierer S, Liepold T, Jahn O, Pöhlmann S. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. J Virol., 2014, 88(2): 1293-307. DOI: 10.1128/JVI.02202-13. Epub 2013 Nov 13. PMID: 24227843; PMCID: PMC3911672

[9] Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol., 2020, 92(7): 726-730. DOI: 10.1002/jmv.25785. Epub 2020 Apr 5. PMID: 32221983; PMCID: PMC7317908.

[10] Tikellis C, Bernardi S, Burns WC. Angiotensin-converting enzyme 2 is a key modulator of the renin-angiotensin system in cardiovascular and renal disease. Curr Opin Nephrol Hypertens., 2011, 20: 62-68 https://doi.org/10.1097/MNH.0b013e328341164a

[11] Li, M. Y., Li, L., Zhang, Y., Wang, X. S. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infectious diseases of poverty, 2020, 9(1): 45. https://doi.org/10.1186/s40249-020-00662-x

[12] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y,Wei Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020. https://doi.org/10.1016/S0140-6736(20)30211-7

[13] Karlberg J, Chong D, Lai W. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? Am J Epidemiol, 2004, 159(3): 229-31. https://doi.org/10.1093/aje/kwh056

[14] Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol., 2020, 108(1): 17-41. DOI: 10.1002/JLB.3COVR0520-272R. Epub 2020 Jun 13. PMID: 32534467; PMCID: PMC7323250

[15] Tisoncik, J.R., Korth, M.J., Simmons, C.P., Farrar, J., Martin, T.R. and Katze, M.G. Into the eye of the cytokine storm. Microbiology and Molecular Biology Reviews, 2012, 76(1): 16-32. DOI: 10.1128/MMBR.05015-11

[16] Brierley, M.M., Fish, E.N. IFN-α/β receptor interactions to biologic outcomes: understanding the circuitry. Journal of interferon & cytokine research, 2002, 22(8): 835-845. https://doi.org/10.1089/107999002760274845

[17] Nguyen, K.B., Watford, W.T., Salomon, R., Hofmann, S.R., Pien, G.C., Morinobu, A., Gadina, M., O'Shea, J.J., Biron, C.A. Critical role for STAT4 activation by type 1 interferons in the interferon-γ response to viral infection. Science, 2002, 297(5589): 2063-2066. DOI: 10.1126/science.1074900

[18] Thomson, A.W., Lotze, M.T. eds. The Cytokine Handbook, Two-Volume Set. Elsevier, 2003. https://doi.org/10.1016/B978-012689663-3/50013-2

[19] Noh, M.K., Jung, M., Kim, S.H., Lee, S.R., Park, K.H., Kim, D.H., Kim, H.H. and Park, Y.G. Assessment of IL6, IL8 and TNFα levels in the gingival tissue of patients with periodontitis. Experimental and therapeutic medicine, 2013, 6(3): 847-851. https://doi.org/10.3892/etm.2013.1222

[20] Sun, L., Louie, M.C., Vannella, K.M., Wilke, C.A., LeVine, A.M., Moore, B.B., Shanley, T.P.. New

concepts of IL-10-induced lung fibrosis: fibrocyte recruitment and M2 activation in a CCL2/CCR2 axis. American Journal of Physiology-Lung Cellular and Molecular Physiology, 2011, 300(3): L341-L353. https://doi.org/10.1152/ajplung.00122.2010

[21] Raman D, Sobolik-Delmaire T, Richmond A. Chemokines in health and disease. Exp. Cell Res, 2011, 317: 575-589. https://doi.org/10.1016/j.yexcr.2011.01.005

[22] Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. Nat. Rev. Immunol., 2008, 8: 533-544. https://doi.org/10.1038/nri2356

[23] Kopf M, Bachmann MF, Marsland BJ. Averting inflammation by targeting the cytokine environment. Nat. Rev. Drug Discov., 2010, 9: 703-718. https://doi.org/10.1038/nrd2805

[24] Sethi G, Sung B, Kunnumakkara AB, Aggarwal BB. Targeting TNF for treatment of cancer and autoimmunity. Adv. Exp. Med. Biol., 2009, 647: 37-51. https://link.springer.com/chapter/10.1007 /978-0-387-89520-8_3

[25] Pugin, J., Ricou, B., Steinberg, K.P., Suter, P.M., Martin, T.R. Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS, a prominent role for interleukin-1. American journal of respiratory and critical care medicine, 1996, 153(6): 1850-1856. https://doi.org/10.1164/ajrccm.153.6.8665045 PubMed: 8665045

[26] Imai, Y., Parodo, J., Kajikawa, O., de Perrot, M., Fischer, S., Edwards, V., Cutz, E., Liu, M., Keshavjee, S., Martin, T.R., Marshall, J.C.. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. Jama, 2003, 289(16): 2104-2112. DOI: 10.1001/jama.289.16.2104

[27] Levy, M.M., Fink, M.P., Marshall, J.C., Abraham, E., Angus, D., Cook, D., Cohen, J., Opal, S.M., Vincent, J.L., Ramsay, G.. 2001 sccm/esicm/accp/ats/sis international sepsis definitions conference. Intensive care medicine, 2003, 29(4): 530-538. https://doi.org/10.1007/s00134-003-1662-x

[28] Abraham, E., Glauser, M.P., Butler, T., Garbino, J., Gelmont, D., Laterre, P.F., Kudsk, K., Bruining, H.A., Otto, C., Tobin, E., Zwingelstein, C. Tumor necrosis factor receptor fusion protein in the treatment of patients with severe sepsis and septic shock: A randomized controlled multicenter trial. Jama, 1997, 277(19): 1531-1538. DOI: 10.1001/jama.1997.03540430043031

[29] Wurfel, M.M., Gordon, A.C., Holden, T.D., Radella, F., Strout, J., Kajikawa, O., Ruzinski, J.T., Rona, G., Black, R.A., Stratton, S. and Jarvik, G.P. Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. American journal of respiratory and critical care medicine, 2008, 178(7): 710-720. https://doi.org/10.1164/rccm.200803-462OC PubMed: 18635889

[30] Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020, 50(4): 332-334. DOI:10.1016/j.medmal.2020.03.007

[31] Tan C, Huang Y, Shi F, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol., 2020, 92(7): 856-862. DOI: 10.1002/jmv.25871

[32] Han, H., Ma, Q., Li, C., Liu, R., Zhao, L., Wang, W., Zhang, P., Liu, X., Gao, G., Liu, F. and Jiang, Y. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerging Microbes & Infections, 2020, 9(1): 1123-1130. https://doi.org/10.1080/22221751.2020.1770129

[33] Del Valle, D.M., Kim-Schulze, S., Huang, H.H., Beckmann, N.D., Nirenberg, S., Wang, B., Lavin, Y., Swartz, T.H., Madduri, D., Stock, A., Marron, T.U. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nature medicine, 2020: 1-8. https://doi.org/10.1038/s41591-020-1051-9

[34] Ni, M., Tian, F. B., Xiang, D. D., Yu, B. Characteristics of inflammatory factors and lymphocyte subsets in patients with severe COVID-19. Journal of Medical Virology, 2020. https://doi.org/10.1002/jmv.26070

[35] Cartier, A., Côté, M., Lemieux, I., Pérusse, L., Tremblay, A., Bouchard, C., Després, J. P. Age-related differences in inflammatory markers in men: contribution of visceral adiposity. Metabolism, 2009, 58(10): 1452-1458. https://doi.org/10.1016/j.metabol.2009.04.025

[36] Gong, J., Dong, H., Xia, S.Q., Huang, Y.Z., Wang, D., Zhao, Y., Liu, W., Tu, S., Zhang, M., Wang, Q., Lu, F. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. MedRxiv,, 2020. DOI: https://doi.org/10.1101/2020.02.25.20025643

[37] De Wit, E., van Doremalen, N., Falzarano, D. et al. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol, 2016, 14: 523-

  DOI: https://doi.org/10.30564/jer.v2i1.2517

534.
https://doi.org/10.1038/nrmicro.2016.81
https://www.nature.com/articles/nrmicro.2016.81.pdf?origin=ppub

[38] Park WY, et al. Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am. J. Respir. Crit. Care Med., 2001, 164: 1896-1903.
https://doi.org/10.1164/ajrccm.164.10.2104013
PubMed: 11734443

[39] Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, Mou HM, Wang LH, Zhang HR, Fu WJ, Luo T, Liu F, Guo QN, Chen C, Xiao HL, Guo HT, Lin S, Xiang DF, Shi Y, Pan GQ, Li QR, Huang X, Cui Y, Liu XZ, Tang W, Pan PF, Huang XQ, Ding YQ, Bian XW. A pathological report of three COVID-19 cases by minimal invasive autopsies. Zhonghua Bing Li Xue Za Zhi, 2020, 49(5): 411-417. (in Chinese)
DOI: 10.3760/cma.j.cn112151-20200312-00193
PMID: 32172546

[40] Gupta, R., Ghosh, A., Singh, A.K., Misra, A. Clinical Considerations for Patients with Diabetes in Times of COVID-19 Epidemic. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 2020, 14: 211-212.
https://doi.org/10.1016/j.dsx.2020.03.002

[41] Cameron, M.J., Ran, L., Xu, L., Danesh, A., Bermejo-Martin, J.F., Cameron, C.M., Muller, M.P., Gold, W.L., Richardson, S.E., Poutanen, S.M., Willey, B.M. Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. Journal of virology, , 2007, 81(16): 8692-8706.
DOI: 10.1128/JVI.00527-07

[42] Cheung, C. Y., L. L. Poon, I. H. Ng, W. Luk, S. F. Sia, M. H. Wu, K. H. Chan, K. Y. Yuen, S. Gordon, Y. Guan, J. S. Peiris. Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis. J. Virol., 2005, 79: 7819-7826.
DOI: 10.1128/JVI.79.12.7819-7826.2005

[43] Lo, A.W., Tang, N.L., To, K.F. How the SARS coronavirus causes disease: host or organism?. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, , 2006, 208(2): 142-151.
https://doi.org/10.1002/path.1897

[44] Prompetchara, E., Ketloy, C., Palaga, T.. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol, 2020, 38(1): 1-9.
http://apjai-journal.org/wp-content/uploads/2020/03/1.pdf?fbclid=IwAR1kVlFnoc6mobqEy7FDz_93fX__AaY8ZgE4TUwtjzhh8oVqgs82rgf3QoU

[45] Faure, E., Poissy, J., Goffard, A., Fournier, C., Kipnis, E., Titecat, M., Bortolotti, P., Martinez, L., Dubucquoi, S., Dessein, R., Gosset, P. Distinct immune response in two MERS-CoV-infected patients: can we go from bench to bedside?. PloS one, 2014, 9(2): e88716.
https://doi.org/10.1371/journal.pone.0088716

[46] Hamano, E., Hijikata, M., Itoyama, S., Quy, T., Phi, N.C., Long, H.T., Van Ban, V., Matsushita, I., Yanai, H., Kirikae, F., Kirikae, T. Polymorphisms of interferon-inducible genes OAS-1 and MxA associated with SARS in the Vietnamese population. Biochemical and biophysical research communications, 2005, 329(4): 1234-1239.
https://doi.org/10.1016/j.bbrc.2005.02.101

[47] Tang, N.L.S., Chan, P.K.S., Wong, C.K., To, K.F., Wu, A.K.L., Sung, Y.M., Hui, D.S.C., Sung, J.J.Y., Lam, C.W.K. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. Clinical chemistry, 2005, 51(12): 2333-2340.
https://doi.org/10.1373/clinchem.2005.054460

[48] Shao, L., Sperber, K. Impaired regulation of HLA-DR expression in human immunodeficiency virus-infected monocytes. Clinical and Diagnostic Laboratory Immunology, 2002, 9(4): .739-746.
DOI: 10.1128/CDLI.9.4.739-746.2002

[49] Kobasa, D., Jones, S.M., Shinya, K., Kash, J.C., Copps, J., Ebihara, H., Hatta, Y., Kim, J.H., Halfmann, P., Hatta, M., Feldmann, F. Aberrant innate immune response in lethal infection of macaques with the 1918 influenza virus. Nature, 2007, 445(7125): 319-323.
https://doi.org/10.1038/nature05495

[50] Wong, C.K., Tsang, C.M., Ip, W.K., Lam, C.W.K. Molecular mechanisms for the release of chemokines from human leukemic mast cell line (HMC)-1 cells activated by SCF and TNF-α: roles of ERK, p38 MAPK, and NF-κB. Allergy, 2006, 61(3): 289-297.
https://doi.org/10.1111/j.1398-9995.2006.00972.x

[51] Subissi L., Posthuma C. C., Collet A., Zevenhoven-Dobbe J. C., Gorbalenya A. E., Decroly E., Snijder E. J., Canard B., Imbert I. One severe acute respiratory syndrome coronavirus protein complex integrates processive RNA polymerase and exonuclease activities. Proc. Natl. Acad. Sci. U.S.A., 2014, 111: E3900-E3909.
DOI: 10.1073/pnas.1323705111

[52] Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M.,

Shi Z., Hu Z., Zhong W., Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 2020, 30: 269-271
DOI: 10.1038/s41422-020-0282-0

[53] Holshue M. L., DeBolt C., Lindquist S., Lofy K. H., Wiesman J., Bruce H., Spitters C., Ericson K., Wilkerson S., Tural A., Diaz G., Cohn A., Fox L., Patel A., Gerber S. I., Kim L., Tong S., Lu X., Lindstrom S., Pallansch M. A., Weldon W. C., Biggs H. M., Uyeki T. M., Pillai S. K. Washington State 2019-nCoV Case Investigation Team , First Case of 2019 Novel Coronavirus in the United States. N. Engl. J. Med., 2020, 382: 929-936
DOI: 10.1056/NEJMoa2001191

[54] Kirchdoerfer R. N., Ward A. B. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. Nat. Commun., 2019, 10: 2342
DOI: 10.1038/s41467-019-10280-3

[55] Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M., Shi Z., Hu Z., Zhong W., Xiao G., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 2020, 30: 269-271.
DOI: 10.1038/s41422-020-0282-0

[56] Holshue M. L., DeBolt C., Lindquist S., Lofy K. H., Wiesman J., Bruce H., Spitters C., Ericson K., Wilkerson S., Tural A., Diaz G., Cohn A., Fox L., Patel A., Gerber S. I., Kim L., Tong S., Lu X., Lindstrom S., Pallansch M. A., Weldon W. C., Biggs H. M., Uyeki T. M., Pillai S. K., Washington State 2019-nCoV Case Investigation Team , First Case of 2019 Novel Coronavirus in the United States. N. Engl. J. Med., 2020, 382: 929-936.
DOI: 10.1056/NEJMoa2001191

[57] Gao, Y., Yan, L., Huang, Y., Liu, F., Zhao, Y., Cao, L., Wang, T., Sun, Q., Ming, Z., Zhang, L., Ge, J. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science, 2020, 368(6492):779-782.
DOI: 10.1126/science.abb7498

[58] Spinner, C.D., Gottlieb, R.L., Criner, G.J., López, J.R.A., Cattelan, A.M., Viladomiu, A.S., Ogbuagu, O., Malhotra, P., Mullane, K.M., Castagna, A., Chai, L.Y.A. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA, 2020, 324(11): 1048-1057.
DOI: 10.1001/jama.2020.16349

[59] Rochwerg, B., Agarwal, A., Zeng, L., Leo, Y.S., Appiah, J.A., Agoritsas, T., Bartoszko, J., Brignardello-Petersen, R., Ergan, B., Ge, L., Geduld, H. Remdesivir for severe covid-19: a clinical practice guideline. bmj, 2020, 370.
https://doi.org/10.1136/bmj.m2924

[60] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the treatment and management of patients with COVID-19. Clin Infect Dis;ciaa, 2020, 478.
DOI: 10.1093/cid/ciaa478 pmid:32338708

[61] Ye W, Yao M, Dong Y, et al.. Remdesivir (GS-5734) impedes enterovirus replication through viral RNA synthesis inhibition. Front Microbiol, 2020, 11: 1105.
DOI: 10.3389/fmicb.2020.01105 pmid:32595613

[62] National Institutes of Health. COVID-19 treatment guidelines. 2020.
https://www.covid19treatmentguidelines.nih.gov/whats-new/

[63] Gandhi, M., Beyrer, C., Goosby, E. Masks do more than protect others during COVID-19: Reducing the inoculum of SARS-CoV-2 to protect the wearer. Journal of general internal medicine, 2020: 1-4.
https://doi.org/10.1007/s11606-020-06067-8

[64] Centers for Disease Control and Prevention. Regarding the Use of Cloth Face Coverings, Especially in Areas of Significant Community-Based Transmission, 2020.
https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover.html

[65] World Health Organization. Advice on the use of masks in the context of COVID-19. Interim guidance, 2020. Accessible at:
https://apps.who.int/iris/handle/10665/331693

[66] World Health Organization. Advice on the use of masks in the context of COVID-19, Interim guidance, 5 June 2020. Accessible at:
https://www.who.int/publications/i/item/advice-on-the-use-of-masks-in-the-community-during-home-care-and-in-healthcare-settings-in-the-context-of-the-novel-coronavirus-(2019-ncov)-outbreak

[67] Gandhi, M., Yokoe, D.S., Havlir, D.V. Asymptomatic transmission, the Achilles' heel of current strategies to control COVID-19, 2020.
DOI: 10.1056/NEJMe2009758

[68] He, X., Lau, E.H., Wu, P., Deng, X., Wang, J., Hao, X., Lau, Y.C., Wong, J.Y., Guan, Y., Tan, X., Mo, X. Temporal dynamics in viral shedding and transmissibility of COVID-19. Nature medicine, 2020, 26(5): 672-675.
https://doi.org/10.1038/s41591-020-0869-5

[69] Handel, A., Li, Y., McKay, B., Pawelek, K.A., Zarnitsyna, V., Antia, R. Exploring the impact of inoculum dose on host immunity and morbidity to inform model-based vaccine design. PLoS computa-

  DOI: https://doi.org/10.30564/jer.v2i1.2517

tional biology, 2018, 14(10): e1006505.
https://doi.org/10.1371/journal.pcbi.1006

[70] Miller, D.S., Kok, T., Li, P. The virus inoculum volume influences outcome of influenza A infection in mice. Laboratory animals, 2013, 47(1): 74-77.
https://doi.org/10.1258/la.2012.011157

[71] McKenney, D.G., Kurath, G., Wargo, A.R. Characterization of infectious dose and lethal dose of two strains of infectious hematopoietic necrosis virus (IHNV). Virus research, 2016, 214: 80-89.
https://doi.org/10.1016/j.virusres.2015.12.020

[72] Kai, D., Goldstein, G.P., Morgunov, A., Nangalia, V., Rotkirch, A. Universal masking is urgent in the covid-19 pandemic: Seir and agent based models, empirical validation, policy recommendations, 2020. arXiv preprint arXiv:2004.13553.
arXiv:2004.1355 arXiv:2004.13553v1

[73] Niemietz B. Photo of 1918 college football fans wearing face masks points to the past and future. New York Daily News, 2020. Accessible at:
https://www.nydailynews.com/coronavirus/ny-photo-mask-georgia-tech-1918-pandemic-flu-coronavirus-20200525-fbkqrf6tqjgf7plck2emfjdjvi-story.html

[74] Ward A. How masks helped Hong Kong control the coronavirus. Vox, 2020. Accessible at:
https://www.vox.com/2020/5/18/21262273/coronavirus-hong-kong-masks-deaths-new-york

[75] Watanabe M, Caruso D, Tuccinardi D, Risi R, Zerunian M, Polici M, Pucciarelli F, Tarallo M, Strigari L, Manfrini S, Mariani S, Basciani S, Lubrano C, Laghi A, Gnessi L. Visceral fat shows the strongest association with the need of intensive care in patients with COVID-19. Metabolism, 2020, 111: 154319.
DOI: 10.1016/j.metabol.2020.154319. Epub 2020 Jul 23. PMID: 32712222; PMCID: PMC7377788

[76] Petersen A, Bressem K, Albrecht J, Thieß HM, Vahldiek J, Hamm B, Makowski MR, Niehues A, Niehues SM, Adams LC. The role of visceral adiposity in the severity of COVID-19: Highlights from a unicenter cross-sectional pilot study in Germany. Metabolism, 2020, 110: 154317.
DOI: 10.1016/j.metabol.2020.154317. Epub. PMID: 32673651; PMCID: PMC7358176

[77] Iacobellis G, Malavazos AE, Ferreira T. Sep 2. COVID-19 Rise in Younger Adults with Obesity: Visceral Adiposity Can Predict the Risk. Obesity (Silver Spring), 2020, 28(10): 1795.
DOI: 10.1002/oby.22951. Epub. PMID: 32619294; PMCID: PMC7361935

[78] Wajchenberg, B.L., Giannella-Neto, D., Da Silva, M.E.R., Santos, R.F. Depot-specific hormonal characteristics of subcutaneous and visceral adipose tissue and their relation to the metabolic syndrome. Hormone and metabolic research, 2002, 34(11/12): 616-621.
DOI: 10.1055/s-2002-38256

[79] Pedersen, B.K., Febbraio, M.A. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nature Reviews Endocrinology, 2012, 8(8): 457-465.
https://doi.org/10.1038/nrendo.2012.49

[80] Dyck, D.J., Putman, C.T., Heigenhauser, G.J., Hultman, E., Spriet, L.L. Regulation of fat-carbohydrate interaction in skeletal muscle during intense aerobic cycling. American Journal of Physiology-Endocrinology And Metabolism, 1993, 265(6): .E852-E859.
https://doi.org/10.1152/ajpendo.1993.265.6.E852

[81] Romijn, J.A., Coyle, E.F., Sidossis, L.S., Zhang, X.J., Wolfe, R.R. Relationship between fatty acid delivery and fatty acid oxidation during strenuous exercise. Journal of Applied Physiology, 1995, 79(6): 1939-1945.
DOI: https://doi.org/10.1152/jappl.1995.79.6.1939

[82] Robergs, R.A., Frankel, C. Relationship between fatty acid delivery and fatty acid oxidation during exercise. Journal of Applied Physiology, 1996, 81(3): 1450-1452.
https://doi.org/10.1152/jappl.1996.81.3.1450

[83] Spriet, L.L. New insights into the interaction of carbohydrate and fat metabolism during exercise. Sports medicine, 2014, 44(1): 87-96.
DOI: https://doi.org/10.1007/s40279-014-0154-1

[84] Hargreaves, M., Spriet, L.L. Exercise metabolism: fuels for the fire. Cold Spring Harbor perspectives in medicine, 2018, 8(8): a029744.
DOI: 10.1101/cshperspect.a029744

[85] Robinson, S.L. Fat oxidation during exercise: significance, determinants and response to nutrition (Doctoral dissertation, University of Birmingham), 2016.
http://etheses.bham.ac.uk/id/eprint/7079

[86] Glatz, J.F., Luiken, J.J., Bonen, A. Membrane fatty acid transporters as regulators of lipid metabolism: implications for metabolic disease. Physiological reviews, 2010.
https://doi.org/10.1152/physrev.00003.2009

[87] Sahlin, K. Control of lipid oxidation at the mitochondrial level. Applied Physiology, Nutrition, and Metabolism, 2009, 34(3): 382-388.
https://doi.org/10.1139/H09-027

[88] Smith, B.K., Bonen, A., Holloway, G.P. A dual mechanism of action for skeletal muscle FAT/CD36 during exercise. Exercise and sport sciences reviews, 2012, 40(4): 211-217.
DOI: 10.1097/JES.0b013e31825eb263

[89] Franco, C., Brandberg, J., Lönn, L., Andersson,

B., Bengtsson, B.A., Johannsson, G. Growth hormone treatment reduces abdominal visceral fat in postmenopausal women with abdominal obesity: a 12-month placebo-controlled trial. The Journal of Clinical Endocrinology & Metabolism, 2005, 90(3): 1466-1474.
https://doi.org/10.1210/jc.2004-1657

[90] Ronnemaa, T., Karonen, S.L., Rissanen, A., Koskenvuo, M., Koivisto, V.A. Relation between plasma leptin levels and measures of body fat in identical twins discordant for obesity. Annals of internal medicine, 1997, 126(1): 26-31.
https://doi.org/10.7326/0003-4819-126-1-199701010-00004

[91] Dua, A., Hennes, M.I., Hoffmann, R.G., Maas, D.L., Krakower, G.R., Sonnenberg, G.E. and Kissebah, A.H. Leptin: a significant indicator of total body fat but not of visceral fat and insulin insensitivity in African-American women. Diabetes, 1996, 45(11): 1635-1637.
https://doi.org/10.2337/diab.45.11.1635

[92] Banerji, M.A., Faridi, N., Atluri, R., Chaiken, R.L., Lebovitz, H.E. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. The journal of clinical endocrinology & metabolism, 1999, 84(1): 137-144.
DOI: https://doi.org/10.1210/jcem.84.1.5371

[93] Nam, J.S., Cho, M., Park, J.S., Ahn, C.W., Cha, B.S., Lee, E.J., Lim, S.K., Kim, K.R. and Lee, H.C. Triiodothyronine level predicts visceral obesity and atherosclerosis in euthyroid, overweight and obese subjects: T3 and visceral obesity. Obesity Research & Clinical Practice, 2010, 4(4): e315-e323.
DOI: https://doi.org/10.1016/j.orcp.2010.08.003

[94] Yohei Tanaka. Three-dimensional volumetric assessment of body sculpting using a uniform heating radio frequency device in Asians, Journal of Cosmetic and Laser Therapy, 2015, 17(4): 194-199.
DOI: https://doi.org/10.3109/14764172.2015.1007059

[95] Franco, W., Kothare, A., Goldberg, D.J. Controlled volumetric heating of subcutaneous adipose tissue using a novel radiofrequency technology. Lasers in Surgery and Medicine: The Official Journal of the American Society for Laser Medicine and Surgery, 2009, 41(10): 745-750.
DOI: https://doi.org/10.1002/lsm.20876

[96] Franco, W., Kothare, A., Ronan, S.J., Grekin, R.C., McCalmont, T.H. Hyperthermic injury to adipocyte cells by selective heating of subcutaneous fat with a novel radiofrequency device: feasibility studies. Lasers in surgery and medicine, 2010, 42(5): 361-370.
DOI: https://doi.org/10.1002/lsm.20925

[97] del Pino Emilia, M., Rosado, R.H., Azuela, A., Graciela, M.G., Argüelles, D., Rodríguez, C., Rosado, G.M. Effect of controlled volumetric tissue heating with radiofrequency on cellulite and the subcutaneous tissue of the buttocks and thighs. Journal of drugs in dermatology: JDD, 2006, 5(8): 714-722.
PMID: 16989185

[98] Paul, M., Mulholland, R.S. A new approach for adipose tissue treatment and body contouring using radiofrequency-assisted liposuction. Aesthetic plastic surgery, 2009, 33(5): 687-694.
DOI: 10.1007/s00266-009-9342-z

[99] Kapoor, R., Shome, D., Ranjan, A. Use of a novel combined radiofrequency and ultrasound device for lipolysis, skin tightening and cellulite treatment. Journal of Cosmetic and Laser Therapy, 2017, 19(5): 266-274.
DOI: https://doi.org/10.1080/14764172.2017.1303169

[100]Ranasinghe, C., Ozemek, C., Arena, R. Exercise and well-being during COVID-19-time to boost your immunity. Expert Review of Anti-infective Therapy, 2020, 1-6.
DOI: https://doi.org/10.1080/14787210.2020.1794818

[101]Simpson, R. J., Kunz, H., Agha, N., Graff, R. Exercise and the regulation of immune functions. In Progress in molecular biology and translational science, Academic Press, 2015, 135: 355-380.
DOI: https://doi.org/10.1016/bs.pmbts.2015.08.001

[102]Nieman, D. C., Wentz, L. M. The compelling link between physical activity and the body's defense system. Journal of sport and health science, 2019, 8(3): 201-217.
DOI: https://doi.org/10.1016/j.jshs.2018.09.009

[103]Burtscher, J., Burtscher, M., Millet, G. P. (Indoor) isolation, stress and physical inactivity: vicious circles accelerated by Covid-19?. Scandinavian journal of medicine & science in sports, 2020.
DOI: https://doi.org/10.1111/sms.13706

[104]Martin, S. A., Pence, B. D., Woods, J. A. Exercise and respiratory tract viral infections. Exercise and sport sciences reviews, 2009, 37(4): 157.

[105]KOSTKA, T., BERTHOUZE, S., LACOUR, J. R., BONNEFOY, M. The symptomatology of upper respiratory tract infections and exercise in elderly people. Medicine & Science in Sports & Exercise, 2000, 32(1).
PMID: 10647528 DOI: 10.1097/00005768-200001000-00008

[106]Matthews, C. E., Ockene, I. S., Freedson, P. S., Rosal, M. C., Merriam, P. A., Hebert, J. R. Moderate to

DOI: https://doi.org/10.30564/jer.v2i1.2517

vigorous physical activity and risk of upper-respiratory tract infection. Medicine and science in sports and exercise, 2002, 34(8): 1242-1248.
DOI: 10.1097/00005768-200208000-00003 PMID: 12165677

[107]Wong, C. M., Lai, H. K., Ou, C. Q., Ho, S. Y., Chan, K. P., Thach, T. Q., Peiris, J. S. M. Is exercise protective against influenza-associated mortality?. PLoS One, 2008, 3(5): e2108.
https://doi.org/10.1371/journal.pone.0002108

[108]Nieman, D. C., Johanssen, L. M., Lee, J. W. Infectious episodes in runners before and after a roadrace. The Journal of sports medicine and physical fitness, 1989, 29(3): 289-296.
PMID: 2635263

[109]McFadden Jr, E. R., Ingram Jr, R. H. Exercise-induced asthma: Observations on the initiating stimulus. New England Journal of Medicine, 1979, 301(14): 763-769.
DOI: 10.1056/NEJM197910043011406

[110]George SA, Khan S, Briggs H, Abelson JL. CRH-stimulated cortisol release and food intake in healthy, non-obese adults. Psychoneuroendocrinology, 2010, 35(4): 607-612. Available from:
https://dx.doi.org/10.1016/j.psyneuen.2009.09.017

[111]Chiodini I, Di Lembo S, Morelli V, Epaminonda P, Coletti F, Masserini B, Scillitani A, Arosio M, Adda G: Hypothalamic-pituitary-adrenal activity in type 2 diabetes: Diabetes Care, 2007, 30(1): 83-88.
https://doi.org/10.2337/dc06-1267

[112]Hill EE, Zack E, Battaglini C, Viru M, Viru A, Hackney AC. Exercise and circulating cortisol levels: The intensity threshold effect. Journal of Endocrinological Investigation, 2008, 31(7): 587-591. Available from:
https://dx.doi.org/10.1007/bf03345606

[113]Skoluda N, Dettenborn L, Stalder T, Kirschbaum C. Elevated hair cortisol concentrations in endurance athletes. Elsevier BV, 2012. Available from:
https://dx.doi.org/101016/j.psyneuen.2011.09.001

[114]Landt, M., Lawson G., Helgeson J., Davila-Roman, V., Laderson J., Jaffe, A., Hickner, R. Prolonged exercise decreases serum leptin concentrations. Metabolism, 1997, 46(10): 1109-1112.
DOI: https://doi.org/10.1016/S0026-0495(97)90200-6

[115]Sofra, X. How to get rid of visceral fat: a randomised double-blind clinical trial. Journal of Aesthetic Nursing, 2020, 9(7): 268-275.
DOI: https://doi.org/10.12968/joan.2020.9.7.268

[116]Sofra, X. Gain without pain: beyond sport effortless exercise solutions. Journal of Aesthetic Nursing, 2020, 9(5): 202-210.
DOI: https://doi.org/10.12968/joan.2020.9.5.202

[117]Sofra X. The Importance of Systemic Balance in Safeguarding Health: A Randomized Double-Blind Clinical Trial on VLDL, Triglycerides, Free T3, Leptin, Ghrelin, Cortisol and Visceral Adipose Tissue. Health, 2020, 12(8).
DOI: https://doi.org/10.4236/health.2020.128078

[118]Sofra, X., Badami, S. Adverse Effects of Sedentary Lifestyles: Inflammation, and High-Glucose Induced Oxidative Stress-A Double Blind Randomized Clinical Trial on Diabetic and Prediabetic Patients. Health, 2020, 12(08): 1029. Article ID:102260, 20 pages
DOI: https://doi.org/10.4236/health.2020.128076

[119]Sofra, X., Lampe, N. Technological Advances in Accelerated Wound Repair and Regeneration. Health, 2020, 12(7): 717-737.
DOI: 10.4236/health.2020.127053

[120]Sofra, X., Lampe, N. A Randomized Longitudinal Double-Blind Clinical Trial on Long-Term Neuropathic Symptomatology Relief & Pain Analgesia. Health, 2020, 12(07): 738. ID:101363,12 pages
DOI: 10.4236/health.2020.127054

[121]Sofra, X., Badami, S. A Review of COVID-19 associated factors: CRP, Creatinine, Bilirubin, VLDL, HDL, Triglycerides, Cortisol and Thyroid Function. J Endo Metabol Res, 2020, 1(2): 1-17.
https://www.maplespub.com/webroot/files/A-Review-of-COVID19-associated-factors-CRP-Creatinine-Bilirubin-VLDL-HDL-Triglycerides-Cortisol-and-Thyroid-Function_1601046593.pdf

[122]Sofra, X. Dynamics of Female Sexuality; Hidden Emotional Issues. Health, 2020, 12(6): 694-708.
DOI: 10.4236/health.2020.126051

[123]Sofra, X., Lampe, N. Empowering the woman: a comprehensive model of sexual anti-ageing. Journal of Aesthetic Nursing, 2020, 9(3): 118-127.
DOI: https://doi.org/10.12968/joan.2020.9.3.118

[124]Sofra, X. The Affinity between Obesity and COVID-19. J Endo Metabol Res, 2020, 1(2): 1-13.
https://maplespub.com/webroot/files/The-Affinity-between-Obesity-and-COVID-19_1602748373.pdf

[125]Sofra X, Badami S. A Review of COVID19 associated factors: CRP, Creatinine, Bilirubin, VLDL, HDL, Triglycerides, Cortisol, and Thyroid Function.J Endo Metabol Res., 2020, 1(2): 1-17.
https://maplespub.com/article/A-Review-of-COVID19-associated-factors-CRP-Creatinine-Bilirubin-VLDL-HDL-Triglycerides-Cortisol-and-Thyroid-Function