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ARTICLE

The Danger within: Covid-19 Affinity for ACE2 Receptors in Adipose Tissue and Testes. The Protective Effects of Estradiol, Fitness, and Weight Management

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ABSTRACT

The imminent danger of the Covid-19 pandemic has accelerated research in pharmaceuticals that either target the viral Spike proteins fusion with ACE2 receptors, or the infectious RNA replication that often overwhelms immune defences. The scope of this review was to elucidate the main human vulnerabilities to Covid-19, including the accumulation of ACE2 receptors in testes, adipose tissue, thyroid, heart and kidneys that escalate viral affinity in males, the aged, and certain medical conditions, including diabetes, CVD, and pulmonary diseases. Pre-existing inflammation inherent in obesity may exacerbate the "cytokine storm," a rampaging immune reaction during the course of Covid-19 that is deleterious to the host. We examined the molecular dynamics illustrating the action of new therapeutics necessary for Covid-19 patients; the estradiol advantage hypothesis; alternative therapies including hormone replacement procedures and mesenchymal stem cells; plus preventive and protective interventions. The current perspective also explored the primary components of dysregulated health predisposing individuals to Covid-19, including hormonal imbalance, increased lipids and lipoproteins, thyroid dysfunction, degraded fitness, and age-related testosterone decline accompanied by cortisol increase that provokes stress eating behaviours and weight accumulation. Obesity increases the probability of Covid-19 infection due to its abundance of ACE2 receptors; while physical activity may decrease Covid-19 vulnerability, by reducing fat and increasing muscle mass that manifests a relatively inhibited ACE2 expression. Several weight management solutions feature lasers and radiofrequency which diminish subcutaneous adiposity but do not enhance fitness. A data metanalysis of seven recently published clinical studies on 95 obese individuals, 73 males and 22 females with an average BMI of 30.9, demonstrated visceral fat reduction combined with increased skeletal muscle mass. It also revealed a statistically significant decrease in BMI, lipids, lipoproteins, inflammation and toxicity as measured by CRP, Creatinine and Bilirubin respectively, juxtaposed by optimally healthier levels of Cortisol, Testosterone, Free T3, IGF-1, Insulin, and the appetite controlling hormones Leptin and Ghrelin.

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1. Introduction

Coronavirus is an enveloped viral conglomerate, synthesized by around 30,000 nucleotides, and expressed into a wide variety of diseases that vary from influenza, to the severe acute respiratory syndrome (SARS), the Middle East respiratory syndrome (MERS), and its current evolved version of SARS-Cov-2 or coronavirus disease 2019 (Covid-19) that has currently infected over thirty four million individuals globally, with over a million, and constantly rising, mortality rates [1].

2. The Covid-19 Affinity for ACE2 Receptors

The Covid-19 two main genes ORF1a and ORF1b encode sixteen non-structural proteins, and four structural proteins: the spike (S), divided into S1 / S2 subtypes, membrane (M) and envelope (E) proteins on the viral surface, and the nucleocapsid (N) proteins, associated with the viral RNA. The S glycoproteins reflect the characteristic viral morphology surrounded by "coronas" the Greek word for crowns. S1 subunit recognizes and binds to angiotensin-converting enzyme 2 (ACE2) receptors, and S2 releases the fusion peptide to secure the connection [2,3]. ACE2 is a membrane-bound enzyme. A Disintegrin And Metalloprotease 17 (ADAM17) is able to cleave ACE2 and cast it into the blood and body fluids, rendering the S1 /ACE2 fusion less likely [4].

The S1/ACE2 affinity has been documented for over 15 years [5-7]. The M and E proteins are in charge of the viral assembly and encapsulation of genetic material respectively [8,9]. The N proteins are intertwined with the viral genome and are involved in replicating and transcribing the viral RNA, eventually overwhelming the human biomolecular network. Due to the imminent threat of the pandemic most research has focused on therapeutics rather than prevention. A series of studies postulate that theophylline and pyrimidone can prevent the replicating ability of the N protein, by blocking contact of the protein's N-terminus with RNA, thus inhibiting viral multiplication [10]. Covid-19 does not respond to most nucleotide analogues (NA), designed to interfere with viral replication, due to the Covid-19 inherent Exonuclease (ExoN) domain that compromises NAs; however, it appears to be responsive to the new NA drug Remdesivir, that features the active metabolite, GS441524 [11]. Another therapeutic research target is drugs intended to obstruct the Covid-19 entry into the human system associated with TMPRSS2 inhibitors, such as camostat mesylate [12], ACE2 receptor blockers, or calmodulin antagonists [13]. Nevertheless, caution should be taken with ACE inhibitors often used to treat diabetes and heart disease. ACE inhibitors prevent the conversion of angiotensin I into Angiotensin II, a peptide in the renin-angiotensin system (RAS) that increases blood pressure. However, ACE inhibitors do not block the ACE2 receptors, because ACE and ACE2 are different entities. What can actually stop the virus from binding to the ACE2 receptor is ADAM17, which is elevated by Angiotensin II. ADAM 17 cleaves ACE2 from the cellular membrane. Consequently, ACE2 sheds into body fluids. ACE inhibitors ultimately block Angiotensin II production resulting in insufficient amounts of ADAM17. Without ADAM17, ACE2 receptors cannot shed into body fluids; they remain available to fuse with the viral S protein, ultimately infecting the human system [14]. On the other hand, there are medical conditions like neurogenic hypertension where obstructing Angiotensin II via ACE inhibitors is necessary [15]. Hence, the dilemma on whether or not to use ACE inhibitors with an individual who suffers from both Covid-19 and hypertension. ACE inhibitors will reduce Angiotensin II and moderate high blood pressure. On the other hand, diminished Angiotensin II will restrict ADAM17, and consequently ACE2 shedding that could potentially protect against the S/ACE2 fusion, exposing the individual to a widespread Covid-19 infection. Inescapable side effects are always an issue in treating an unhealthy body.

3. Why are Males more Vulnerable to Covid-19?

Research has repeatedly confirmed that Covid-19 exhibits a greater affinity for males. ACE2 receptors are again protagonists in elucidating the increased fatalities observed among men rather than women [16,17], due to the high incidence of ACE2 receptors in male tissues [18]. ACE2 is largely expressed in spermatogonia in human testes, the androgen producing Leydig cells and Sertoli cells involved in the nourishment of spermatozoa in humas testes; this ACE2/male tissues bond also exposes the male reproductive system to possible malfunction following Covid-19 infection [19,20]. Liu et al, analysed both embryonic primordial germ cells (PGCs) and adult Sertoli cells and postulated that all testis cells are enriched in ACE2 ex-

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pression starting from the embryonic stage all the way to adulthood [21]. There is an additional process increasing the probability of infection in males. The androgen receptor (AR) that is largely expressed in male tissues, promotes the expression of type II transmembrane serine protease (TMPRSS2) which acts as a catalyst priming both the viral S glycoprotein and the organ's ACE2 receptor, thus accelerating the fusion of coronavirus' Spike (S) protein with ACE2 receptors, inevitably infecting the body with Covid-19 [22-24].

4. The Importance of ACE2 Expression in Vital Organs

Although ACE2 receptors, prepared by proteases like TMPRSS2 may be the point of viral entry, autopsies of Covid-19 patients revealed a higher incidence of the cathepsin L1 protein (CTSL) rather than ACE2 receptors in the lungs. These investigators found a dysfunctional biological landscape characterized by deteriorated protein translation and lipid metabolism as well as substantially damaged lungs, kidneys, spleen, liver, heart, thyroid, and testes featuring a reduced number of Leydig cells [25]. Their results, however may reflect the lethal aftereffects of Covid-19 rather than the initial phase of the infection. In fact, CTSL is another protease facilitating the fusion of the Covid-19 S protein with ACE2 receptors [26]. Additionally, Li et al. who examined 31 different human tissues, found that ACE2 expression in the lungs was in fact moderate [27], suggesting the possibility that the increased CTSL in the lungs found post-mortem may reflect the virus exploiting CTSL to increase its probability of successful fusion with ACE2 receptors. Li et al. found that ACE2 receptors were more abundant in testes, adipose tissue, heart, thyroid and kidneys with a minimum expression in the muscles, blood and blood vessels. Although ACE2 receptors in most vital organs were equivalent in males, females, old, young, Asian and non-Asian populations, the immune responses widely varied in the four groups delineating greater vulnerability among the male and older groups. The increased incidence of ACE2 in male tissues explains the younger men's susceptibility to Covid-19; while the dimension of immunity, including evidence that age-related testosterone decline affects the activity of respiratory muscles, elucidates the Covid-19 vulnerability of older males who manifest an age-related testosterone decline [28,29].

Overall, focusing on one component, for example testosterone, will leave us with contradictory findings, where both high and low testosterone may be associated with increased Covid-19 vulnerability due to the multifactorial causation of viral infections. A more comprehensive perspective is necessary that spotlights increased ACE2 expression in other tissues, differential immunity responses between males / females, the old /young, differential levels of inflammation as well as the very important dimension of hormonal imbalance that becomes prominent with aging.

One aspect of hormonal imbalance, delineated by the thyroid disorder, has been directly connected to Covid-19, indicating a malfunction in transforming free thyroxine (T4) to free triiodothyronine level (Free T3) [30,31]. Additionally, thyroid dysregulation affects disorders presenting the highest incidence of Covid-19 mortality rates, such as Diabetes and CVD [32-35]. Adrenals have a moderate ACE2 expression, yet, research reveals that increased levels of the stress hormone, cortisol, decreases the chances of surviving Covid-19. High cortisol concentrations have been linked to diabetes and heart disease [36-38].

5. Hormones, Inflammation and Alternative Treatment Modalities

The lower number of overall Covid-19 female fatalities has highlighted the anti-inflammatory effects of estradiol [39]. There is evidence from animal models that estradiol is associated with a twofold decrease of ACE2 receptors in the female kidney [40]. Normally, ACE2 is highly expressed in the kidneys, therefore, the estradiol suppression of ACE2 receptors in the female kidneys may be partly responsible for their lower mortality rates. A recent review examined evidence that the anti-inflammatory effects of steroids 17b-estradiol (E2) and progesterone (P4) may be able to counteract the deleterious effects of the hyper-inflammatory state associated with the cytokine storm, where white blood cells indiscriminately attack both the virus and the vital organs that contain it [41]. Interestingly, a study of 68,466 Covid-19 cases found that premenopausal females had a 15% higher incidence of infection than males while postmenopausal women evidenced an equivalent susceptibility to men; yet, males demonstrated 50% higher mortality rates. In other words, premenopausal women were slightly more susceptible to the disease than men, however, they were able to overcome it more efficiently than men. Fatality risk was reduced by 50% in postmenopausal women treated with estradiol. However, estradiol treatment had no effect on premenopausal women who manifested optimal estradiol levels in their systems [42]. In conclusion, indiscriminate administration of estradiol to all women may not have the expected desirable effects with regards to Covid-19. Importantly, the evidence of increased susceptibility risk among premenopausal women should be taken into consideration.

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This higher susceptibility may be due to the inflammatory C-reactive protein (CRP) being higher in females than males, as a survey on 22,000 individuals indicated [43]. The hypothesis being that the higher the initial inflammatory state, the higher the possibility of contracting the virus; however due to estradiol's anti-inflammatory influence counteracting the effects of the cytokine storm, female fatality rates are lower than men. Earlier research indicated that estradiol and cyproterone acetate (CPA) hormone therapy on postmenopausal women had no effects on CRP; however, estradiol plus norethindrone acetate and levonorgestrel significantly increased CRP unlike the no-treatment control group that displayed no CRP changes [44]. These results suggest caution with hormonal replacement therapy cocktails (HRT) that can potentially result in hormonal imbalance, and possibly trigger unwanted processes increasing inflammation. Silvestri et al reported that although HRT raises CRP, it actually appears to decrease other inflammatory markers such as interleukin-6 (IL-6), soluble thrombomodulin (TM) plasma levels, and E-selectin concentrations [45]. TM is often associated with organ failure[46] and the risk of haemorrhage[47], which signify the presence of inflammation. On the other hand, IL-6 can act as a pro-inflammatory cytokine and an anti-inflammatory myokine, so again, results may have been confounded by the sample selection threat to validity. Moreover, CRP has been traditionally featured as a consistently reliable marker of inflammation [48]. In conclusion, HRT should take into consideration age, health status, and the possibility of inducing hormonal imbalance or initiating undesirable processes leading to inflammation.

A recent study postulates that human umbilical cord mesenchymal stem cells (MSC) had a positive effect on one Covid-19 patient [49]. Additional research reported a significant improvement in respiratory symptoms and reduced inflammation after injecting eleven Covid-19 patients with MSC [50]. However, the samples of both studies were too small to serve as valid and conclusive evidence that MSC can be clinically useful in the treatment of Covid-19.

6. Covid-19 Preference for Adipose Tissue

The primary expression of ACE2 receptors in adipose tissue, heart and thyroid is consistent with research evidencing higher Covid-19 fatality rates among obese individuals, and patients suffering from cardiovascular disease (CVD), hypertension, and diabetes [51-55]. The relatively lower ACE2 expression in muscle tissues renders physical activity, and exercise alternatives as optimal protective methods to safeguard health [56,57].

The need for exercise or an equivalent alternative become prominent in light of evidence that body mass index (BMI) over 25 is associated with a fatality rate increase of 88% after contracting Covid-19 [58]. Visceral adiposity has been associated with inflammatory markers like C-reactive protein (CRP), tumour necrosis factor-a (TFN-a) and interleukin-6 (IL-6) that have been prominently featured in Covid-19 patients [59-62]. Age is positively correlated both with visceral adipose tissue increase and CRP, TFN-a and IL-6 [63]. Covid-19 disease severity and poor prognosis are closely associated with elevated inflammatory markers including interleukins (IL-2, IL-6, IL-8), CRP and TNF-a [65]. Interleukins, tumour necrosis factors, and interferons are involved in the "cytokine storm syndrome" (CSS), an overzealous immune defensive activity that spirals out of control damaging the vital organs of the host [64-66]. The higher the initial level of inflammation, due to obesity or other factors, the greater the chance of the lethal effects of the cytokine storm. The fusion of the S Covid-19 glycoprotein with the ACE-2 receptors that are abundant in adipose tissue, trigger a chain of events, such as overproduction of Angiotensin II, a proinflammatory cytokine, that promotes A Disintegrin And Metalloproteinase 17 (ADAM17). ADAM17 is instrumental in the ACE2 shedding process that may reduce viral entry into the body, therefore, acting as a protective agent; yet, as Angiotensin II increases ADAM17, it ultimately activates TNF-a, and amplifies IL-6 along with other parameters, rapidly progressing to a hyperinflammatory state that precipitates multi-organ injury or failure [67-69].

In conclusion, Covid-19 is a complex medical 'double edged-sword' posing major pharmaceutical dilemmas, progressing globally with infections and fatalities, despite the diagnostic and drug research it has accumulated, which have not yet guaranteed a complete cure. Hence, the necessity of gearing some of Covid-19 research towards prevention. An obvious target is weight management to reduce obesity that is featured as one of the major factors increasing global Covid-19 susceptibility and mortality rates.

7. Lasers and Radiofrequency Techniques for Weight Loss

A number of radiofrequency (RF) technologies claim virtually instant subcutaneous lipolysis, however, they offer no clear data on long term results regarding weight rebound. Additionally, they present no evidence supporting increased muscle mass or detoxification caused by the actual technology rather than relying on exercise, or the efficiency of the body to perform this function [70-75]. Research that combines RF and cryolipolysis on the reduction of

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subcutaneous fat, reported improvement in 73.46% of the patients, a statistically non-significant result; 22.44% of these patients experienced no change, and 4.08% of them disclosed that RF had deleterious effects on their appearance [76]. Most RF lipolysis studies primarily address the subcutaneous fat area. One study published in the Cairo University Bulletin, which is not a peer reviewed journal, claim visceral fat reduction, however, there is no evidence specific to visceral fat, and upon examination it appears that the reduction seen pertained to overall fat [77].

Reports on the medical uses of RF concur on the increased presence of inflammation. A study on 130 patients delineated a significant increase in the inflammatory marker CRP at the level of $p<0.01$ statistical significance [78]. Research exploring RF medical interventions revealed an increase in both oxidative stress and inflammation biomarkers [79]. Another study on ninety patients undergoing RF treatments documented elevated creatine kinase, CRP, Troponin-P and increased fibrinogen [80]. This data is not directly connected to Covid-19 patients, but it cautions against the application of RF technologies on this population, or even preventatively, since RF induced increase of inflammation and prothrombotic markers could be deleterious to the overall health status.

Laser technology has also claimed subcutaneous lipolysis [81-89]. A review evaluating laser induced complications on 537 cases found only one case of skin infection, and four skin burns, rendering laser weight loss procedures relatively safe [90,91]. A more detailed review, however, has compiled a number of side effects following laser treatments, including skin burns, dysesthesia, superficial thrombophlebitis, hematoma, nerve injury, and some rare incidences of pulmonary embolism [92]. A number of investigators make claims about the anti-inflammatory effects of low level laser therapy (LLLT) and present cases of pain analgesia, reduced oedema, and improvement of some pulmonary diseases [93-99]. A recent LLLT review proposes that this type of therapy should be used to counteract the cytokine storm of Covid-19, however they present no clinical studies involving Covid-19 patients (100).

Some investigators have reported visceral fat reduction after combining LLLT and exercise; yet, it is not clear whether the effects on visceral fat were due to the laser rather than the exercise, and a replication of this study by the same investigators did not substantiate the evidence of the visceral fat reduction [101,102].

8. Exercise and its Alternative

Physical fitness safeguards health and protects the body before contracting the virus, as well as following infection by reinforcing immunity during the initial stages of the disease [103-107]. There is evidence that engaging in moderate intensity gymnastics reduces the risk of respiratory symptoms [108-110]. Research that explored the immunity status of 273 runners demonstrated that regular sustained physical activity resulted in the lowest incidence of viral infections [111]. On the down side, exploration of visceral fat reduction via exercise has demonstrated modest findings. One study found a statistically insignificant decrease of visceral fat and fatty liver that was not accompanied by weight reduction [112]. Research on 160 healthy Korean adults used computed tomographic scanning to test the results of exercise on inflammation and visceral fat; they found that visceral fat was the best predictor of inflammation as measured by CRP levels and insulin resistance. These investigators reported significantly lower visceral fat, yet in the absence of any improvement in physical fitness or BMI decrease [113]. In conclusion, exercise appeared to help, but it required extensive commitment and long term effort to reach optimal results.

On the other hand, there is some evidence that exercise may trigger asthma [114]. Strenuous exercise is connected to increased cortisol, which as noted previously, is associated with diabetes, heart disease and increased Covid-19 mortality rates [115,116]. Strenuous gymnastics result in an inverse cortisol/testosterone relationship, where both cortisol increase and testosterone decrease are bound to elevate stress, fatigue, and hunger which ultimately undermines the advantages of exercise [117,118]. Cortisol induced stress-eating behaviours are reinforced by the decrease of the anorexic hormone, leptin, that is compromised by strenuous activity [119]. Additionally, interleukin-6 appears to increase following excessive exercise that is often necessary to reduce visceral fat, [120] a problematic event, since an initial high inflammatory state may reinforce the occurrence of the Covid-19 induced cytokine storm after infection.

A series of recent studies report statistically significant decreases in lipids, visceral fat and the absence of hepatic steatosis in patients previously diagnosed with fatty liver. Specifically, the clinical trials delineate a statistically significant decrease in the very-low density lipoprotein (VLDL) and triglycerides, juxtaposed by an increase in the high-density lipoprotein (HDL). Additionally, they demonstrate increased fitness and normalized levels of Insulin Growth Factor-1 (IGF-1), the metabolic hormone Triiodothyronine (Free T3), Insulin, Testosterone, Cortisol, the anorexic hormone Leptin and the orexigenic one, Ghrelin, after 10-12 treatments with an alternative to exercise, originally invented in London University. Some of these studies rely on small samples demonstrating reduced inflammation and oxidative damage as measured

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by wound healing, neuropathic pain analgesia, as well as statistically significant decreases in CRP, creatinine, and bilirubin [121-129]. We used T-tests for dependent means to analyse the raw data derived from 95 subjects, 73 females and 22 males, that participated in these clinical trials. Table 1 depicts the statistical significance values, and the average percentage increase or decrease of each variable. Thirty-five out of the 95 subjects were healthy adults. The remaining sixty patients suffered by at least one or more medical disorders: Fifteen were diagnosed with diabetes, twenty with prediabetes; eleven had hypertension, ten presented hyperphagia, fifteen had hepatic steatosis and twenty-one had hypothyroidism.

9. Discussion

Covid-19 is a global lethal pandemic that has stirred an enormous body of clinical data including both therapeutic methods and preventive interventions. Research primarily targets the Covid-19 point of entry via the fusion of the S glycoprotein with ACE2 receptors, or the involvement of the N protein in the RNA viral replication. The abundance of ACE2 receptors in adipose tissue and the testes renders obese males highly susceptible to decease. The heart, liver, and thyroid are also enriched with ACE2 expression, precipitating increased mortality rates among CVD and diabetic patients, as well as overweight individuals with excess visceral fat that often results in non-alcoholic hepatic steatosis. The diminished incidence of ACE2 receptors in muscle tissue spotlights physical activity or its alternatives as a protective shield against the virus, due to their propensity to utilize fat as an energy source to build muscle. However, strenuous activity can be detrimental by increasing inflammation and the stress hormone, cortisol, while decreasing testosterone and the anorexic hormone leptin leading to increased food consumption, and

Table 1. T-Tests Statistical Significance Results on Blood Tests and Measurement Variables of a totals of 95 overweight individuals with an average BMI>25, after 12 treatments with a new, health enhancing methodology

	Mean	S^2 *=SS/df*	*T Value*	*p Value*	*Probability*	*Comments*
VLDL 25 HA / 20 PMD	-1.19	0.31	-9.35	<0.00001	P<0.00001	VLDL was Reduced by -41.59%
Triglycerides 25 HA / 40 PMD	-1.25	0.61	-6.94	<0.00001	P<0.00001	Triglycerides were reduced by -31.96
HDL 30 PMD	9.34	23.66	10.52	<0.00001	P<0.00001	HDL was increased by +19%
Free T-3 45 HA / 10 PMD	0.93	0.13	11.62	<0.00001	P<0.00001	Free T3 was increased by +41.07% WNR
Leptin 10 HA / 10 PMD	1.82	2.68	4.98	0.00004	P<0.0001	Leptin increased by +13.41% WNR
Ghrelin 10 HA / 10 PMD	-43.55	962.79	-6.28	<0.00001	P<0.00001	Ghrelin decreased by -8.28% WNR
Bilirubin 10 PMD	-0.08	0.12	-7.26	0.00002	P<0.0001	Bilirubin decreased by -69.23% WNR
Creatinine 10 PMD	-0.24	0.04	-4.06	0.00143	P<0.01	Creatinine decreased by -19.67% WNR
CRP 10 PMD	-0.59	0.16	-4.72	0.00055	P<0.001	CRP decreased by -36.87% WNR
Cortisol 35 HA	-18.26	142.98	-6.66	<0.00001	P<0.00001	Cortisol decreased by -13.08% WNR
Testosterone 35 HA	2.9	4.6	6.05	<0.00001	P<0.00001	Testosterone increased by +43% WNR
VAT 35 HA / 60 PMD	-4.68	7.12	-13.6	<0.00001	P<0.00001	VAT decreased by -21.95%
Overall Fat 50 PMD	-4.98	6.43	-13.88	<0.00001	P<0.00001	Overall Fat decreased by -13.42%
BMI 60 PMD	-2.3	1.28	-15.73	<0.00001	P<0.00001	BMI decreased by -10%
BMR 10 HA	91.6	3782.04	4.71	0.00055	**P<0.001**	BMR increased by +91.60%
SMM 35 HA / 15 PMD	+4.3	0.45	+13.49	<0.00001	P<0.00001	SMM increased by +40.7%
IGF-1 35 HA				<0.00001	P<0.00001	IGF-1 increased by +19.68
Blood Glucose Fasting 15 D	-61.88	7675.12	-8.11	<0.00001	P<0.00001	50% normal after 12 treatments
Blood Glucose PP 15 D	-63.07	7353.79	-845	<0.00001	P<0.00001	33% normal after 12 treatments
Insulin Fasting 20 PD	-30.71	5961.47	−2.97	0.01031	P < 0.01	100% normal after 12 treatments
Insulin PP 20 PD	−129.43	18065.62	−7.20	0.00009	P < 0.0001	100% normal after 12 treatments
Weight Loss 10 HA / 50 PMD	-6.49	9.34	-11.63	<0.00001	P<0.00001	Average Weight loss -7.22 kilograms
Above Umbilicus Measurement 50 PMD	-8.04	9.54	18.22	<0.00001	P<0.00001	Average cm loss -9.375 cm
Umbilicus Measurement 50 PMD	-8.93	12.31	-17.81	<0.00001	P<0.00001	Average cm loss -9.1 cm
Below Umbilicus Measurement 50 PMD	-9.33	20.1	-14.56	<0.00001	P<0.00001	Average cm loss -9.635 cm

Abbreviations: WNR: Within Normal Range / CRP: C-Reactive Protein / HA: Healthy Adults / PMD: Patients with Medical Disorder / VLDL: Very-Low Density Lipoprotein / HDL: High Density Lipoprotein / VAT: Visceral Adipose Tissue / BMI: Body Mass Index / BMR: Basal Metabolic Rate / SMM: Skeletal Muscle Mass / PP: Postprandial / IGF-1: Insulin Growth Factor-1 / D: Diabetics / PD Prediabetics

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eventual fat accumulation. This process is exacerbated by age-related testosterone decline, juxtaposed by upsurged cortisol. The anti-inflammatory properties of estradiol are highlighted within the moderation of hormonal balance. Overall, adiposity is featured as the epicentre of inflammation, which increases the probability of the cytokine storm rampaging the body, following Covid-19 infection. This lethal process is facilitated and accelerated by the plenitude of ACE2 receptors in adipose tissue.

There are several weight management techniques, including different versions of lasers and RF, some of which may escalate inflammatory conditions, and none of which contributes to increased fitness. A metanalysis of recently published clinical trials that included 95 individuals, 73 females and 22 males with an average BMI of 30.9, featured an exercise alternative as a protective method to safeguard immunity with a special focus on prevention. None of these clinical trials involved Covid-19 patients or claimed to address a Covid-19 therapeutic intervention. The purpose was defined as investigating effective methods to reinforce health by sufficiently decreasing visceral adiposity and lipoproteins, while increasing skeletal muscle mass and overall hormonal balance. One of the clinical trials [124] on twenty diabetic and prediabetic patients presented evidence of a significant reduction in both fasting and postprandial glucose and insulin. Seven patients with hepatic steatosis underwent sonography that revealed no fatty liver after twelve treatments. Ten of the subjects diagnosed with hyperphagia, reported normal appetite after 12 treatments. IGF-1, Free T3, Leptin and Testosterone were elevated, yet they remained within the normal range. Cortisol and Ghrelin decreased, yet without descending into abnormality. Despite its significant results the twelve procedures performed in these clinical trials demonstrated that the higher the degree of obesity the less the chance that the BMI decrease was within the confines of optimal weight, possibly indicating the necessity for more treatments or the inclusion of a well-controlled diet plan. Additionally, most of the studies did not use ultrasound or magnetic resonance imaging techniques that are experimentally more reliable in assessing visceral adiposity.

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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.

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