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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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ARTICLE

Etiological Spectrum with Diagnosis and Prognosis of Central Diabetes Insipidus needs Long Term Followup: A Single Centre Experience

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ABSTRACT

Introduction: Central Diabetes insipidus (CDI) is a rare disorder caused by vasopressin deficiency characterized by the excretion of copious volumes of unconcentrated urine. **Objective:** To assess the etiological, clinical, biochemical and radiological spectrum of Central DI in our institute and long term follow up of these cases. **Material and Methods:** 32 patients with Central DI admitted in Department of Endocrinology, Guwahati Medical College, Assam in the last 2.5 years were included. Detailed clinical assessment, biochemical evaluation and MRI (Magnetic Resonance imaging) brain were done in all the patients. Central DI without any identifiable cause was considered Idiopathic and those with structural lesion in hypothalamic pituitary region were considered organic. **Result:** Idiopathic CDI was present in 12(37.5%) patients and 20(62.5%) patients had organic CDI with acute onset of presentation. 12(60%) patients with organic CDI present with neurological symptoms but 8(40%) patients had no neurological symptoms even with organic cause. Pituitary dysfunction was common in organic CDI as compared to idiopathic CDI. Paediatric patients commonly present with organic cause for CDI with low cortisol most common hormonal deficit. One patient of idiopathic CDI with normal stalk thickness at baseline presented with clinical and radiological features of LCH(Langerhans cell histiocytosis) on follow up. **Conclusion:** Organic CDI more likely to have acute onset of presentation than idiopathic CDI and even in absence of neurological features. Paediatric patients commonly have organic cause for CDI. We propose the paramount importance of long-term clinical follow-up and reassessment of endocrine function in patients with CDI for definitive diagnosis of autoimmune and inflammatory causes of idiopathic CDI and timely treatment of pituitary hypofunction.

1. Introduction

Diabetes insipidus is a rare disease with a non-univocal reported prevalence of 1:25,000 [1] and characterized by the excretion of copious volumes of unconcentrated urine, results from either impaired vasopressin secretion, impaired renal response(-nephrogenic), excessive fluid intake (primary polydipsia) or increased metabolism of the hormone (gestational diabetes insipidus). A combination of hormonal, clinical, and neuroradiologic evaluation is required for differentiation between their causes, pathophysiology, and for effective

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management. Vasopressin is synthesized by neurons of the hypothalamic paraventricular and supraoptic nuclei and secreted by the posterior pituitary gland [2]. Central nervous system (CNS) tumours, post-neurosurgical or accidental trauma, autoimmune, infiltrative diseases and rarely genetic mutations are known causes of central DI [3]. There are many diagnostic and therapeutic challenges in CDI which may result in delayed during evaluation for more common aetiologies of polydipsia and polyuria, and often requires formal water deprivation testing [2]. After the diagnosis, further work-up to determine the aetiology of CDI and additional pituitary hormone deficiencies is required; however, there is lack of clear guidelines regarding laboratory and imaging studies to obtain and at what intervals these investigations to be repeated. Desmopressin (DDAVP) with an extended duration of action is a synthetic analog of arginine vasopressin and is the mainstay of therapy for CDI. Given the number of diagnostic and therapeutic challenges associated with CDI, we performed a retrospective chart review of a cohort of patients with CDI followed at the in order to describe our experience and to contribute further to generalizable knowledge about the diagnosis and management of CDI.

2. Method

Study was conducted at Guwahati Medical College and Hospital. The aim was to characterize the etiological spectrum of central DI and to determine whether clinical, biochemical and specific MRI characteristics(pituitary stalk thickness, posterior pituitary bright spot) could provide clinician guidance with regard to the etiology and follow up of these patients.Total of 32 patients attending department of Endocrinology over a period of 2.5 years with history of polyuria and polydipsia were included in study after obtaining written informed consent. Patient with history of Diabetes mellitus, Head injury, irradiation, diuretics, renal failure, RTA, Hypercalcemia, hypokalaemia, transient Diabetes insipidus were excluded from the study. Central DI without any identifiable cause was considered Idiopathic and those with structural lesion in hypothalamic pituitary region were considered organic REF. Patient characteristics age, sex duration of clinical symptoms prior to diagnosis in those presenting with CDI, pituitary hormone evaluation, family history, neuroimaging study results, and pathology findings were recorded. The frequencies of various aetiologies of CDI as well as characteristic magnetic resonance imaging (MRI) findings were determined. CDI was diagnosed either by water deprivation testing or by the presence of concurrent polyuria, hypernatremia, elevated serum osmolality, low urine osmolality, and low urine specific gravity. The prevalence of anterior pituitary hormone deficiencies at each patient's presentation and the incidence of hormone deficiencies acquired later in the disease course were also evaluated over period of 12 months. The hormonal deficiency was confirmed by laboratory evidence of insufficient hormone production.

3. Results

Total of 32 subjects included in study (14 male and 18 female), mean age was 37.2±18.8 years (Table 1). The mean duration of symptoms in our study group was 15.4±11.2 months with organic CDI having more acute presentation as compared to Idiopathic CDI (12months vs 21 months). All patients underwent MRI Brain and 12 (38%) patients on the basis of absence of any identified organic cause were diagnosed as Idiopathic CDI (Figure 1) and 20 (68%) patients with organic aetiology were diagnosed as organic CDI. The organic causes includes craniopharyngioma 7 (22%), granulomatous 3 (9%), Rathke's cyst 2 (6%), pituitary adenoma 6 (19%), meningioma 1 (3%), glioma 1(3%).In our study group most of children had organic CDI(craniopharyngioma 3 patients and glioma 1 patient). Polyuria and polydipsia was the most common presenting complain present in all the subjects (Table 2). Other complains includes headache 12 (40%), vomiting 6 (20%), seizure 5 (16%), visual disturbances 3 (10%), short stature 2 (6.6%). Neurological features and anterior pituitary hormonal deficiency were common in organic CDI as compared to Idiopathic CDI but some patients in organic CDI present with hormonal deficiency even in absence of neurological features.16 patients underwent formal water deprivation test while rest of patient already fulfilled criteria for Diabetes insipidus. Biochemically hyperprolactinemia was most common hormonal derangement and present in 15 patients (46%), other deficiency includes hypothyroidism 11 patients (34%), low cortisol 13 patients (40%), hypogonadism 8 patients (25%) and GH deficiency 8 (25%) patients (Figure 2). Pituitary bright spot was absent in all patient with Idiopathic DI as compared to 13(65%) of organic DI (Table 3). 8 (40%) patients of organic DI had pituitary stalk thickening as compared to 1(8.3%) patient of Idiopathic DI. On 12 months follow up 2 patients in Idiopathic DI had pituitary stalk thickening with progressive pituitary hypofunction in the form of 2 patients had hypothyroidism at 6 month and 1 patient developed hypogonadism at 12 months follow up (Table 4). One of the patient initially diagnosed with Idiopathic CDI developed progressive skeletal manifestation of LCH in the form of proptosis of unilateral eye along with ear discharge at 12 month follow up which was later diagnosed with bone marrow biopsy and radiological imaging (Fig-

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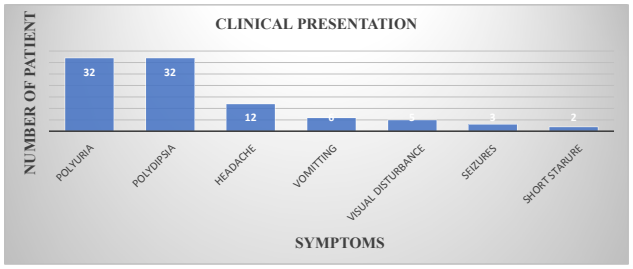
ure 3). At follow up of 12 month 2 additional patients in organic CDI lost pituitary bright spot and 1 patient developed new onset low cortisol and 2 patient hypothyroidism on 6 month and 12 month follow up respectively (Table 4). Low cortisol (75%) was the most common hormonal deficiency in paediatric patients followed by GH deficiency (62.5%) and hypothyroidism (50%), hyperprolactinemia (50%), hypogonadism (37.5%). All patients with CDI were treated with either nasal or oral DDAVP.

Table 1. Baseline characters and aetiology of CDI

N=32	BASELINE CHARACTERISTICS
AGE (YEARS)	37.2±18.8
SEX M:F	14:18
Duration of symptoms(months)	15.4±11.2
Etiology- Idiopathic Craniopharyngioma Granulomatous Rathke's cyst Pituitary adenoma Meningioma Glioma	12 7 3 2 6 1 1

Table 2. Presenting complain of subjects



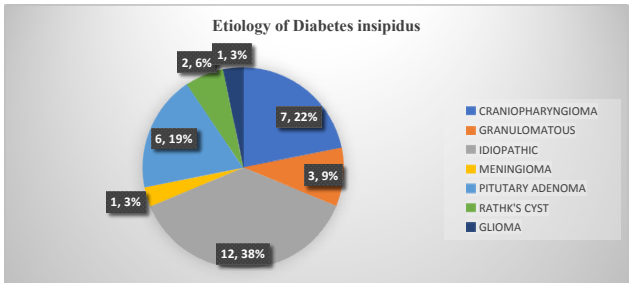


Figure 1. Etiology of CDI

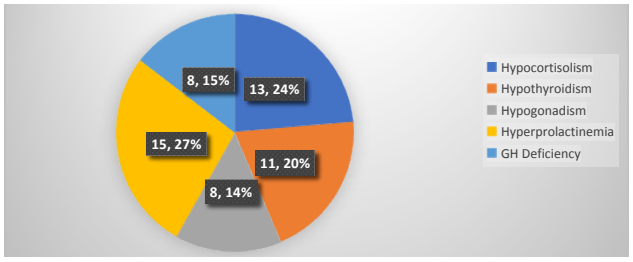


Figure 2. Hormonal profile of Subjects

Table 3. Radiological and hormonal profile of Idiopathic and organic CDI

	IDIOPATHIC CDI(N-12)	ORGANIC CDI (N-20)	P VALUE
Age	41±17	30.6±18.5	-
Sex(M:F)	7:5	7:13	0.3
Duration of symptoms(month)	**21 (10-48)**	**12 (6-24)**	**0.04**
Short stature	0	2 (28%)	NS
Neurological features	**2 (16%)**	**12 (60%)**	**0.04**
P pituitary bright spot Absent	12 (100%)	13 (65%)	-
Pituitary Stalk thickening	1 (8.3%)	8 (40%)	-
Hypogonadism	0	8 (40%)	0.02
Hyperprolactinemia	1 (8%)	14 (70%)	0.002
Hypocortisolism	1 (8%)	12 (60%)	0.01
Hypothyroidism	1 (8%)	10 (50%)	0.04
GH Deficiency	1 (8%)	7 (35%)	0.05

Table 4. Follow up of Idiopathic and organic CDI

	Idiopathic central diabetes insipidus(N-12)			Organic central diabetes insipidus(N-20)		
	Baseline	6 month	12 month	Baseline	6 month	12 month
Pituitary stalk thickening (Number of patients)	1	-	2	8	-	8
Bright spot present	0	-	0	7	-	5
Bright spot absent	12	-	12	13	-	15
Hypothyroidism	1	2	2	10	10	12
Hypogonadism	0	0	1	8	8	8
Hypocortisolism	1	1	1	12	13	13
hyperprolactinemia	1	1	1	14	14	14
GH deficiency	0	0	1	7	7	7

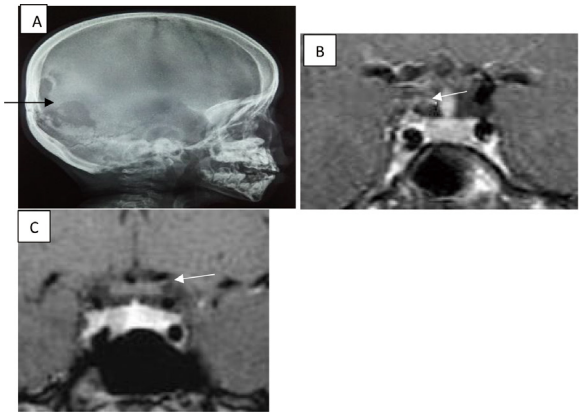


Figure 3. Cranial X ray with MRI images of subject with LCH

Notes: (Image A) X ray skull showing punched out lesion involving occipital and temporal region (Black arrow). T1W MRI image showing

normal pituitary stalk at baseline (image B white arrow) which shows thickening at 12 months follow up (image C white arrow).

4. Discussion

In our study 12(38%) patients had Idiopathic DI as compared to 20(68%) patients with organic DI. In a similar study Mohamad Maghnie[9] evaluated central diabetes insipidus in children and young adults and found 52% had idiopathic DI and intracranial tumour in 22% patients which is similar to our study group (28%). Natascia Di Iorgi [3] on the other hand found 71.8% with a presumable idiopathic form of CDI and 28% organic DI at presentation. In our study, organic DI subjects had significantly more acute presentation of symptoms like headache and visual disturbance (p-0.04). In our study, craniopharyngioma was the most common organic cause of CDI in paediatric patients (6 out of 8 patients), which was very similar to study by David Werny [10] in paediatric patients where most common single diagnosis was craniopharyngioma (25.2%). In our study anterior pituitary hormonal deficiency was present at diagnosis in 14(70%) patients in organic CDI as compared to 1(8%) patient in Idiopathic DI group which is similar to study by Masri-Iraqi H [11]. Natascia Di Iorgi [3] on the other hand showed that out of 61 idiopathic DI 35 patients (81.4%) showed at least 1 anterior pituitary defect within the first 2 years. Hee Joung Kim [12] found that 6 patients (20%) out of 30 Idiopathic DI had deficits in anterior pituitary hormone at diagnosis. The most common hormonal abnormality in our study was hyperprolactinemia 15(46%) patients, followed by low cortisol 13(40%) patients, hypothyroidism 11(34%) patients, hypogonadism 8(25%) patients, GH deficiency 8(25%).In paediatric patients low cortisol (75%) was the most common hormonal deficiency followed by GH deficiency(62.5%) which is in contrast to study by David Werny [10] and Janel D [13] where GH deficiency was the most common concurrent hormone deficiency followed by ACTH deficiency and TSH deficiency. On follow up of idiopathic DI 6 monthly, 2 patients in Idiopathic DI had pituitary stalk thickening with progressive pituitary hypofunction in the form of 2 patients had hypothyroidism at 6 month and 1 patient each developed hypogonadism and GH deficiency at 12 months follow up. One of the patient initially diagnosed with Idiopathic DI developed progressive skeletal manifestation of LCH (Langerhans cell histiocytosis) in the form of proptosis of unilateral eye along with ear discharge at 12 month follow up which was later diagnosed with bone marrow biopsy and radiological imaging. David Werny [10] In 22 patients with initially idiopathic CDI, four were found to have an underlying cause on follow up of 1.6 years and found that no concerning MRI changes were detected after 3 years from initial CDI diagnosis. Natascia Di Iorgi [3] on the other hand in 61 idiopathic CDI patients, 11(13%) received a specific diagnosis within 2.5 years. Our patient had normal stalk thickness at initial diagnosis which is in contrast to David Werny [10] study where the percentage of patients with an underlying cause was higher in those with initial pituitary stalk thickening. We didn't find any change in size of pituitary gland of patients of idiopathic DI at follow up of 12 months while Natascia Di Iorgi[3] found a change in the size of anterior pituitary on follow up MRI scan. In our study pituitary bright spot was absent in 13(65%) patients of organic CDI and 8(40%) patients had pituitary stalk thickening. At follow up of 12month, 1 patient in organic CDI developed new onset low cortisol and 2 patient developed hypothyroidism which underscore the importance of endocrine follow up in these patients.

5. Conclusion

(1) In conclusion, children and adults with organic central diabetes insipidus has acute onset of symptoms as compared to idiopathic CDI

(2) Organic CDI should be suspected even in the absence of neurological features

(3) Diagnosis of idiopathic CDI in children's should be made with extreme caution because of high frequency of CNS malformations and organic cause, and only after extensive evaluation, including MRI of the brain even in those with normal pituitary stalk thickness

(4) Careful monitoring of signs or symptoms of organ involvement by LCH is recommended after the diagnosis of idiopathic CDI

(5) Continued screening for endocrine dysfunction is warranted for timely diagnosis of hormonal deficiency and appropriate treatment, though further studies are needed to determine the most appropriate screening interval

(6) We suggest systematic neuroimaging, endocrine follow-up for definitive diagnosis of autoimmune and inflammatory causes of idiopathic CDI and timely treatment

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ARTICLE

Adrenomedullary Function in Cohort of Brazilian Pediatric Patients with Classic Congenital Adrenal Hyperplasia

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ABSTRACT

Congenital Adrenal Hyperplasia is a group of autosomal recessive disorders resulting from deficiency of enzymes essential for the synthesis of cortisol. Disease of the adrenal cortex, but there may be involvement adrenomedullary. Cortisol and epinephrine are directly related to the individual's stress response. Lower values of epinephrine in children with congenital adrenal hyperplasia could be related to increased clinical complications and hospitalizations rate. We evaluated the serum values of metanephrines and normetanephrines in children and adolescents with classic congenital adrenal hyperplasia and primary hypothyroidism and possible correlations with disease and hospitalizations. Cross-sectional study involved 29 patients (10 simple virilizing and 19 salt-wasting), and control group of 28 patients with primary hypothyroidism (10 overt and 18 subclinical). There were no differences in age ($p = 0.24$) and metanephrine ($p = 0.34$) or normetanephrine values ($p = 0.85$) between groups. Hospitalization rate was higher in the cases than in the controls (51 x 12). We conclude the serum values of metanephrine and normetanephrine in patients with congenital adrenal hyperplasia were within the normal values of reference, with no significant difference of group with primary hypothiroidism. The number of hospitalizations in the case was high in relation to the control, mainly in salt-wasting.

1. Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders resulting from genetic defects which cause a deficiency of enzymes essential for the synthesis of cortisol and, sometimes, aldosterone. The most frequent form of the disease, accounting for 90-95% of all cases of CAH, involves a mutation causing deficiency of the enzyme 21-hydroxylase (21-OHlase). The clinical manifestations of CAH depend on the degree of enzyme deficiency, ranging from milder to more severe forms[1].

Three major clinical phenotypes have been described: salt-wasting (SWCAH), which affects 75% of patients with the classic form; simple-virilizing (SVCAH), which affects the remaining 25%; and nonclassical CAH. Treatment aims at adequate glucocorticoid replacement, with or without mineralocorticoids as needed, in order to prevent adrenal crisis and minimize the virilizing effects of the disease [1-3].

The most common form of CAH (classic 21-hydroxylase deficiency) affects approximately 1:15,000 live births

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[4,5]. Since the introduction of cortisone therapy by Wilkins et al. in the early 1950s, children with CAH have been able to survive to adulthood [2]. In Brazil, the incidence of SWCAH ranges from 1: 7,500 to 1: 10,000 live births [6].

Although CAH is a disease of the adrenal cortex, there might be an impairment of the adrenomedullary function in these patients. The medulla represents about 10% of the adrenal gland and is responsible for the production of epinephrine (80%) and norepinephrine (20%), in addition to minimal amounts of dopamine. These hormones are secreted into the bloodstream upon direct stimulation of the adrenal glands by sympathetic nerves [7].

Epinephrine synthesis is related to the presence of cortisol, produced in the adrenal cortex. Cortisol induces the enzyme phenylethanolamine-N-methyl transferase enzyme, which catalyzes the conversion of norepinephrine to epinephrine in marrow chromaffin cells [7].

Cortisol and epinephrine are directly related to the individual stress response, and act to prevent hypoglycemia as counterregulatory hormones. Thus, lower values of epinephrine in children with CAH may be related to increased complication and hospitalization rates [8].

The objective of the study was to compare the serum values of metanephrine and normetanephrine in pediatrics patients with classic CAH to those of patients with primary hypothyroidism, as well as to assess potential correlations with disease control, clinical complications, and the hospitalization rate.

2. Patients and Methods

A cross-sectional study of 29 patients with classic CAH (*cases*) and 28 patients with primary hypothyroidism (*controls*) was conducted at the endocrinology outpatient clinic of a pediatric university hospital, from 2017 to 2019. Patients with other associated diseases and/or using medications that could alter the dosage of catecholamines, such as tricyclic antidepressants, levodopa, drugs containing adrenergic receptor agonists (eg decongestants), amphetamines, buspirone, psychoactive agents, prochlorperazine, reserpine were excluded. In addition, patients were instructed not to drink soft drinks, coffee, tea, or use tobacco before the exams were collected. All patients underwent a complete physical examination, and had blood collected for serum dosage. The levels of of androstenedione, testosterone, metanephrine, and normetanephrine were measured for *cases*, while free thyroxine (fT4), thyrotrophin (TSH), metanephrine, and normetanephrine were measured for controls.

Normetanephrine and metanephrine were measured in plasma by high-performance liquid chromatography (HPLC) and radioimmunoassay (RIA), respectively. The reference ranges were < 90 pg/mL for metanephrine and < 196 pg/mL for normetanephrine.

Depending on whether their androstenedione levels were within or outside normal range, patients with CAH were classified as having good control or poor control, respectively.

The study was approved by the institution's research ethics committee.

3. Statistical Analysis

The hypothesis of normality was rejected by the Shapiro-Wilk test; thus, nonparametric measures were used. The Mann-Whitney *U* test was used for comparison of age, metanephrine, and normetanephrine between the two groups (case vs. control) and subgroups thereof, while the chi-square test was used to compare sex distribution.

The statistical significance threshold was set at 5%. All analyses were processed in the SAS® System software environment, version 6.11 (SAS Institute, Inc., Cary, North Carolina).

4. Results

The clinical characteristics of patients in the case group and control group are shown in table 1.

All patients were receiving glucocorticoid replacement therapy (22 were using prednisolone and 7 dexamethasone). The median hydrocortisone equivalent dose was 9.76 mg/m^2/day, and the mean was 10.57 ± 7.37 mg/m^2/day. Of the 10 patients with SVCAH, 5 also received fludrocortisone regularly for mineralocorticoid replacement, with the mean and median dose of 0.05 mg/day; of the 19 patients with SWCAH, 17 were also on fludrocortisone, at the mean dose of 0.22 mg/day (median, 0.20 mg/day).

Table 1. Clinical characteristics of cases and controls

Clinical features	Cases (CAH)	Controls (hypothyroidism)
N	29	28
Female	15	16
Prepubescent	16	8
Pubescent	13	20
Age (years)		
Range	0.41-20	4.9-15.25
Median	7.41	11.63
Mean ± SD	9.32 ± 6.31	11.25 ± 2.48
SWCAH / SVCAH	19 / 10	-
Median / mean hydrocortisone equivalent dose, mg/m^2/day	9.76 / 10.57 ± 7.37	-
Overt / subclinical hypothyroidism	-	10/18

Notes: SD, standard deviation; SWCAH, salt-wasting congenital adrenal hyperplasia; SVCAH, simple virilizing congenital adrenal hyperplasia.

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Of the 28 patients with hypothyroidism, 10 of them had overt hypothyroidism, diagnosed after 2 years of age, and had serum fT4 values within the normal range at the time of the study, with replacement doses of levothyroxine ranging from 1 to 2.17 mg/kg/day. The remaining 18 were diagnosed with subclinical hypothyroidism and maintained T4L values within the normal range throughout their follow-up, without the need for replacement with levothyroxine.

Table 2 reports the age and metanephrine and normetanephrine levels of cases and controls, and the corresponding descriptive statistic (p-value) of the Mann-Whitney test. The median age in the control group is higher than in the case group, because of the later age of onset of acquired hypothyroidism. Thus, as noted in Table 1, there are no infants or preschool children in the control group. In the case group, there were 2 infants and 2 adults (aged 20), which explains the greater deviation of age in this group. Nevertheless, the age difference was not significant ($p = 0.24$).

The median (interquartile range) plasma metanephrine level was 33 (25-42) in the case group, and 38 (31-42) in the control group ($p = 0.34$). The median normetanephrine level was 77 in both groups, with an interquartile range of 58-99 in the case group and 64-92 in the control group ($p = 0.85$).

According to the chi-square test, the proportion of females in the case group (51.7%) was not significantly different from that of the control group (57.1%), with $p = 0.68$.

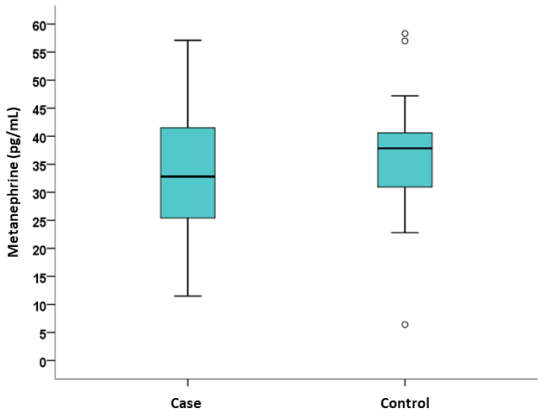
Table 2. Age, and metanephrine and normetanephrine values by group (cases versus controls)

Variable	Cases (n = 29)				Controls (n = 28)				p-value
	Median	IQR			Median	IQR			
Age (months)	89	49	-	174	140	121	-	160	0.24
Metanephrine (pg/mL)	33	25	-	42	38	31	-	41	0.34
Normetanephrine (pg/mL)	77	58	-	99	77	64	-	92	0.85

Note: Mann-Whitney test. IQR, interquartile range (Q1-Q3).

Figure 1(a) shows the trend of metanephrine values, which varied from approximately 25 to 40 pg/mL in the case group and from 30 to 40 pg/mL in the control group. Figure 1(b) shows the trend in normetanephrine values, which ranged from approximately 60 to 100 pg/mL in the case group and from 70 to 100 pg/mL in the control group. Outliers were disregarded in the box plot, since they would have skewed the analysis.

Figure 1(c) we observe the mean, maximum and minimum values of metanephrine (pg/mL) of the case group studied according to the disease form (SVCAH and SWCAH). The values varied in SVCAH and SWCAH approximately of 22 to 47 and from 23 to 40, respectively. In figure 1. (d) we observe the mean and maximum and minimum normetanephrine values (pg/mL) of the SVCAH and SWCAH subgroups studied. The trend of values in SVCAH varies from approximately 60 to 100 and from 60 to 90 in SWCAH. Again, outliers were disregarded in the box plot, since they would cause deviation in the analysis.



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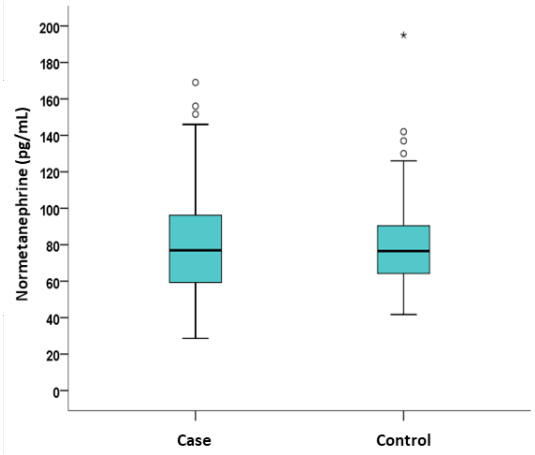

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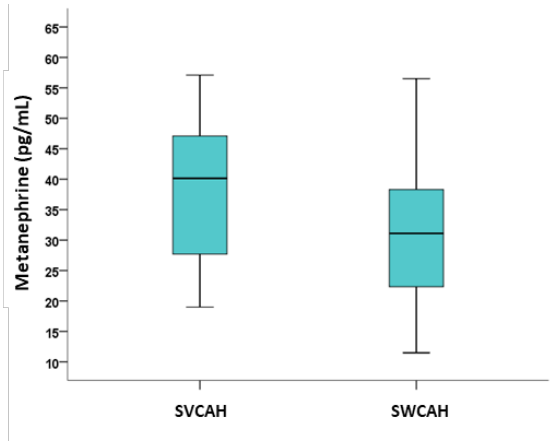

(c)

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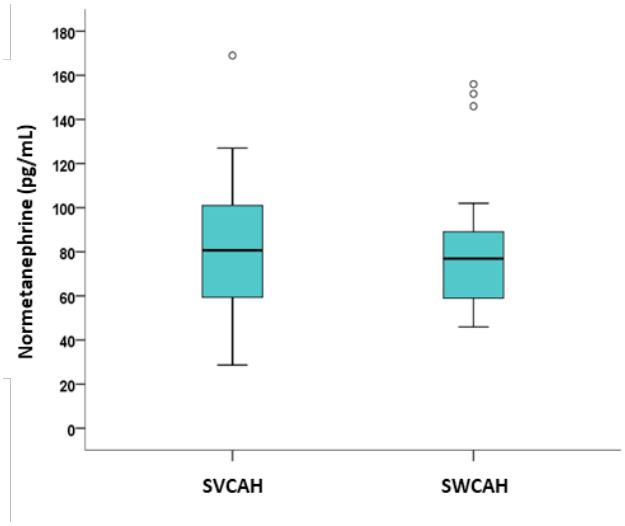

(d)

Figure 1. Box plots of serum levels metanephrine (pg/mL) and normetanephrine s (pg/mL): (a) metanephrine, cases vs. controls; (b) normetanephrine, case vs. controls; (c) metanephrine, cases SVCAH vs. SWCAH; (d) normetanephrine, cases, SVCAH vs. SWCAH

The number of hospitalizations was significantly higher in the case group (n=51) than in the control group (n=12). Of the hospitalizations in the case group, 43 occurred in patients with SWCAH and 8 in those with SVCAH. (In this assessment, we excluded hospitalizations for elective procedures). Figure 2 shows this relationship.

As for reasons for hospitalization in the case group (SVCAH and SWCAH), 55% of them were due to infectious processes (n = 28), abdominal infections (n = 12) being the most frequent, followed by respiratory infections (n = 10), sepsis (n = 3), renal infections (n = 2), neurological infections (n = 1) and other infectious causes (n = 1). In 37% of cases, hospitalization occurred due to dehydration (n = 19) and in the remaining 8% (n = 4) other causes (low weight, acute hemorrhagic edema of infancy, trauma). In the control group, the reasons for hospitalization for infections were reported in 83% of patients, with respiratory infections being the most frequent (n = 6), followed by gastroenteritis (n = 1), neurological infection (n = 1) and other infectious causes (face cellulitis and bacterial superinfection in chickenpox) (n = 2). In the remaining hospitalizations, 17% (n = 2) were referred to as other causes and the reason for hospitalization was arthralgia.

The median number of hospitalizations was 2.0 in the case group and 1.5 the control group. The mean was 4.4 in the case group, versus 3.3 in the control group.

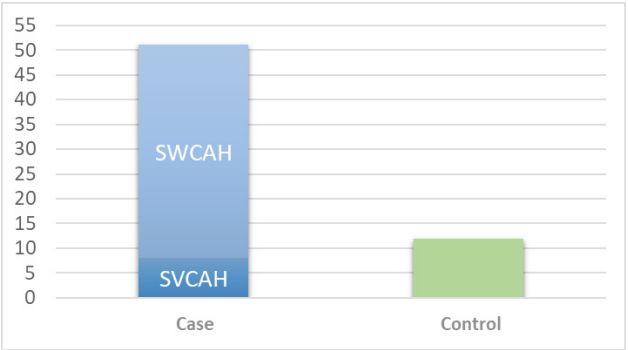

Figure 2. Number of hospitalizations in the case (SVCAH + SWCAH) and control groups

5. Discussion

Few studies have assessed the adrenomedullary function in patients with CAH. Ours is the first to assess a broader pediatric age group and compare it to a control group. In the group of patients with CAH, there are approximately twice as many patients with the salt-wasting form (65%) as compared to simple virilizing (34%). This proportion shows the higher prevalence of the most severe form of presentation of the disease, similar to the literature [1,4].

The control group of the study was composed of patients with primary hypothyroidism, whether overt or subclinical (only elevated TSH values), who presented serum fT4 values within the normal range at the time of assessment. The group was selected to be the control group, because, while clinically and laboratory compensated, they do not generally present problems that can interfere with the results. And, since collections are collected from exams regularly, their inclusion in the study would not cause extra procedures. None of the 18 patients with subclinical hypothyroidism used levothyroxine at the time of the study as they all maintained serum fT4 values within the normal range.

In our control group, we found no differences in metanephrine and normetanephrine serum values between patients with untreated subclinical hypothyroidism and those with overt hypothyroidism treated with levothyroxine. In a previous study by Kim et al, there was no difference in catecholamine levels between patients with congenital hypothyroidism and euthyroid controls [7].

In the case group, both patients with SWCAH and those with SVCAH showed plasma metanephrine and normetanephrine levels within the normal reference range, with no statistically significant difference. This differs from three published studies that studied adrenal medullary function in patients with equivalent epidemiological

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profiles.

Kim and colleagues [7] evaluated adrenal medullary activity in 21 newborns, 9 with CAH (case group) and 12 with congenital hypothyroidism (control group). Newborns with CAH showed significantly lower plasma levels of adrenaline than controls, indicating that adrenomedullary function may be impaired during fetal development and at birth.

Merke *et al* [8] evaluated 97 individuals, 38 of whom had CAH, 39 healthy controls, and 20 who had undergone bilateral adrenalectomy. Significantly lower plasma levels of epinephrine, metanephrine, and normetanephrine were observed in patients with CAH and in adrenalectomized controls in relation to healthy individuals.

Lisá *et al* [9] studied 37 patients with moderate or severe SWCAH and found low plasma levels of metanephrine and normetanephrine[9]. It should be noted in our study that even patients with poor disease control had metanephrine and normetanephrine levels within the normal range.

In both the SVCAH and SWCAH subgroups, there was a greater variation in metanephrine levels than in normetanephrine, although they remained within the reference range, as shown in Figure 1(c).

When assessing the number of hospitalizations, we observed a 4.2-fold higher rate in the case group compared to the control group, being the main cause as infectious pathologies, among them gastroenteritis, followed by dehydration. In addition to a trend towards a higher number of hospitalizations in patients with SWCAH, when compared to SVCAH. This shows a greater number of clinical complications by patients with the most severe form of the disease. Similarly, Merke et al. described that the number of hospitalizations and hospitalizations in patients with CAH was significantly higher in the group with SWCAH than in those with SVCAH in the first 2 years after diagnosis, and that adrenal crisis was the main cause of hospitalization [8,10].

Probably, patients with CAH, when submitted to stressful situations, such as fever, infections and other clinical complications, present a deficit in the metabolic and hormonal response, reflecting the greater number of hospitalizations in this group [4,10,11].

In addition to another factor that may have influenced the number of hospitalizations between the case and control groups, it is the age group difference between them. The population of the case group in our study had a median age below that of the control group, 89 months and 140 months, respectively, the age group most prone to infectious processes. Moreira and Novaes [12] showed the highest number of hospitalizations in Brazil, in the age group of children under one year old, from 1 to 4 years old, and from 5 to 9 years old in relation to the age group of 10 to 19 years old12.

Finally, our study assessed plasma metanephrine and normetanephrine levels in a very broad age group of patients (up to 20 years old). Perhaps a study with a larger sample is needed to evaluate specific pediatric age groups, such as the neonatal period, childhood, and adolescence. This would provide a broader view of adrenal medullary function in the pediatric population and, consequently, broaden our understanding of the pathophysiology of adrenal medullary impairment in individuals with CAH.

We conclude that the plasma levels of metanephrine and normetanephrine in patients with CAH in this study were within normal reference range. There was no significant difference in metanephrine or normetanephrine between the case group (SVCAH and SWCAH) and the control group. However, the number of hospitalizations in the patients with CAH was much higher than in the group with hypothyroidism, and patients with SWCAH had a higher number of hospitalizations than those with SVCAH, reflecting the broad spectrum of disease severity.

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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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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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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

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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,

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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

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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

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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%

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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

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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

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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%

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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

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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.

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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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REVIEW

Correlation between Prostatic Calculi and Benign Prostatic Hyperplasia

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ABSTRACT

Prostatic calculus is a common disease of the urinary system, Prostate stones are more common in middle-aged and elderly men, With the development of ultrasonic diagnosis, more and more patients with prostate stone were found in physical examination, According to research shows, The vast majority of patients with benign prostatic hyperplasia in the pathogenesis of examination was found to have prostate stones, but so far the correlation between prostate stones and benign prostatic hyperplasia is still not very clear,Benign prostatic hyperplasia is an important factor affecting the physical and mental health and quality of life of the elderly male, With an increasing trend of population aging in China more quickly, this problem is more and more outstanding, but also allows us to further study the relationship between prostate stones and benign prostatic hyperplasia.

1. Introduction

Benign prostatic hyperplasia (BPH) is one of the common diseases in middle-aged and elderly men. About 48.91% of men will have clinical symptoms when they are over 50 years old. Prostate stones belong to urinary system stones. In the past, because of the deep lesion, small stone and affected by the surrounding anatomical level, it is difficult to find the traditional examination. Nowadays, the development of ultrasound detection system provides an important basis for the diagnosis of prostate stones, and its sensitivity is up to 95%. Through the prostate color ultrasound [3]. It can determine the location, size and shape of prostate stones, so as to provide an important basis for the choice of treatment options. According to the literature [4], 79% of patients with benign prostatic hyperplasia were found to have prostate stones during physical examination; 60% - 70% of patients with normal prostate were detected with prostate stones. Although more and more patients with prostate stones have been detected, it still does not attract the attention of doctors and patients. The main reason may be that most patients with prostate stones have no clinical symptoms. According to relevant studies, 89.47% of the patients under 30 years old have no symptoms, and 81.10% of them are asymptomatic from 31 to 49 years old [5]. Whether prostate stones are related to the occurrence, development and clinical symptoms of benign prostatic hyperplasia; whether prostate stones can become a risk signal for predicting the degree of benign prostatic hyperplasia need further clinical research to confirm.

2. Prostate Stones

Prostate stones usually occur in middle-aged and elderly patients, most of them are primary stones. According to the location of the stones, they can be divided into true

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and false types. True stones are rare, mostly produced in prostate vesicles and glandular tubes. Pseudostones originate from urinary calculi. System stones appear in the prostate segment of urethra or urinary stones enter into the urethra of prostate segment due to infection Through the glandular duct. Usually, the prostate stones are hard, round, oval or irregular in shape, with smooth surface; they are brown in color, similar to chestnut and soybean, and some are scattered in the whole gland, and some are limited to the gland leaves. Generally, the diameter is less than LCM, and there are also huge stones more than several cm. * small stones are mostly located in the middle of the gland. The causes are often related to prostate inflammation, hyperplasia of prostate, retention of prostate gland fluid, metabolic disorder, and occasionally in [6] of tuberculosis patients. The composition of prostatic stones and urine reflux in prostate gland duct, age of patients * [7], urinary system infection [8], prostate performance decline [9], secretion retention [10], calcium and phosphorus metabolism disorder are related. USTA MF et al. [11], and concluded that the positive rate of prostate stones in prostate related diseases such as benign prostatic hyperplasia and prostate cancer will also be significantly increased. Sutor et al. [12], through long-term clinical research, it is concluded that prostate stones can be formed by the retention of calcium salt and magnesium phosphate contained in the prostatic gland fluid. Shen Xuecheng et al. [14] concluded that prostate stones and nanobacteria infection have a significant relationship. Similarly, shoskes et al. [15], through clinical research, found that prostate stones are more common in patients with CPPs, which is closely related to the progress of inflammation, the site of bacterial infection and the duration of symptoms. Through the above research, we can easily find that prostate stones are closely related to urinary tract infection. Because prostate stones are often small in size, they usually have no special clinical manifestations [17] most patients are only found in physical examination. However, when the stones are large, complicated with prostatitis and prostatic hyperplasia, bladder irritation, ejaculation pain, hematuria and dysuria may occur.

3. The Relationship between Prostatic Calculus and Benign Prostatic Hyperplasia

The incidence of prostate stones in prostate diseases is high [18]. Most of the patients with prostate stones are accompanied by hyperplasia of glands, which can be confirmed by many clinical studies. Jin Xu [19] et al. After 680 patients were examined by color Doppler ultrasound of prostate, 251 cases were found to have prostate stones. Among these patients, 195 cases were accompanied with prostatic hyperplasia, 12 cases were with prostatic cyst, and 28 cases were with prostatitis. All 680 patients were divided into 40 ~, 50 ~, 60 ~, 70 ~, 80 ~, and the positive rate of prostate stones in each group was (percentage) The results showed that the positive rate of prostatic calculi increased with age, and the majority of patients with prostate stones were accompanied with hyperplasia of glands. Fang Zheng [20] et al. Selected 295 cases of patients with prostate stones detected by transrectal color Doppler ultrasound of prostate. The age range of the selected patients was 21-86 years old. After clinical examination, it was concluded that there were 3 cases of gonorrhea, 7 cases of acute and chronic urethritis, 22 cases of acute and chronic prostatitis, 248 cases of benign prostatic hyperplasia, and the remaining 15 cases were healthy people. The results showed that the positive rate of prostate stones increased significantly with the increase of age. Once again, the vast majority of patients with prostate stones were associated with benign prostatic hyperplasia.

Shixing Li et al. Methods: 400 patients after transurethral plasmakinetic resection of prostate were selected and divided into stone group and non stone group, 130 cases in stone group and 270 cases in non stone group The results showed that the average age of patients in the stone group was younger (70.2 ± 5.4 years old), significantly lower than that in the non Stone Group (78.8 ± 7.3 years old) ($P < 0.01$). The average weight of prostate in the stone group (weighed with balance after operation) [(20.4 ± 7.8) g] was significantly smaller than that in the non Stone Group [(50.6 ± 17.3) g] ($P < 0.01$). Among them, 125 cases of patients with postoperative symptoms disappeared or improved, reexamination of color Doppler ultrasound showed that stones completely disappeared; 5 cases of patients failed to remove the stones at the first operation (mistakenly considered that the stone cavity was the rectum and stopped the operation), the symptoms of the patients did not significantly improve after the operation, 3 cases underwent transurethral resection of the prostate to remove the residual glands and remove the stones, the clinical symptoms disappeared; the remaining 1 One patient was transferred to another hospital for radical prostatectomy, the other one refused the second operation and was followed up for 5 years. The results showed that the stone of prostate significantly aggravated the clinical symptoms of patients with benign prostatic hyperplasia, and the average age of patients requiring surgery was 8.6 years earlier, and the weight of prostate needed surgery was reduced by 30.2G. Yubing Wang et al [22]. A total of 392 patients with benign prostatic hyperplasia were selected. Among them, 351 cases were positive for prostate

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stones and 41 cases were negative for prostate stones, The positive rate of stone detection was 89.54%. All the patients were divided into negative group and positive group. Spss19.0 software was used to analyze the statistical data. It was found that the degree of benign prostatic hyperplasia in the positive group was more serious than that in the negative group.

According to the above study, it is not difficult to find that the vast majority of patients with prostate stones accompanied by hyperplasia of the prostate, and the positive rate of prostate stones with the increase of age will be significantly increased. In Guoxian Zhao's research, [5] found that the incidence rate of prostatic stones in the group over 50 years old was 48.91%, while that in the patients with prostatic calculus and benign prostatic hyperplasia was as high as 68.52%, while those in the group under 30 years old were 89.47%. 31 to 49 years old asymptomatic patients were as high as 81.10%.. In the study of 275 cases of prostate stones by Li Wei Zhong [23], 192 cases were found to be 69.8%. 147 cases (53.5%) were younger than 30 years old. Whether this shows that early detection of prostate stones is a dangerous signal of rapid progress of benign prostatic hyperplasia, or that prostate stones aggravate the clinical symptoms of patients with benign prostatic hyperplasia, making patients have to accept surgery when the size of prostate gland does not reach the conventional surgical indications, these problems need further clinical scientific research to confirm. This is an important factor affecting the physical and mental health and quality of life of middle-aged and elderly male patients. With the increasing trend of aging population in China, this problem is particularly prominent, which also forces us to further study the correlation between prostate stones and benign prostatic hyperplasia.

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