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COVID-19 : A Risk for Diabetes Induced Male Subfertility

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ABSTRACT

The latest corona virus epidemic COVID-19 triggered by the SARS-Cov2 virus has become exponentially high across the globe. Moderate and extreme pneumonia along with respiratory distress, fever, fatigue and malaise are clinically decripted among infected persons. Patients with severe COVID-19 can also develop a systemic inflammatory response that leads to multisystem organ dysfunction. Case studies across many countries suggest that severe acute respiratory syndrome corona viruses (SARS-CoV and SARS-CoV-2) can invade islet cells via angiotensin converting enzyme-2 (ACE-2) receptors and is responsible for reversible β-cell damage and transient hyperglycemia and diabetic ketoacidosis. Also, hypercytokinemia might have indirect destabilizing effect on pancreatic islets in COVID-19 patients that accelerate development of insulin resistance and type 2 Diabetes Mellitus (T2DM). Testicular resistance of insulin and altered insulin signalling on the other hand is responsible for decreased steroidogenesis by Leydig cells. Cytokine and chemokines in diabetic testicular tissue also induce sperm cell apoptosis. Additionally, ACE2 expression in the testis is restricted to the Leydig and Sertoli cells in humans which suggests that SARS-Cov2 has the likelihood of infecting the male gonad. Autopsied testicular and epididymal tissues of COVID-19 patients also showed signature of inflammation and germ cell apoptosis. This review work hypothesize that the male subfertility observed in COVID 19 survivors may be due to direct invading of SARS Cov 2 virus in testis or by development of diabetes and transient glucose metabolic disorders.

Keywords: COVID-19, Male Subfertility, Diabetes, Male Reproductive health, Pancreatic islets damage

INTRODUCTION

The COVID-19 pandemic is the greatest longstanding global health crisis of recent times. This pandemic resulted in severe economic and socio-political crisis around the world. Severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) is the virus that caused the global transmittable disease was

first reported on December 31, 2019 (Yoshimoto, 2020). It is a highly contagious virus that can be transmitted from person to person via aerosolized droplets, direct contact and oro-fecal route. Progressive respiratory failure along with high core body temperature is the primary cause of death in the coronavirus disease 2019 (COVID-19) pandemic. The lungs from patients with COVID 19 showed severe endothelial injury associated with the presence of the intracellular virus and disrupted cell membrane (Zhang *et al*., 2020). Among the recent coronavirus outbreaks in the new millennium (SARS CoV: 2002–2003, MERS CoV: 2012, SARS CoV-2: 2020), SARS CoV-2 cryptically had the foremost devastating world impact. Although coronavirus disease 2019 (COVID-19) is suspected to originate from an animal host (zoonotic origin) followed by human-to-human transmission, the possibility of other routes should not be ruled out (Ye *et al*., 2020).

The order of SARS CoV-2 (NCBI Reference Sequence: NC_045512.2) is analogous to the order of the coronavirus that caused the SARS pandemic in 2003 (SARS CoV, NCBI Reference sequence: NC_004718.3). SARS CoV-2 (NC_045512.2) has a total of eleven genes with eleven open reading frames (ORFs), ORF1ab, ORF2 (Spike protein), ORF3a, ORF4 (Envelope protein), ORF5 (Membrane protein), ORF6, ORF 7a, ORF 7b, ORF8, ORF 10 (Nucleocapsid phosphoprotein) (Machhi *et al*., 2020).

The main-host receptor of SARS Cov 2 is angiotensin-converting enzyme 2 (ACE-2), which is a prime constituent of renin-angiotensin-aldosterone system (RAA). Angiotensin-converting enzyme 2 (ACE-2) is expressed in respiratory mucosa, alveolar epithelial cells and similarly in specific cells residing in ascending and descending loop of Henle, Leydig cells and adipose tissue, pancreatic beta cells and seminiferous tubule cells (Zhao *et al*., 2014). Beyond the life-threatening pulmonary complications of SARS-Cov 2, the widespread organ specific manifestations of COVID-19 are already established. Those damaging pathological effects include cardiovascular and renal manifestations, endothelial cell damage and thromboinflammation, neurological and ophthalmological manifestations and dysregulated immune response (Sette and Crotty, 2021; Behzad *et al*., 2020).

Immunological Responses of COVID-19 Infection

Viral infection of mammals activates intracellular pattern recognition receptors that sense pathogen-associated molecular pattens, such as double-stranded RNA or uncapped mRNA. The recognition of pathogen-associated molecular patterns results in subsequent cytolytic immune responses, mainly through the type 1 interferons (IFN) and natural killer cells (Amarante-Mendes *et al*., 2018). Validation of many clinical cases reveal that a subgroup of patients with severe COVID-19 might have a secondary cytokine storm syndrome (hemophagocytic lymphohistiocytosis) that proceed to fatal hypercytokine-mia with multiorgan failure, the foremost potential grievous event associated with COVID-19 (Johnny and Younis, 2020). Cytokine storm in system facilitates the pathological process of various grievous manifestations of COVID 19: acute respiratory distress syndrome (ARDS), thromboembolic diseases such as acute ischemic strokes caused by giant vessel occlusion and myocardial infarct, acute urinary organ injury and vasculitis (Kawasaki-like syndrome in children and renal vasculitis in adult) (Copperchini *et al*.,2020, Jun, 2020).

The dysregulated adaptive immune system response to SARS Cov 2 results in cytokine storm including IL-6, IL 1 beta, IL 12 and IL 15, Tumor necrosis factor alpha (TNF alpha), chemokine (C-C motif ligand 2(CCL-2)/monocyte chemo-attractant protein 1 chemokine (MCP-1), c-Jun N terminal Kinases (JNK), which belong to the mitogen activated protein kinase family and are responsive to stress stimuli, such as cytokines and nuclear factor-kappa B (NF-kB) (Jesenak *et al*., 2020). This response catalyzes induction of chemotactic factors and adhesion molecules which eventually boost up monocyte recruitment and downstream cytokines/chemokines, extracellular signal-regulated kinases/p38 mitogen-activated kinases (ERK ½-p38 MAPK) signalling proteins that are reactive to ACE2-Ang (1-7)—MasR axis anti-inflammatory actions (Sette and Crotty, 2021).

Critical COVID-19 patients also reported a sudden decline of health status approximately two weeks after onset and clinically presented with infiltration of monocytes and macrophages into lung lesions, decrease of lymphocytes such as natural killer (NK) cells in peripheral blood and reduced NK cell cytotoxicity. Sustained rise in plasma level of IL 6 is also responsible for reduced NK cell numbers

(Wang *et al*., 2020). Several reports show overall lymphopenia with a drastically reduced number of both CD4 and CD8 T cells in COVID-19 patients. Highly disrupted levels of inflammatory response, reduced population of T_{reg} cells, atrophy of the spleen and lymph nodes along with decreased count of lymphocytes in lymphoid organs, hypercoagulability, thrombosis are also reported in severe COVID-19 patients (Chen *et al*., 2020, Jesenak *et al*.,2020).

Pancreatic Immune Cells and Inflammatory Milieu

Like almost all organs in the human body, human pancreas is immunologically tolerated regardless of the presence of innate and adaptive immune cells that on time mediate protective immune responses against pathogens (Cardozo *et al*., 2001; Ortis *et al*., 2010) .This is accepted that CD8+ helper (Th) cells, B cells, macrophages present in pancreatic cells secrete an array of pro-inflammatory cytokines and *in-vitro* studies shown that such molecules can induce apoptosis in rodent and human beta cells. It is interesting that islet-infiltrating macrophages are a major source of IL-1 and other cytokines in response to increased levels of nutrients (glucose, saturated fatty acids), endocannabinoids and islet amyloid polypeptide (IAPP) (Westwell-Roper and Ehses, 2014)

Type 1 diabetes (T1D) is a chronic disease caused by the selective destruction of the insulin-producing pancreatic beta cells by infiltrating immune cells (Ortis *et al*.,2010). It is suggested that during the progression of human type 1 diabetes, a polarization of CD4+ T helper cells takes place, leading to a predominance of the Th-1 phenotype with a significant down regulation of Th-2 response. Pro inflammatory cytokines especially IL-1β aids the expression of inducible nitric oxide (iNOS) and thereby escalate the production of nitric oxide (NO) and causing local nitrosative stress (Russell and Morgan, 2014). NO inactivates the enzymes of beta cell mitochondria that contain iron-sulfur centers or clusters. Further, NO produced by iNOS directly encourages the expression and activities of both constitutive and inducible isoforms of COX, further augmenting the overproduction of these proinflammatory mediators, NO and prostaglandins and thereby sustaining the inflammatory state and continuing destruction of the beta cells (Broniowska *et al*., 2014).

Pancreatic SARS-COV 2 Infection and Type 1 Diabetes

Involvement of several enteroviruses within beta cells of islet of Langerhans for destruction and functional impairment of the said cells and thereby causing type I diabetes is already established. It is hypothesized that an initial (acute) viral infection of the beta cells leads to setting up of a more sustained inflammation in which the beta cells survive but have altered functional properties (An *et al*., 2017). Extensive dataset supports the hypothesis that both acute and chronic infection favours insulin resistance and hence a risk factor for individuals with pre-diabetes to develop type 2 diabetes mellitus (Yang *et al*.,2018). Following cellular entry viral and bacterial pathogens is known to regulate ceramide (a sphingolipid) which opposes insulin signalling and alters glucose homeostasis. It binds with saturated fatty acids and inflammatory cytokines to the progression of insulin resistance. Viral infections are also associated with the development of pancreatic auto-antibodies leading to insulin-dependent Diabetes Mellitus or type I Diabetes Mellitus (Op de Beeck and Eizirik, 2016).

Literature survey suggests that severe acute respiratory syndrome coronaviruses (SARS-CoV and SARS-CoV-2) can enter islet cells via angiotensin converting enzyme-2 (ACE-2) receptors and cause reversible β-cell damage and transient hyperglycemia and diabetic ketoacidosis (Boddu *et al*.,2020). Virally driven hyperinflammation is causing hyperosmolarility and ketoacidosis in hospitalized patients for which high doses of insulin is warranted (Rubino *et al*.,2020).

Cytokines might have indirect effect on pancreatic islets secondary to severe lung infection in COVID-19 patients and may be responsible for the accelerated development of type 2 Diabetes Mellitus (T2DM) as one of its acute and suspected long term complications. Additionally, the redox storm resulting nitrosative stress within the islets may cause beta cell dysfunction and loss via apoptosis (Hayden, 2020).

Patients without any history of diabetes can acquire new-onset Diabetes Mellitus when infected with COVID 19 (Viswanathan *et al*., 2021; Rubino *et al*., 2020). It is also presumed that the viral infection of COVID-19 might have direct or indirect impact to cause metabolic dysfunction and diabetes mellitus in particular. Hemostasis alterations

and severe vasculitis accompanied by COVID-19 may be due to dysregulation of lipid transport and reduced HDL functionality (Sorokin *et al*., 2020).

Further, follow up study on SARS-CoV survivors has suggested that SARS-CoV may compromise pancreatic islets function and cause acute insulin dependent diabetes mellitus (Yang *et al*., 2010). Various glucose metabolic disorders including high blood sugar, insulin resistance and type I or II diabetes were also reported in a considerable proportion of the recovered SARS patients (Wu *et al*., 2017). Perturbed metabolic process of lipid and related dysfunctions like hyperlipidaemia, abnormal glucose metabolism, and cardiovascular anomalism were also reported in SARS conquerors even after a decade of contagiousness (Wu *et al*., 2017).

Diabetes: A Potential Cause of Impaired Male Reproductive Function

Diabetic and dyslipidemic men are commonly associated with an increased risk of developing erectile dysfunction and penile vascular impairment. Scrotal lipomatosis, a condition with fat deposition in scrotal area promotes the rise of scrotal temperature causing germinal atrophy and spermatogenic arrest (IIacqua,2018). Potential causes of hyperglycemia induced subfertility include impaired function of the hypothalamic-pituitary-gonadal axis, increased DNA damage, distress in the system by advanced glycation end products and their receptor, oxidative stress, increased endoplasmatic reticulum stress, impaired mitochondrial function and disrupted sympathetic innervation (Maresch *et al*.,2018). Increased oxidative stress due to hyperglycemia causes excessive production of free radicals that eventually induce sperm DNA fragmentation and reduce the production of sperm fertility proteins such as cystatin C and dipeptidyl peptidase 4, which ultimately affects mitochondrial metabolism and motility of sperm (An *et al*., 2017). Uncontrolled diabetes also changes protamine 1/protamine 2 ratio, an indicator of DNA instability and sperm degeneration (Pavlinkova *et al*., 2017).

Testosterone aromatization into estradiol by adipocytes can induce hypogonadism and excessive accumulation of lipid leads to adipocytes rupture that induce a pro-inflammatory state. Consequently, the steroidogenesis machinery is compromised, and the testosterone synthesis decreases, further promoting hypogonadism (An *et al*., 2017; Amaral *et al*., 2018). Meanwhile, the mitochondrial membrane potential is also affected, threatening the 'nurturing' of developing germ cells by sertoli cells. Diabetic men have a dramatically higher percentage of sperm with nuclear and mitochondrial DNA fragmentation and that the damage is oxidative in nature. Sperm DNA damage is known to be associated with the decreased embryo quality, the lower implantation rates, and, possibly, the early onset of some childhood diseases (Ilacqua, 2018). The mitochondrial superoxide anion concentration was found to be higher in Diabetes Mellitus 2 than in Diabetes Mellitus 1 patients. Indeed, lipid peroxidation increases only in type 2 diabetes patients, especially in relation to the higher concentration of seminal fluid leukocytes of this group of patients (Amaral *et al*., 2018). In type 2 diabetic patients, the heightened lipid peroxidation and mitochondrial superoxide anion may decrease MMP and consequently be accountable for a greater sperm motility decline than in type 1 diabetic patients. In diabetic rat model, specifically, the activation of NF-κB, with increases in TNF-α, iNOS and IL-6 levels, have been reported (Pavlinkova *et al*., 2017; Zhao *et al*.,2014). An up-regulation of pro-apoptotic p53, Bax/Bcl-2 ratio, caspase-8 and caspase-9, the confirmed contributors of intrinsic and extrinsic apoptotic signalling, which lead to the activation of caspase-3 also reported in the said model (Nna *et al*., 2018).

SARS CoV 2: Effect on Male Reproductive System

ACE2 expression in the testis is restricted to the Leydig and Sertoli cells in humans which suggests that SARS-Cov2 has the likelihood of infecting the male gonad and the recent detection of SARS-CoV 2 in the patient's semen further confirms and authenticates the idea that SARS CoV2 uses the same ACE2 receptor used by its cousin, the SARS CoV virus, with the help of TMPRSS2 (Transmembrane protease serine 2) (Chen *et al*., 2020[a]).To further investigate and analyse the types of testicular cells vulnerable for SARS CoV-2 viruses, Scientists have studied single celled ACE2 expression in the human testes. ACE2 is mainly expressed in spermatogonia, Leydig and Sertoli cell, while spermatocytes and spermatids had very low expression (Chen *et al*., 2020[b]). Interestingly, TMPRSS2 expression is similar to ACE2, where TMPRSS2 was also enriched in spermatogonia and spermatids. It has been also shown that ACE2 positive spermatogonia cells

express genes that are essential for virus reproduction and transmission, while ACE2 positive Leydig and Sertoli cells express genes that are relevant for cell-cell junctions and immunity. Accordingly, all these results emphasize the risk of COVID-19 on testicular microenvironment and spermatogenesis (Wang *et al*.,2020; Johny and Younis, 2020).

As Sertoli Cells have receptors of SARS CoV 2, they could be infected by the virus and their functions and metabolism are altered as reflected in decreased production of lactate and acetate (Bendayan *et al*., 2021). Also, autopsied testicular and epididymal specimens of covid 19 are presented with interstitial edema , RBC exudates and apoptotic cells . Elevated population of CD 3+ and CD 68+ in the interstital cells of testicular tissue and the presence of IgG within seminiferous tubules was also observed (Li *et al*.,2020).

COVID-induced Diabetes as a Challenging Factor for SARS CoV 2 Infected Males

It might be speculated that SARS-CoV-2 enter islets in some affected persons and cause acute β-cell dysfunction followed by hyperglycemia and transient type II diabetes mellitus. New-onset diabetes and severe metabolic complications of pre-existing diabetes ,including diabetic ketoacidosis is presented in COVID-19 patients. Male reproductive system is vulnerable in COVID 19 patients as sperm count and seminal plasma quality is compromised. This review hypothesize that the gonadal dysfunction noted in COVID-19 patients may be due to direct effect of cytokines and inflammation in the testicular or epididymal tissueusing ACE2 or may be due to progressive development of diabetes induced metabolic and immunological challenges because type 1 diabetes could hamper sperm metabolic machinery and thereby physiological functions of sperms. Long term insulin resistance of testicular tissue affects steroidogenesis and thereby causes hypogonadism.

CONCLUSION

According to worldwide clinical study database COVID-19 could increase the global burden of diabetes and glucose metabolic disorders and this review focussed on the risk of subfertility in COVID-19 survivors of reproductive age. The recovered patients should be careful about their family planning also. This impending issue of young fertile generation should be addressed carefully for future generation and benefit of human accomplishment worldwide. However, with more investigations and reports scientists could be able to identify the exact mechanism and correlation between COVID 19 infection, type 1 diabetes and challenging male fertility.

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