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Review article

COVID-19 and Pre-diabetes: Co-existence of two comorbidities matters

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ABSTRACT

With the increasing cases of corona infection, the anxiety and concern of the common population regarding the precautions to be taken, transmission of the novel coronavirus, and the possibility of further complications is on the rise. This pandemic however, can be conquered by the population ontaking the appropriate measures. With the immense prevalence of diabetes mellitus in the global population, with over 425 million people living with diabetes, the association between COVID-19 and Diabetes Mellitus is of concern. However pre diabetes is of greater concern, as many people aren't aware that they belong to the pre-diabetic population and the association between COVID-19 and pre diabetes has not been extensively explored yet. Diabetic people as well as pre diabetic people, once infected with the novel coronavirus tend to show complications and have the most severe form of the infection, added to this is the difficulty in treating such patients because of the elevated glucose levels and compromised immune system. The possible proposed mechanisms by which coronavirus and diabetes and pre diabetes are linked have been discussedbelow as they have nearly the same pathophysiology. Diabetes and pre-diabetes seen in pregnant, paediatric, and geriatric population and their association with COVID-19 have also been discussed below. Telemedicine has helped in straightening the curve and is becoming popular among the population. Many medications have also been started to be used throughout the globe by various doctors. Research regarding various treatment methods is well underway and is discussed below.

Abbreviations List: SARS = Severe Acute Respiratory Syndrome, MERS-CoV = Middle East Respiratory Syndrome Coronavirus (MERS-CoV), ICTV = International Committee on Taxonomy of Viruses, E = Envelope, S = spike, M = membrane, VN = virus neutralizing, N = Nucleocapside, ARDS = Acute respiratory Distress Syndrome, ACE2 = Angiotensin Converting Enzyme Receptor 2, DIC = Disseminated Intravascular Coagulation, DPP-4 = Dipeptidyl Peptidase-4.

INTRODUCTION

Coronavirus strain SARS-CoV-2, commonly known as COVID-19 virus or simply coronavirus has spread fast across the globe affecting a large proportion of the human population creating panic and worry far and near. The world has been striving against this microscopic virus for more than a year now. The International Committee on Taxonomy of Viruses (ICTV) announced "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)" as the name of the new virus and WHO announced "COVID-19" as the name of this new disease on 11 February 2020 [1, 2]. The current coronavirus outbreak is similar to the 2002–2003 outbreak of Severe Acute Respiratory Syndrome (SARS-CoV-1) and 2012 outbreak of Middle East Respiratory Syndrome Coronavirus (MERS-CoV). This pandemic came knocking on the door of the worldon December 31, 2019 when China reported to the World Health Organization (WHO), a series of pneumonia like cases in Wuhan, the capital of Hubei Province. Outbreak of the novel coronavirus (COVID-19) was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020 the as shown in figure 1 [3].

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This pandemic has brought together the whole world in not only identifying and containing the virus but also in developing a cure or vaccine.

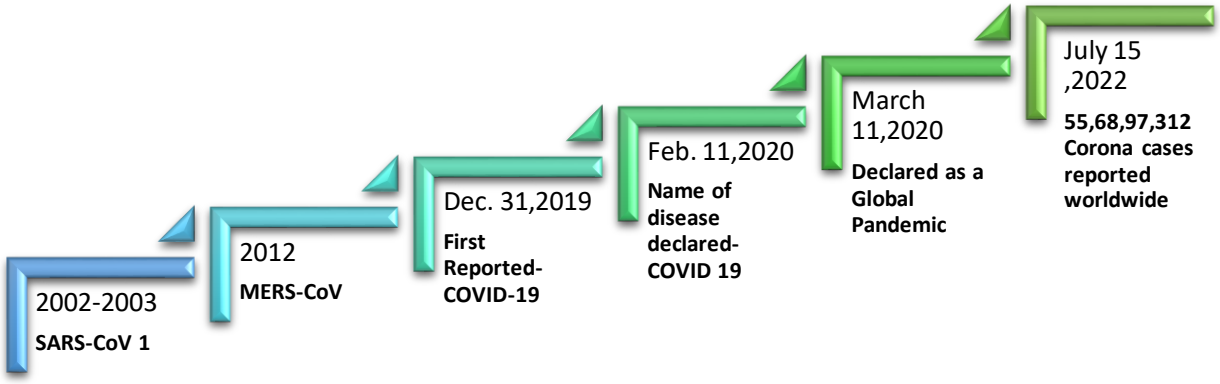

Figure 1: Progression of COVID -19

COVID-19 can be spread through either person to person transmission or community spread. Person to person transmission can be through droplets, aerosolised transmission, surface transmission, faecal-oral, etc. Community spread is when the person gets infected without the knowledge of any contact with an infected person. The virus can be spread through people having symptoms or asymptomatic individuals or pre-symptomatic individuals [4]. Currently in the world (as on 14th July 2022), there are 56,68,97,312 coronavirus cases of which 63,56,812 have died. According to the present data, Unites States has the highest number of cases followed by India, Brazil, France and Germany. Quarantine of individuals for containment of the disease, risk assessment andmanagement of health workers who are exposed to the virus, rational use of personal protective equipment for the disease, advice on the use of masks, guidance on water, sanitation, hygiene and waste management, are some of the many precautions advised [5].

INTRODUCTION OF COVID-19 VIRUS

SARS-CoV-2, (Coronavirus) belongs to the subfamily Orthocoronavirinae, in the family Coronoaviridae, order Nidovirales and realm Riboviria. With reference to the original SARS-CoV virus, the National center for Biotechnology Information taxonomy Browser has given the full taxonomic designation of COVID-19 virus as: Viruses, Riboviria, Nidovirales, Coronavirineae, Coronaviridae, Orthocoronavirinae, Betacoronavirus, Sarbecovirus [6].

Coronaviruses are one of the largest among RNA viruses. They are enveloped viruses having positive sense single stranded RNA genome and a nucleocapsid of helical symmetry. The genome size varies from 26 to 32 kilobases making it one of the largest. The genome has a 5' methylated cap and 3' polyadenylated tail. They have characteristic club shaped spikes projecting from their surface which in electron micrograph creates an image reminiscent of the solar corona and hence its name. The envelope in electron micrograph appears as a distinct pair of electron-dense shells i.e. shells which are relatively opaque to the electron beam used to scan the virus particle. The lipid double layer of the viral envelope has the envelope (E), spike (S) and membrane (M) structural proteins anchored in it, their ratio i.e the E:S:M being approximately 1:20:300. The neutralizing and inhibiting antibodies against the E antigen are induced by the E antigens. Similarly, the S and M proteins act as antigens producing their corresponding antibodies like the vial neutralizing (VN) andtibodies and antibodies that neutralize virus in the presence of complement as shown in Figure 2.

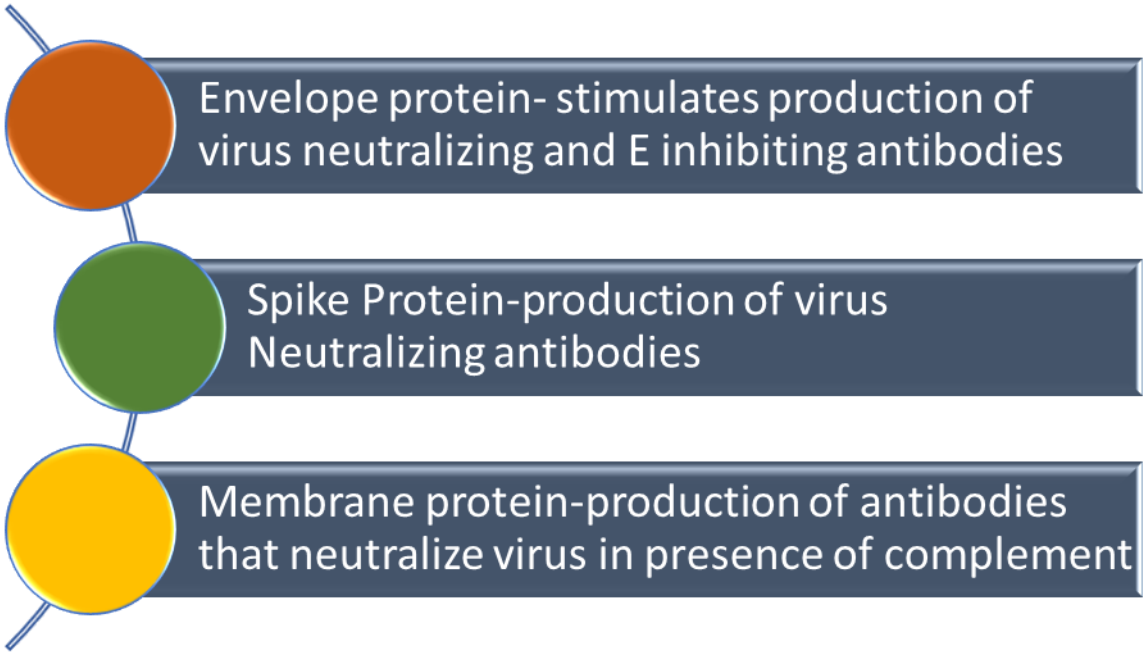

Figure 2: Structural Proteins anchored on viral envelope

On an average a coronavirus particle has 74 surface spikes, these spikes are actually homotrimers of the S protein consisting of S1 (forming the head of the spike and has Receptor Binding Domain) and S2 subunits (forming the stem and anchors the spike in viral envelope and on protease activation enables fusion). The E and M protein are important in forming the viral envelope and maintaining its structural shape.

Multiple copies of the nucleocapsid (N) proteins form the nucleocapsid which remains inside the envelope, and is bound to the positive sense single stranded RNA genome. This takes the form of a continuous beads-on-a-string type conformation. This envelope is responsible for protection of the virus when it is penetrates inside the host cells[7].

It is the S protein of the coronavirus i.e. the coronavirus spike protein which binds to the ACE 2 receptors and causes the cellular injury, leading to further complications. Principles of cell mediated immunity and antibody stimulation response needs to be explored more deeply to develop clear ideas about how the specific antigens and their epitopes from a natural corona virus infection induce a protective immune response in humans. Fever, cough, tiredness and shortness of breath are the major signs and symptoms due to the affected respiratory system as shown in the figure 3[8].

GENERAL CLINICAL SIGNS AND SYMPTOMS OF COVID-19

The virus can cause a range of symptoms, from mild illness to pneumonia. Mild to moderate cases have typically fever, cough, tiredness and shortness of breath as the cardinal signs and respiratory symptoms as shown in figure 3. As the disease progresses to more severe cases, further complications can ensue like pneumonia, severe acute respiratory syndrome and sometimes death [9].

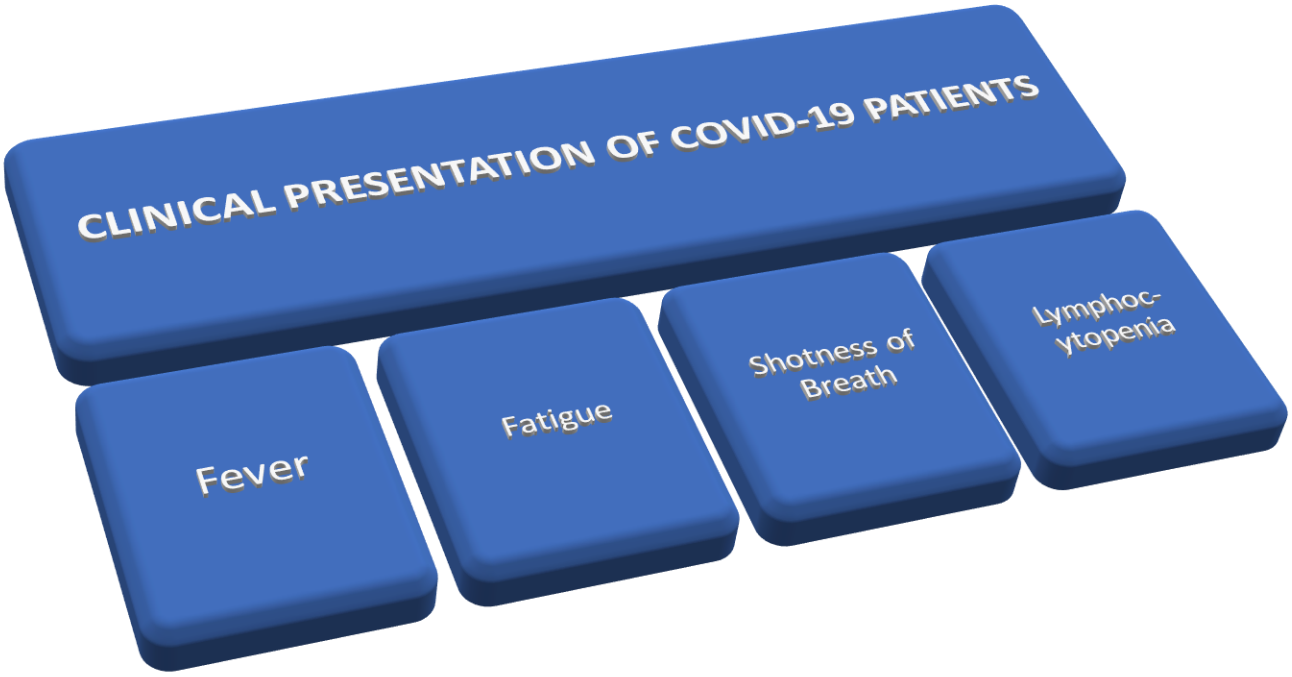

Figure 3: Clinical Presentation of COVID-19

COMPLICATIONS OF CORONA VIRUS INFECTION

For most individuals, the illness that comes from the infection of the virus causes symptoms which may be relatively mild and manageable at home. However, for older individuals orindividuals having other illnesses such as diabetes or heart disease or those who are pre-diabetic have increased risk for the more serious form of COVID-19. Some people, one in six will have complications including some that are life threatening. Many of these complications are caused by a condition known as cytokine release syndrome or a cytokine storm, that is there is a flood in blood stream with inflammatory proteins called cytokines which can kill tissues and damage organs such as lungs, heart and kidneys. The complications of COVID-19 include acute respiratory failure, Pneumonia, Acute Respiratory Distress Syndrome (ARDS), acute liver injury, acute cardiac injury, secondary infection caused by bacterial infections of streptococcus and staphylococcus, multi organ failure, etc [10].

GENERAL LABORATORY FINDINGS AND PRESENTATIONS OF COVID-19 PATIENTS

COVID-19 has affected individuals without any age or gender bias, however the median age group for susceptible individuals has been found to be around 47-59 years. The clinical spectrum of COVID-19 is very diverse. In adults and children initially there may be only a mild flu like symptoms. But due to various reasons, some may rapidly progress to acute respiratory Distress Syndrome (ARDS) that is very prone to lead to respiratory failure and severe cardiac complications like arrhythmias and acute cardiac injury. If not detected and treated promptly multiple organ failure along with death may ensue rapidly. Smell and taste disorder such as anosmia and dysgeusia have also been frequently found in COVID-19 patients in Italy.

Laboratory examination reveals most patients have normal or decreased white blood cell counts, particularly lymphocytopenia. In severe cases, neutrophil count, inflammatory markers, D-dimer, blood urea and creatinine levels are higher. Chest CT scans reveal ground glass opacifications with or without consolidative abnormalities which are also likely to bebilateral, have a peripheral distribution and involve the lower lobes, however some individuals also present with normal CT and some may also show abnormalities prior to appearance of symptoms.

Diagnosis is done only by microbiologic analysis. The patients having symptoms and those who meet the criteria, put forward by various organisations according to resources andvarious other factors have to be tested for COVID-19 virus as well as other respiratory pathogens like influenza,

respiratory syncitial virus, etc. Common laboratory tests are more frequently using real time PCR (RT-PCR) as the current diagnostic method for diagnosis of COVID-19 as this technique as a high sensitivity for detecting positive nucleic acid of SARS-CoV-2 in sputum, throat swabs and lower respiratory tract secretions [11].

LABORATORY FINDINGS AND PRESENTATIONS IN PRE-DIABETIC AND DIABETIC INDIVIDUALS WITH COVID-19

It has been found out that people with pre-diabetes and diabetes are at an increased risk of SARS-CoV-2 infection, and if infected they tend to do less well as compared to the general population. This is due to the fact that there is glycosylation of the spike protein of SARS-CoV-2, which regulates the binding to angiotensin converting enzyme receptor 2 (ACE2) on host tissue. Due to this increased glycosylation, there is increased entry of SARS CoV2 into host cells, thus higher blood glucose levels leading to increased susceptibility of the individual to infection and manifests a more severe form of the disease [12]. Individuals with Type 2 Diabetes Mellitus and infected by novel coronavirus have been found to be more in number when compared to individuals with type 1 diabetes mellitus and infected with the virus. Infected and pre-diabetic/diabetic individuals have found to be febrile and often anorexic, unwilling to eat or drink much and therefore having dehydration [13]. C-reactive protein and ferritin are slightly higher in patients with diabetes mellitus than those without, also there is slightly higher serum levels of interleukin 6 (IL-6). Individuals with diabetes and higher BMI are found to be more likely to require a ventilator.

PATHOLOGICAL/IMMUNOLOGICAL BASIS OF COMPLICATIONS OF COVID-19 INFECTIONS.

Many complications may arise after coronavirus infection as shown in figure 4, which may include:

1.Acute respiratory failure: Acute respiratory failure has found to be the leading cause of death. It is due to the lungs not pumping enough oxygen into blood or not taking out enough carbon dioxide, both of these problems can also occur at the same time.

2.Pneumonia: Alveoli in the lungs become inflamed and filled with fluid, puss and cell debris, thus making it difficult to breathe properly and transfer enough oxygen required for proper functioning of the body.

3.Acute Respiratory Distress Syndrome (ARDS): This is the most common complication causing difficulty in breathing and requiring assistance in breathing such as ventilators until recovery.

4.Cardiovascular Complications: Cardiovascular complications including hypotension and tachycardia are common whereas bradycardia and cardiomegaly are less common with cardiac arrhythmia being the rarest [14]. Infection may also cause acute cardiac Injury [15].

5.Acute Liver injury: Sudden Liver injury and liver failure are life threatening complications. Severely ill patients pose greater risk of liver damage.

6.Acute Kidney Injury: It is also not a common complication but if happens is very grave and can even cause chronic kidney diseases which require long term management. Infection by SARS-CoV-2 can cause acute kidney injury due to acute tubular necrosis induced by sepsis, hydration, cytokine storm syndrome, rhabdomyolysis and hypoxia. Direct virus invasion to renal tubular cells and interstitium or glomeruli is possible, also ACE2 receptors are extensively present in renal cells. Kidney injury as a complication of COVID-19 is associated with higher mortality [16].

7.Neurological Symptoms: It has been observed that there is an onset of neurological symptoms in some COVID patients which may be a warning sign of the novel coronavirus infection. Some COVID-19 patients have displayed confusion and seizures that can be associated with inflammation of the brain [17].

8.Disseminated Intravascular Coagulation (DIC): It is one of the common complications. It is due to abnormalities in blood clotting mechanism which can lead to internal bleeding or organ failure.

9. COVID-19-associated coagulopathy: It leads to increased blood clot formation in the body. Researchers believe that the virus itself may be causing a new clotting condition marked by the different protein levels in blood. It is different from DIC and can be understood due to the difference in protein levels in blood than that caused by Disseminated Intravascular Coagulopathy (DIC).

10.Secondary Infection: Secondary infection is not a common complication but it is possible. Staphylococcus and Streptococcus bacterial infections are common when the individual is recovering from viral infection.

11.Septic Shock: Septic shock can be fatal if not treated properly.

12.Multisystem Inflammatory Syndrome In Children (MIS-C) or paediatric multisystem Inflammatory Syndrome (PMIS): It causes symptoms like fever, bellypain, diarrhoea, rash, headache and confusion. Syndrome is similar to Kawaski Syndrome (toxic shock Syndrome) which causes inflamed blood vessels in children.

13.Rhabdomyolysis: It is a very rare complication. It causes increased myoglobin levels in blood due to muscle breakdown and tissue death. Kidneys should be able to flush

the myoglobin out or else it can cause death [18].

COVID-19 IN PRE-DIABETIC POPULATION

Pre-diabetes (or intermediate hyperglycemia) refers to the state in which the blood glucose concentration is above normal but not high enough to diagnose type 2 diabetes. Pre-diabetes is triggered by the decrease in insulin sensitivity and reduced pancreatic beta cell functioning which leads to glycemic dysregulation. This dysregulation in glucose concentration leads to moderate hyperglycemia, which is associated with many microvascular and macrovascular complications, cognitive dysfunction and variations in blood pressure. The body will compensate for this hyperglycemic state through various mechanisms like increasing the insulin secretion by pancreatic beta cells and reducing the insulin clearance by liver, however after a certain limit, there is severe hyperglycemia leading to type 2 diabetes mellitus. Also, there is evidence that exposure to COVID-19 causes direct injury to the pancreatic beta cells which is substantiated by the fact that there is elevated expression of the SARS-CoV receptor, angiotensin converting enzyme 2 in the islets of Langerhans, making it more dangerous and leading to severe complications in the pre-diabetic population [19].

COVID-19 & DIABETES MELLITUS

Diabetes has found to be one of the primary risk factors and comorbidities associated with increased complications in coronavirus infections. Studies have also revealed COVID-19 is associated with hyperglycaemia particularly in the elderly with type 2 diabetes. Epidemiological observations in regions heavily affected by SARS-CoV-2 and reports from the Centers for Disease Control and Prevention (CDC) and other national health centres and hospitals proved that the risk of a fatal outcome from COVID-19 is up to 50% higher in individuals with diabetes than in those who do not have diabetes.

Individuals with all forms of diabetes are at increased risk of fatal outcomes if infected however the increased incidence of pre-diabetic and type 2 diabetes mellitus and fatal outcomes can be due to the fact that pre-diabetes and type 2 diabetes is prevalent in older people who are also associated with cardiovascular diseases. It is difficult to treat those pre-diabetic and diabetic patients who develop a viral infection as their blood glucose levels fluctuate due to rapid fluctuations in their blood glucose levels. Possibly, hyperglycemia in these patients also increases complications like nephropathy, neuropathy and retinopathy. The probable causes for these are i) a longer recovery period due to a compromised immune system, and ii) increased chances of thrival of the virus an environment of elevated blood glucose. That is why the conditions like pre-diabetes, type 1 and type 2 diabetes are related with poor outcome in COVID-19 [20]. On investigation it has been found that patients with type 2 diabetes are more in number than patients with type 1 diabetes followed by the other types of diabetes [21].

The reason behind diabetic individuals being more susceptible to fatal outcomes can be because of defects in innate immunity affecting phagocytosis, neutrophil chemotaxis and cell mediated immunity.

There are majorly two potential mechanisms which indicate the link between pre-diabetes/diabetes and adverse outcomes in coronavirus infection.

The First one being when the virus tries to enter the target cells, it takes over the major endocrine pathway which is involved in the regulation of blood pressure, metabolism and inflammation. The S protein of the virus i.e. the coronavirus spike protein binds to the (Angiotensin Converting Enzyme 2) ACE2 receptors and thus reducing its expression leading to cellular damage, hyperinflammation and respiratory damage. ACE2 is widely expressed in the respiratory tract, heart, kidneys, intestines, cerebral neurons, endothelium of arteries and veins, immune cells and pancreas. Acute hyperglycaemia has found to upregulate the expression of ACE2 which may facilitate viral cell entry, however chronic hyperglycaemia is known to downregulate its expression making the cells vulnerable to inflammatory and damaging effects of the virus. The expression of ACE2 on pancreatic beta cells may have a direct effect on the beta cells and suggests that diabetes can not only lead to severe complications on infection of the virus but infection of the virus can also induce new onset diabetes. Facts supporting this statement include the increased admissions of severe diabetes ketoacidosis and the tremendous increase in insulin requirements in patients with infection.

The second mechanism involves the enzyme dipeptidyl peptidase-4 (DPP-4). DPP-4 enzyme is an extensively expressed type 2 transmembrane glycoprotein which plays a major role in glucose and insulin metabolism and also increases inflammation in type 2 diabetes. DPP-4 was earlier identified as the functional receptor for the virus responsible for MERS. Antibodies directed against DPP-4 inhibited human coronavirus-Erasmus Medical center (hCovV-EMC) infection of primary cells. Whether there is a connection between COVID-19 and DPP-4 inhibitors used to treat diabetes is currently unknown, however if this is known it will enhance the scope for finding therapeutic treatments for COVID-19 [22].

COVID-19 & PRE-DIABETES/DIABETES IN PREGNANT PATIENTS:

Gestational Diabetes is seen during pregnancy and is a

condition marked by high blood sugar levels usually tested around 26 weeks, it has no specific or clear symptoms. The elevation is due to the hormones released by placenta during pregnancy. This condition can rarely cause delivery issues, health problems for the baby or type 2 diabetes in the mother. Gestational diabetes is not grave as the mother usually gets full recovery post pregnancy and hence no further complications.

Pregnancy increases the susceptibility of the individual to develop complications in COVID-19 infection as being pregnant causes the immune system to be compromised and pre-diabetes and diabetes increases the severity of the complications.

Pregnant women experience more immunologic and physiologic changes which makes them more prone to the viral infection. It had been seen that in respiratory illnesses and coronaviruses, such as SARS-CoV and MERS-CoV, pregnancy may increase the risk of severe illness, morbidity, or mortality andthere has been cases of pregnancy loss, miscarriage and still birth in women with SARS-CoV and MERS-CoV, however none have been reported till date regarding SARS-CoV2 [23].

COVID-19 &PRE-DIABETES/DIABETES IN PAEDIATRIC PATIENT:

The most common features seen in paediatric patients having novel coronavirus infection is fever and cough. In contrast to observations in adult patients, paediatric cases showed a higher proportion of fever, vomiting, and diarrhoea on admission [24]. For laboratory findings, procalcitonin elevation should be checked which is not seen in adults. Pulmonary lesions are also common on examination using chest CT. Ground-glass opacities, consolidation with halo sign, fine mesh shadow and tiny nodules can also be seen on chest CT. Consolidation with surrounding halo sign is a typical sign in paediatric patients [25]. Infants and young children have relatively more severe illness than older children.Management is mainly by supportive care. As of now, no vaccine or specific chemotherapeutic agents are approved for children [26]. People with Diabetes are not more susceptible to coming down with COVID-19.

COVID-19 AND PRE-DIABETES/DIABETES IN GERIATRIC POPULATION:

Elderly people and people with pre-existing medical conditions such as pre-diabetes, diabetes, heart disease, asthma, etc are more vulnerable to becoming severely ill with the COVID-19 virus [27].

The mechanism of action of coronavirus may pose a higher risk of infection to older adults because spike proteins present on the virus anchor it to ACE-2 receptors on cells in the lower respiratory tract. Majority of the adults older than age 60 have hypertension, chronic kidney disease (CKD), and diabetes. Many of these patients use ACE inhibitors and angiotensin-receptor blockers (ARBs) which upregulate ACE-2 receptor. Thus it is hypothesized that older individuals with such comorbidities have an elevated risk of and experience a more severe course of infection with SARS-CoV-2.

The general presenting features include fever, cough, dyspnoea, shortness of breath and fatigue. An analysis by the joint WHO-China fact-finding mission found that patients older than age 60 and those with comorbidities like diabetes had the highest risk for severe disease and even death [28].

ROLE OF TELEMEDICINE IN COVID-19 AND PRE-DIABETES/DIABETES

Telemedicine aims at providing quick medical services. This has been greatly used amid the coronavirus lockdown. The Ministry of health And Family Welfare (MoHFW), India has also put forward certain rules and regulations to abide regarding telemedicine. Telemedicine has made healthcare accessible and affordable with the help of electronic means like telephonic or video conversations for diagnosis and treatment [29]. Telemedicine becomes the safest and yet most economical means of consulting a doctor during these difficult times without the worry of being surrounded by various pathogens in the hospital or consulting clinic. Diabetic Individuals who require assistance or advice from their doctors or practitioners can easily consult with them without any difficulty.

TREATMENT

Many medications have been started and are under research throughout the globe by various doctors and scientists. The reason for the difficulty in developing treatments in viral illnesses are because the antiviral drug must be able to target a precise part of the virus's life cycle which is inevitable for it to reproduce. Also the antiviral drug must be able to kill the virus without killing the host cell. Added to this is the fact that viruses are highly adaptive and undergo mutation in every generation for adapting and developing resistance against the

drugs [30]. The various medications under consideration and in use include:

1) Dexamethasone

Dexamethasone is a corticosteroid known for its anti-inflammatory and immunosuppressant effects. Dexamethasone trials were conducted in hospitalized patients with COVID-19 in the United Kingdom's national clinical trial RECOVERY and was found to have benefits for critically ill patients.

According to the initial findings, the treatment using dexamethasone has proven to reduce mortality by about one third for patients on ventilator and mortality was cut by about one fifth for patients requiring only oxygen [31].

2.**Remdesivir**

The antiviral drug, Remdesivir was approved by the FDA to be used to treat COVID-19 infected adults and children of 12 years and more, who have been hospitalized for COVID-19. Clinicals trials indicate that remdesivir fastens the recovery time.

Several clinical trials, evaluating remdesivir for the treatment of COVID-19 are currently underway [32].

3. Monoclonal Antibody treatment

Currently two monoclonal antibody treatments are in use, both of which have been approved by the FDA for emergency use authorization (EUA) for the treatment of COVID-19 in non -hospitalised adults and children over the age of 12. They are Bamlanivimab made by Eli Lilly and a combination therapy of two monoclonal antibodies, Casirivimab and Imdevimab made by Regeneron [33].

4. Plasma Therapy

FDAhas approved individual exploratory treatment for COVID-19 infections in which the patient receives convalescent plasma in life threatening cases. This method has only been approved for the treatment of COVID-19 and not for the prevention of infection [34].

COVID-19 VACCINE

Within a time frame of just a year various governments, multilateral organizations and various private firms all over the world have come forward to develop and distribute safe and effective vaccines.

There are presently more than 60 COVID-19 vaccine candidates in clinical development and just over 170 in pre-clinical development. The vaccine is aimed to be distributed throughout the population with people more at risk prioritized. There are four categories of vaccines currently in clinical trial [35]. They are:

1. Whole virus

While using the whole virus approach it can be live attenuated vaccine which uses the weakened form of the virus which can still replicate and cause a immune response or it can be inactivated vaccines in which the genetic material of the virus has been destroyed such that it can't replicate, but still can trigger an immune response.

2. Protein Subunit

The vaccines make use of protein pieces of pathogen to trigger an immune response. These types of vaccines make use of adjuvants also to help boost the immune response.

3. Nucleic acid

These vaccines make use of genetic material like RNA or DNA of the virus. In the COVID-19 vaccine, the viral spike protein is used. The genetic material inside the host cell will produce the antigen which will trigger the immune response.

4. Viral Vector

These vaccines make use of a harmless virus, which is different from the virus the vaccine is targeted at, to deliver genetic instructions into the cell.

Currently many vaccines have been authorized to prevent COVID-19 [36].

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