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A Brief Analysis of the Pathogenesis of COVID-19 Complicated with Diabetes Mellitus

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Abstract: COVID-19 began to break out in 2019 and is still popular all over the world. Now it has become a major public health problem in the world. According to various studies, half of COVID-19 patients are often accompanied by chronic diseases, and chronic diseases combined with COVID-19 will increase COVID-19's case fatality rate to a certain extent. COVID-19 belongs to the category of "epidemic disease" in traditional Chinese medicine and is highly contagious. Most doctors in our country think that the key to the pathogenesis lies in spleen deficiency and damp pathogen, and because of different regions, climates and individual differences, the pathogenesis differentiation of patients is different. According to this characteristic, many doctors in our country have put forward their own opinions. Diabetes is a chronic metabolic disease characterized by elevated blood glucose level, which belongs to the category of "diabetes" in traditional Chinese medicine. The main pathogenesis of traditional Chinese medicine is Yin deficiency and dryness and heat, which is one of the common chronic diseases in China. In order to better understand the occurrence and development of COVID-19 with diabetes, based on the existing research and the understanding of many doctors, the author discusses the pathogenesis of COVID-19 with diabetes from the two aspects of traditional Chinese medicine and western medicine, hoping to be helpful to the clinical work.

1. Introduction

COVID-19 is extremely contagious and is still popular in most parts of the world. It broke out in Wuhan, China in December 2019, and then gradually spread to all parts of the world in a very short time. Related studies have shown that more than half of COVID-19 patients are accompanied by various chronic basic diseases, such as diabetes, cardiovascular, cerebrovascular diseases and so on[1]. Among them, COVID-19 with diabetes has a higher incidence and a poor prognosis. It is reported that the proportion of diabetes infection in COVID-19 's patients is 10.1% / 20.0% [2][3]. According to a study by the Chinese Center for Disease Control and Prevention[4], the overall mortality rate of COVID-19 is 2.3%, and the mortality rate of diabetes mellitus is 7.3%. The data show that COVID-19 has a higher case fatality rate of diabetes than COVID-19 's fatality rate. This may indicate that the prognosis of diabetic patients infected with COVID-19 is worse than that of COVID-19 patients.

Therefore, it is of great significance for clinical work to study the occurrence and development of COVID-19 complicated with diabetes. This paper analyzes the pathogenesis of traditional Chinese medicine and western medicine to understand the interaction between COVID-19 and diabetes. In order to have a more comprehensive understanding of the disease, and better guide the clinical work, improve the clinical treatment and prognosis of patients.

2. The western medicine pathogenesis of COVID-19

COVID-19 is an acute respiratory infectious disease with strong infectivity, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[5]. There are many kinds of glycoprotein structures on the surface envelope of SARS-CoV-2, among which the most closely related to virus infectivity is prickle glycoprotein (spike glycoprotein,S protein). The binding region of S protein receptor has strong affinity with human receptor angiotensin converting enzyme 2 (ACE2)[6], so COVID-19 has strong infectivity in human population. Because ACE2 is widely distributed in various organs and tissues of the human body, such as heart, lung, brain, kidney, small intestine and so on, SARS-CoV-2 invasion will cause not only respiratory system disorders, but also other multi-system dysfunction, including acute respiratory distress syndrome (ARDS), acute heart injury, acute kidney injury and so on[7]. Among them, the occurrence of acute respiratory distress syndrome is closely related to cytokine storm, which can cause uncontrolled inflammatory response in lung tissue, and excessive immune response makes a large number of immune cells activate and gather in the lung[8].

Since COVID-19 became popular, the virus has mutated frequently under extensive replication in a short period of two years through genomic variation and deletion. The known variants include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529)[9]. The transmission ability of the mutant strain is getting stronger and stronger, and the adaptive mutation is carried out in the direction of reducing the sensitivity of neutralizing antibody.

3. COVID-19 's understanding of the pathogenesis of traditional Chinese medicine

After observing many clinical cases of COVID-19, Chinese doctors summed up the rules and found that they were highly contagious and the symptoms of the infected people were similar, which belonged to the category of epidemic disease in Chinese traditional medicine. In the understanding of western medicine, although all COVID-19 patients are infected with the same virus, according to the observation of existing cases, it is found that the clinical symptoms of patients are also different under different regional conditions. Chinese doctors consider its influencing factors may be due to different geographical locations, different climatic conditions, different personal physique, and different pathogenesis of patients after pathogenicity. Many doctors in our country have put forward their own dialectical ideas on COVID-19 's understanding of the pathogenesis of traditional Chinese medicine.

After summarizing the current understanding of doctors, it is found that COVID-19 's TCM etiology is mainly "damp evil", which can be divided into three types: warm-damp epidemic pathogen, cold-dampness epidemic pathogen and epidemic pathogen with dryness. According to individual differences, climate and geographical location, the specific TCM syndrome differentiation of patients can be divided into cold-dampness epidemic, damp-temperature epidemic, dampness toxin epidemic, dampness toxin and dryness epidemic, if both cold, heat and dryness are included, there are warm-damp epidemic pathogen, cold-dampness epidemic evil, epidemic evil sandwiched dryness and so on [10].

Jia Zhenhua[11] and Zhang Boli[12] think that COVID-19 feels the "poison of winter temperature", and its clinical symptoms are characterized by both warm evil and toxic evil. Xue Boshou[13] and

Tong Xiaolin[14] think that cold-dampness epidemic toxin is pathogenic, and its clinical characteristics are cold-damp epidemic pathogen. Wang Yongyan [15] and Fan Fuyuan[16] thought that COVID-19 's clinical symptoms were characterized by both "dryness" and "dampness".

Chinese doctors make a dialectical analysis of COVID-19 from a variety of syndrome differentiation angles. If the method of syndrome differentiation is different, the pathogenesis is not the same. From the perspective of syndrome differentiation of viscera, Academician Tong Xiaolin[14] believes that COVID-19 belongs to the "cold-damp epidemic". The patient feels cold and dampness and the evil of the epidemic is violent. Evil qi invades the human body through mouth, nose and skin, causing lung defense to lose consciousness and dampness to trap spleen soil. Even spread to the heart, liver, kidney, the syndrome is mainly yang. Starting from the syndrome differentiation of the six meridians, Shi Guangwei[17] thought that COVID-19 had abnormal gasification function of "sun opening", "Shaoyang pivot" and "Taiyin opening", and put forward that "opening the sun, harmonizing Shaoyang and closing Taiyin" was the core of COVID-19 's treatment.Chai Ruiai[18], a famous traditional Chinese medicine, knew COVID-19 from the perspective of syndrome differentiation of Sanjiao, and believed that at the initial stage, evil qi entered through the mouth and nose, and the first attack was on the lung system. In addition, there was latent heat in the lungs, which was contained in the lungs. However, the epidemic toxin is mainly damp, turbid and filthy, and dampness pathogens are most likely to hurt the spleen and soil in the middle jiao. Therefore, the spleen and stomach of Zhongjiao is often taken as the focus of the disease. In the middle stage of the disease, damp-heat contains turbid phlegm or phlegm-heat, which leads to turbid phlegm or phlegm-heat obstructing the lungs, while damp-heat of spleen and stomach in middle jiao and damp-heat of large intestine in lower jiao form stomach-fu-heat knot. Huang Wenzheng[19], from the point of view of syndrome differentiation of Wei, Qi, Ying and Blood, thinks that the pathogenic "Qi" belongs to the evil of dampness and toxin, and the pathogenesis is characterized by dampness, heat, poison and blood stasis. In the middle stage, from toxin-heat syndrome to blood stasis syndrome, the disease changes from qi syndrome to blood syndrome in the syndrome differentiation of six meridians. Based on the theory of membrane, Wang Jinzhong[20] and others think that COVID-19 has the syndrome of cold-dampness, dampness and heat due to qi stagnation and dampness. In addition, from the point of view of three factors(Geography, climate differences, and individual differences), by comparing the cases of COVID-19 patients from different geographical locations in Wuhan, Jilin, Beijing and Shanghai, Wuhan[21] patients are mainly cold-damp attacking lung type and dampness blocking middle coke type; Jilin[22] patients are mainly cold-dampness obstruction, dampness-depressing heat, warm toxin damage collaterals; Beijing[23] patients are heavier than dampness, "heat is damp depression", heat potential is not very; Shanghai[24] patients are rich in dampness and toxin, diffusing Sanjiao, consuming gas and injuring yin.

4. The correlation between COVID-19 and diabetes mellitus

4.1 Mutual influence on the pathogenesis of western medicine

According to research, diabetes patients will have varying degrees of blood glucose fluctuations after being infected with SARS-CoV-2, and the mortality of COVID-19 patients with diabetes will also increase[25]. When patients have both viral infection and hyperglycemia, the patient's condition is more critical, severe pneumonia is more likely to occur, and the risk of death increases[26]. The role between COVID-19 and diabetes is two-way, both acting on the human body at the same time, will affect each other, interact with each other, produce some irreversible damage to the human body, and affect the development and prognosis of the disease.

4.1.1 Effect of COVID-19 on diabetes mellitus

COVID-19 can cause an increase in blood sugar, and its mechanism may be caused by the following reasons:

Immune injury: Chinese scholars such as Yang Jinkui have found that ACE2 is expressed in pancreatic tissue, so severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) can invade pancreatic tissue through ACE2 as a receptor. Pancreatic tissue injury leads to islet cell dysfunction, imbalance of blood glucose regulation, and the risk of diabetes will increase[27]. Some studies have found that the COVID-19 virus SARS-CoV-2 and SARS-CoV, which caused the pandemic, have genetic similarities at the genetic level, with nucleotide homology of more than 85%[28], and have the same entry receptor ACE2[29] when invading the human body, with a similarity of 96%. Therefore, it is speculated that the mechanism and target of injury of the two viruses may be the same, and SARS-CoV-2 will also attack the pancreas, resulting in islet cell damage and blood glucose fluctuation.

Cytokine storm: COVID-19 patients in the course of the development of cytokine storm will occur in the body, that is, the body after stimulation produced an over-immune state[30]. Cytokine storm releases a large number of inflammatory factors, such as interferon-gamma (INF--γ), interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor-α (TNF- α) and so on. The activation of inflammatory factors, including these, happens to be closely related to insulin resistance and diabetes[31]. When the signal transduction starts after the activation of inflammatory cytokines, it will hinder the insulin signal transduction in insulin-sensitive cells, resulting in a decrease in insulin sensitivity, a decrease in the ability of insulin to regulate blood glucose balance, and an increase in blood glucose and blood lipids, which in turn leads to insulin resistance[32][33].

Liver injury: COVID-19 patients are often complicated with liver injury. Liver plays an important role in glucose metabolism. When hepatocytes were injured, the ability of liver to synthesize hepatic glycogen decreased, the inactivation of glucagon in the liver decreased, the number of specific insulin receptors on hepatocyte membrane decreased, and advanced glycation end products (AGEs) increased, which led to insulin resistance, islet β-cell failure and increased blood glucose[34].

Drug effects: the commonly used drugs in COVID-19 patients are hormones, antiviral drugs and so on. Drug interactions can also affect blood sugar fluctuations in patients. For example, glucocorticoids have anti-inflammatory effects. Chen Shi and other scholars[35] found that 53% of patients used glucocorticoids. But one of the side effects of glucocorticoids is to raise blood sugar. Luo Wei[36] found that in the treatment of COVID-19 patients treated with glucocorticoid, the blood glucose increased, and the hypoglycemic effect of insulin was not obvious. Other therapeutic drugs such as lopinavir / ritonavir and interferon-α can also affect the blood sugar of patients. Studies have found that antiviral drugs such as lopinavir and ritonavir can interfere with insulin secretion and damage the first and second phase insulin secretion more than peripheral insulin resistance, resulting in impaired glucose tolerance[37] and elevated blood sugar. α-interferon can enhance the secretion of glucagon, growth hormone and adrenocortical hormone, and enhance insulin resistance. It can also enhance the expression of compatibility complex 1ax 2 antigens in islet cells, produce a variety of islet antibodies, destroy islet β cells, and increase blood glucose[38]. These drugs commonly used in the treatment of COVID-19 will destroy the blood glucose balance in the body to varying degrees and cause blood glucose fluctuations.

4.1.2 Effect of diabetes mellitus on COVID-19

Diabetes affects the role of COVID-19 in the following aspects:

Aggravation of inflammation in patients with diabetes: there is mild chronic inflammation in patients with diabetes, which may promote cytokine storm, resulting in an increase in mortality in COVID-19 patients[39]. Guo[40] published the first study on the biochemical characteristics of COVID-

19 diabetic patients. By comparing the biochemical indexes between diabetic patients and non-diabetic patients, the results showed that the absolute lymphocyte count of diabetic patients was significantly lower than that of non-diabetic patients, and the absolute neutrophil count of diabetic patients was significantly higher than that of non-diabetic patients. A similar study[41][42] also compared the clinical characteristics of COVID-19 patients with and without diabetes. The results also showed that some infection indicators such as neutrophil / lymphocyte ratio, high-sensitivity C-reactive protein and procalcitonin levels were higher in diabetic patients. Studies have shown that the higher ratio of neutrophil receptor and lymphocyte to C-reactive protein, as well as the increase of inflammation-related biomarkers, have been identified as independent risk factors for the prognosis of COVID-19 patients[43][44].

Immunodeficiency in patients with diabetes: in patients with diabetes, persistent hyperglycemia can lead to a series of abnormal metabolic changes[45][46], which together increase the production of superoxides and the activation of inflammatory pathways. leading to immune system dysfunction. In particular, neutrophils have defects in almost all functions, including inflammatory cell migration, release of lysozyme, phagocytosis, production of reactive oxygen species (ROS) and apoptosis[47],which increases susceptibility to invasive novel coronavirus pathogen. Diabetes also weakens the control and clearance of pathogens, leading to adaptive immune system dysfunction. Generally speaking, the maintenance of host immunity and the control of inflammatory injury depend on the homeostasis between pro-inflammatory and anti-inflammatory subsets of CD4+-effector T cells. In patients with type 2 diabetes, T cells are overactivated, which will promote the inflammatory process[48][49], and then affect the disease development of COVID-19 patients.

Diabetic lung injury: COVID-19 is accompanied by obvious lung injury, diabetes may aggravate the degree of injury. A great deal of evidence shows that diabetes is related to abnormal physiological structure of lung tissue and pulmonary dysfunction[50][51], suggesting that diabetes can aggravate lung injury in addition to immune deficiency. Diabetic patients tend to show lower forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) and lower diffusing capacity (DLCO) than non-diabetic patients[52]. Oxidative stress caused by persistent hyperglycemia is the main cause of diabetic lung injury[53].

4.2 Understanding of the pathogenesis of traditional Chinese medicine

Diabetes belongs to the category of "eliminating thirst" in traditional Chinese medicine. the main pathogenesis of eliminating thirst is yin deficiency and dryness and heat. Yin deficiency for a long time consumes qi and hurts yin, resulting in deficiency of both qi and yin, late yin damage and yang, and finally forms the syndrome of deficiency of both yin and yang. Lung, stomach and kidney are the main pathological changes of viscera, especially kidney. COVID-19 in TCM syndrome differentiation is "damp evil" throughout the pathogenesis, according to regional and individual differences, the pathogenesis is slightly different. Many doctors in China believe that spleen deficiency and phlegm-dampness are the key to the pathogenesis of diabetes mellitus complicated with COVID-19.

Zhao Yong et al[54] analyzed and summarized the clinical characteristics of 67 COVID-19 patients and found that the pathogenesis of type 2 diabetes mellitus complicated with COVID-19 was mainly deficiency, dampness, heat, blood stasis and phlegm, and the disease was located in the lung and spleen. Patients with diabetes are physically deficient and are relatively deficient in normal qi, so they are vulnerable to external evil. COVID-19 is an epidemic disease of traditional Chinese medicine, which is highly contagious and is more susceptible to patients with thirst. The course of the thirst patients is long, the overall viscera deficiency, lack of function, the symptoms of the patients show a virtual image. COVID-19 is mainly damp evil after infection, damp evil is most likely to trap the spleen, spleen deficiency weakens the ability of movement and transformation, unable to transport

excessive water dampness, more phlegm dampness, dampness evil is not only the cause of disease, but also the product of pathology. Phlegm-dampness blocking the lungs affects the release and descending of the lungs, leading to cough, asthma and other pulmonary symptoms. Damp evil depression for a long time and heat, or thirst patients with yin deficiency and internal heat, resulting in more patients with fever symptoms, but damp by heat depression, the heat potential is not very, is not the real heat seen high fever. If heat enters the camp and blood, it will produce pathological products such as blood stasis.

Hu Zhipeng et al[55] think that diabetes mellitus complicated with COVID-19 is based on deficiency of spleen qi and internal resistance of phlegm and dampness. Thirst patients with deficiency of body, deficiency of viscera, deficiency of spleen, deficiency of qi and blood, maternal disease and son, so deficiency of lung qi and non-solid external defense, so it becomes a prerequisite for infection of COVID-19. The autopsy results released by Academician Wang Fusheng[56] showed that there were mucus, pulmonary edema and hyaline membrane formation in the lung tissue of patients with COVID-19 death, and mucus, edema and pulmonary hyaline membrane all belong to phlegm and dampness in the understanding of traditional Chinese medicine. Phlegm-dampness is the main feature of the pathogenesis of this disease.

To sum up, COVID-19 complicated with diabetes will lead to an increase in mortality. The pathogenesis of western medicine is related to immune injury and cytokine storm. The key of TCM pathogenesis lies in spleen deficiency and phlegm-dampness. The author expounds the pathogenesis of COVID-19 through the combination of traditional Chinese and western medicine, hoping to further understand the occurrence and development of COVID-19 's disease course under the condition of basic diseases, which will help to better guide clinical work and seek maximum benefits for patients.

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