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Covid 19 Infection in Diabetic Patients Regarding Clinical Manifestation and Serious Outcome Including Icu Admission

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Abstract

Background: Age, hypertension, diabetes mellitus, obesity, cardiovascular illnesses, chronic obstructive pulmonary disease, and cancer are all associated with a higher risk of death from Coronavirus disease-19 (COVID-19). Patients with hyperglycemia on the COVID-19 have severe clinical issues, a higher rate of ICU admissions, mechanical ventilation, and a marked increase in inflammatory markers. The goal of therapeutic approaches should be to make it easier for patients to access the healthcare system. To lower the risk of problems and relieve the strain on healthcare systems, blood glucose control and comorbidities must be personalised. Studying the severity of COVID 19 infection in diabetic patients and serious outcomes, such as ICU admission and invasive ventilation, along with mortality rates, is the goal of this work. Diabetes is one of the most prevalent diseases.

Key words: Covid 19 infection, diabetic patients, clinical manifestation, serious outcome, ICU admission**.**

1. Introduction

Single-stranded RNA viruses, such as coronaviruses [CoVs], infect both humans and animals. As a cause of acute upper respiratory infection (URI), the human coronaviruses (HCVs) were discovered in 1962. HCoVs have been linked to severe RTIs in the upper and lower respiratory tracts increasingly often in recent years. Patients with impaired immune systems and elderly people have been shown to be more susceptible to pneumonia. [1]

During the last two decades, two very deadly human coronaviruses have been found, namely SARS-CoV and MERS-CoV, which arose in various parts of the globe [2].

In Wuhan, China, on December 31, 2019, a novel coronavirus strain was discovered and dubbed SARS-Cov-2 by the International Committee on Taxonomy of Viruses [ICTV] from patients with pneumonia of unknown origin.

SARS-CoV-2 was shown to be a beta-coronavirus, which is one of the four types of coronaviruses. [4]

Insulin deficiency, insulin action deficiency, or both may cause hyperglycemia in people with diabetes mellitus. [5]

Diabetes-related long-term damage, immune system malfunction, and organ failure, particularly in the eyes, kidneys, nerves, heart, and blood vessels, are all linked to high blood sugar levels [5].

COVID-19 patients are more likely to have diabetes mellitus [DM], which has been linked to catastrophic consequences, such as ICU hospitalisation, invasive ventilation and mortality as a result of persistent inflammation and an inadequate immune response [6,7].

Patients with better-controlled blood glucose had a considerably lower risk of all-cause death and harmful sequelae than those with poorly-controlled blood glucose [8].

Diabetic patients with COVID 19 infection will be studied to see how severe the clinical manifestations of COVID 19 infection are, with an emphasis on ICU admission and invasive ventilation as well as death rates.

1.1. Covid 19 Infections

Wuhan, China, was hit hard in December 2019 by a rash of severe, unusual respiratory diseases. SARS-CoV-2, a novel coronavirus from the Coronaviridae family, was immediately recognised as the causative agent of these unusual infections and given the name "SARS-CoV-2."

In 2002–2003, the SARS coronavirus [SARS-CoV] was shown to be remarkably related to this virus. [9,10]

It was believed that the epidemic began as a result of a zoonotic transmission from seafood markets in Wuhan, China, which the WHO dubbed coronavirus disease 2019, or simply COVID-19. Cases of the illness have been documented in over 200 countries worldwide, with the spread being attributed to human-to-human transmission. 11 and 12

WHO classified COVID-19 a pandemic on March 11, 2020, after it was declared a public health emergency on January 30, 2020 by the World Health Organization (WHO). An epidemic of severe pneumonia that began in China has already spread throughout the globe thanks to SARS-CoV-2. [13]

As the virions' spikes range in size from 9 nm to 12 nm, the SARS-CoV-2 has a solar corona-like look with its 60-140 nm diameter and prominent spikes. [14]

1.2. Clinical Presentation

When it comes to COVID-19, the average duration from exposure to beginning of symptoms is roughly five days [2-7]. Within 11 days of infection, 97.5 percent of those who develop symptoms will do so. [15]

7 [3-9] days is the median [interquartile range] time from the beginning of symptoms to the time of hospitalisation. Hospitalized patients range in age from 47 to 73, with a male predominance of around 60 percent in most cohorts. [16]

Most COVID-19 patients at the hospital are between the ages of 74 and 86.

It is important to note that COVID-19 has a wide range of symptoms.

In a study of 44 672 COVID-19 patients in China, 81 percent had mild manifestations, 14 percent had severe manifestations, and 5 percent had critical manifestations [defined by respiratory failure, septic shock, and/or multiple organ dysfunction]. [17,18]

Despite the fact that only 25 percent of infected patients have comorbidities, 60 percent to 90 percent of infected patients who are hospitalised have comorbidities. Hypertension, diabetes, cardiovascular disease, chronic lung illness, chronic renal disease, malignancy, and chronic liver disease are among the most prevalent comorbidities among hospitalised patients. Approximately 48 percent to 57 percent of hospitalised patients have these conditions. 19 and 20

It is estimated that up to 90% of hospitalised patients have fever, dry cough (60-86%), shortness of breath (53-58%), exhaustion (38%), nausea/vomiting or diarrhoea (15%), and myalgia (45%) as their most prevalent symptoms. [21]

Non-classical symptoms, such as isolated gastrointestinal issues, may also be seen in patients. [22]

1.3. Relation Between Diabetes And Covid 19 Infection

Diabetes mellitus [DM] is one of the most common comorbidities in COVID-19 patients, and it is linked to catastrophic outcomes such as ICU admission, invasive ventilation, and mortality. [23, 24]

Diabetes was shown to be prevalent in 9.7% of COVID-19 patients in a metaanalysis of 1,527 individuals , with the incidence of diabetes in severe cases being roughly double that of non-severe cases .[25]

According to early analysis of a small cohort in Wuhan [26] , In the intensive care unit [ICU] , diabetes accounted for about 20% of admissions. More recent data from Italy revealed that diabetes was present in more than two-thirds of those who died from COVID-19. [27]

so To investigate the association between diabetes, secondary hyperglycemia, and COVID-19, a single-center retrospective analysis of confirmed COVID-19 cases with a total of 80 patients is conducted , together with the possible responding mechanisms.

Grouping of the 80 cases Based on their blood glucose levels, the patients were assigned **into 3 groups** :

1.The euglycemia group :

There were 44 patients in total , 21 males and 23 females , all without a history of diabetes and ranging in age from 27 to 52 years old .

2.The secondary hyperglycemia group:

There were 22 patients , 17 males and 5 females , who satisfied the criteria of having no previous history of diabetes , a haemoglobin A1c [HbA1c] of less than 6.5 percent , random blood glucose >11.1 mmol/L during hospitalization, and normal blood glucose after discharge . Their ages ranged from 40 to 70 years old

3.The diabetes group:

consisted of 14 patients , [10] males and [4] females , all of whom had type 2 diabetes mellitus [T2DM] . They were treated with oral antidiabetics or insulin before being admitted to the hospital , and their ages ranged from 43 to 67.

The median age of the 80 COVID-19 hospitalized patients was 47 years old , and 68 [85%] of them had fever symptoms , while 30 [37.5%] had fatigue symptoms. The other two most common symptoms were cough [56.25%] and chest tightness [33.75%] ,while diarrhoea [11.39%] and dyspnea [10%] were relatively rare.

When compared to the other two groups, the diabetic group had a larger proportion of serious cases [57.14 percent]. Meanwhile, the diabetic group's average age was higher than the other two groups .

from France for 1277 patients aged 18 and above who had a COVID-19 RNA confirmatory nasopharyngeal swab and were hospitalized at our hospital between March 9 , 2020, and June 27, 2020, in order to detect :

(1) the effect of type-2 diabetes on outcomes in COVID-19 patients

(2) the impact of prediabetes on outcomes in COVID-19 patients [28]

It divide the patients into 3 groups :

Diabetic group

HbA1c lab results from the previous year until the day of admission . If the patient has more than one HbA1c test measurement , the most recent one should be considered for the study.

According to the American Diabetes Association , HbA1c levels of less than 6.5 percent were deemed diagnostic of type 2 diabetes

Prediabetes Group

Patients admitted to the hospital with COVID-19 and a HbA1c lab value of 5.7 to 6.4 at admission or within the previous year, whichever came first, were designated as "prediabetes group."

Control [Euglycemic Nondiabetic] Group

The [control , non-diabetic or euglycemic] group" included patients hospitalised with COVID-19 and a HbA1c lab result of less than 5.7 at admission or within the previous year, whichever was more recent, and no mention of type-2 diabetes in their medical history .

- **total of 1277** patients admitted with COVID-19 during the study period
- **434 patients excluded** due to lack of HbA1c and no mention of type-2 diabetes
- **Type-2** diabetes group [$n = 626$]
- **Prediabetes** group [$n = 110$]
- **Controls** [nondiabetic , euglycemic] group [$n = 107$]

By comparing the 3groups for previous comorbidity and mortality rate and need to mechanical ventilation

We can deduce from the foregoing facts that diabetic patients have a higher death rate , require mechanical ventilation , and have more severe symptoms than non diabetic patients . [29]

Involved 288 laboratory-confirmed patients hospitalized between January 15, 2020, and March 10, 2020, in this study, including 24 patients with DM. Clinical Features and Risk Factors of ICU Admission for COVID-19 Patients with Diabetes . Clinical features , signs and symptoms , concomitant disorders , chest computed tomography [CT] and laboratory examination results , as well as the patient's therapy and outcomes , are all collected from clinical electronic records . [30]

Severe cases were characterized as those who met one or more of the following criteria , according to the Chinese diagnosis and treatment guideline for COVID-19

1) **respiratory rate** greater than 30 per minute
2) **oxygen saturation** greater than 93 percent
3) **PaO2/FiO2** greater than 300 mmHg Patients with severe hypoxemia or multiple organ dysfunctions who require high-flow nasal intubation or higher amounts of oxygen support are admitted to the ICU.

The World Health Organization diagnostic criteria for diabetes were

1) **fasting plasma glucose** 7:0 mmol/L [126 mg/dL]
2) **2 hours plasma glucose** 11:1 mmol/L [200 mg/dL] .

Relation Of Covid 19 With Diabetic Complication As DKA

The levels of biomarkers associated with inflammation are greater in diabetics than in non-diabetics. [252] Preexisting type 2 diabetics who had poor glycemic control in the Zhu et al study of 952 COVID-19 patients had a greater risk of mortality, more medical interventions, and multiple organ damage when compared to those who had better control. Diagnosis of diabetic ketoacidosis (DKA) increased significantly over the COVID-19 period in 2020. [31] [32]

COVID-19 patients who had DKA on admission or developed during their hospital stay had a 50% mortality risk in a New York study. In the event of a COVID-19 pandemic, health care providers should concentrate on ensuring that diabetes patients have proper glycemic control. [33] [34]

In diabetic individuals with COVID-19, the pathogenic mechanism that causes acute metabolic issues (DKA and HHNK) is unclear at this moment. A functional receptor for SARS-CoV-2 may be found in the many organs that contain the Angiotensin converting enzyme 2 [ACE2] (myocardial cells, adipose cells, proximal tubule cells of the kidney, endocrine tissues of the pancreas, the stomach, bladder urothelial cells, ileum epithelial cells). The numbers 35 and 36 indicate that

Acute hyperglycemia might be the result of pancreatic tissue damage caused by SARS-CoV-2. By reporting three instances of newly diagnosed diabetes and DKA in patients with COVID-19, Suwanwongse and colleagues hypothesise that COVID-19 exacerbates existing diabetes by increasing the metabolic complications of the disease. [37]

Prediabetic Status and Covid 19

Blood glucose levels in pre-diabetes are greater than usual, but not high enough to qualify as type 2 diabetes. The pre-diabetic condition is caused by glycemic dysregulation, which is brought on by reduced insulin sensitivity and decreased pancreatic beta-cell activity. Chronic microvascular and macrovascular disorders are connected to impaired glucose control and result in moderate hyperglycemia. 39 and 38]

For lengthy periods of time, the body may sustain this intermediate hyperglycemic state by stimulating pancreatic beta cells to produce more insulin and slowing insulin clearance from the liver. [40]

A more severe form of hyperglycemia and, ultimately, type 2 diabetes may emerge when these coping mechanisms are worn out. Covid-19 directly damages beta cells in the pancreas, which produce insulin. [41]

The COVID-19 infection has a cytopathogenic impact, causing damage to several organs, including the islets of Langerhans, as a result of the infection. The findings were explained by the enhanced expression of angiotensin converting enzyme 2 receptors in the islets of Langerhans. Patients with pre-diabetes are more susceptible to insulin resistance, which may lead to hyperglycemia and a worsening of their disease. Diabetic Mellitus (DMT)

One of the most prevalent symptoms of a wide range of disorders, including hyperglycemia, is diabetes mellitus [DM]. Hyperglycemia is caused by a deficiency in insulin production, insulin action, or a combination of the two. [43]

Long-term organ damage, malfunction, and failure in diabetics has been linked to long-term hyperglycemia, notably in the eyes, kidneys, nerves and heart, known as micro and macro vascular problems. Glycation of tissue proteins, known as glycation end products, has been linked to these consequences, as well as increased activity of the polyol pathway and additional pathways yet to be discovered. [44]

There are several ways to categorise diabetes mellitus.

The first classification of diabetes was released in 1979 by the National Diabetes Data Group (NDDG). According to the World Health Organization [WHO], it was approved and revised in 1985. [45]

This NDDG classification of DM was based on the pharmacologic therapy applied and divided in two major groups :

- **Insulin-dependent diabetes mellitus [IDDM]**
- **non-insulin-dependent diabetes mellitus [NIDDM]**

This categorization has various flaws, but the most significant is that several individuals with NIDDM required insulin to control their condition, causing them to be misclassified as either IDDM or insulin-requiring NIDDM.

The current diabetes classification is based on the disease's pathophysiology rather than its therapy.

- **Type I Diabetes**
  - ✓ Immune Mediated
  - ✓ Idiopathic
- **Type 2 Diabetes**
- **Other Types**

- ✓ Genetic Defects of B Cell Function [MODY]
- ✓ Genetic Defects in Insulin Action
- ✓ Endocrinopathies
- ✓ Diseases of exocrine pancreas
- ✓ Drug or chemical induced
- ✓ Infections
- ✓ Other genetic syndromes [Down, Turner, other]

Gestational Diabetes [46]

Complications of Diabetes Mellitus

Increased vascular issues, which contribute to patient morbidity and death, are connected with diabetes.

Complications with the cardiovascular system.

Two to four times the risk of stroke [cerebrovascular] and coronary heart disease [CHD] may be attributed to the presence of macrovascular disorders in the circulatory system, which impact the circulatory system's major arteries. [47]

The migration of leukocytes to the site of arterial damage causes these macrovascular consequences, which are basically accelerated types of atherosclerosis. [48]

Complications of the Microcirculation

Diabetes neuropathy, nephropathy, and retinopathy are all manifestations of diabetic microvascular problems, which include damage to the tiny blood vessels.

Diabetic neuropathic

Patients with diabetes are more likely to develop long-term problems such as diabetic neuropathy, which affects around 60% of patients.

Swelling, loss of feeling, discomfort, and weakness are among symptoms that may lead to amputation. [49]

nephropathy caused by diabetes

Chronic kidney disease (CKD) is the major cause of kidney transplantation in the developed world because of diabetic nephropathy. The indicators of nephropathy include albumin in the urine and an increase in glomerular blood pressure.

In the absence of adequate treatment, the disease persists, resulting in the loss of protein in the urine and a decline in renal function. This leads to end-stage renal disease and kidney failure. Clinical evidence shows that 20% to 30% of individuals with Type 1 Diabetes and 30% to 40% of those with Type 2 Diabetes develop ESRD, according to the data. [50]

Retinopathy in diabetics

One of the primary causes of blindness and visual impairment is diabetic retinopathy, caused by the loss of retinal blood vessels. Appropriate and more prompt therapy may reduce or avoid diabetic retinopathy. [51]

Diseases of the Mouth and Feet

Diabetes may have a harmful influence on the whole body because of its effect on the immune system. Protection against external pathogens such as viruses, bacteria, fungus and protozoa invasions. [52]

When it comes to infections, the most frequent is periodontal disease, which may lead to tooth decay if it isn't addressed properly.[53]

Deficiency of the Immune System and a High Predisposition to Disease

As the insulin-producing B cells in the islet of Langerhans are eventually destructed, insulin synthesis ends as a consequence of the condition.

Autoimmunity is a multifactorial condition that is influenced by both genetics and the external environment. Recently discovered T cells in the immune system have a significant role in TIDM autoimmunity, showing that the immune system's band T cells play an important role in the disease. Diabetes mellitus [DM] patients are more susceptible to infection [54]. Several of these infections may lead to more severe consequences in diabetics than in non-diabetics. Ketoacidosis-infected individuals had a mortality rate of 43%. [55]

A prospective analysis of 101293 adult hospitalised patients found 1640 cases of bacteremia. In a study of 1000 hospitalised patients, two-thirds of the bacteremia was found in people with diabetes, compared to one-third in those without diabetes. [56]

This raises the issue of which pathogenic pathways are to blame for the increased infection incidence in diabetics. For example, the presence of micro and macroangiopathy or neuropathy in this group of diabetics, as well as the large number of pharmaceutical therapies they are taking, might all be contributing factors. [57]

There are two kinds of immune systems: innate and adaptive-humoral or cellular. There is no difference between patients with diabetes and non-diabetic controls when it comes to humoral adaptive immunity, as measured by the quantities of blood antibodies against pneumococcal vaccination. [58]

Humoral Immune Deficiencies Caused by Genetic Defects Anti-Invasion Immunity Complements

Study participants with type 1 diabetes exhibited a lower-than-normal C4 content in their blood in 22 of the 86 individuals studied (26%). There was no evidence that low C4 levels were caused by a lack of consumption. Although identical twins had a C4 concentration below normal, the genes coding for this enzyme are linked to DR3, which is expressed in 95% of Caucasian diabetes patients, compared to just 40% of the general population. According to the authors, a lack of C4 may be inherited. Although C4deficiency has been linked to an increased risk of infection in diabetics, it is not clear if this is the case in healthy people as well. [61]

Cytokines Investigations using whole blood, peripheral blood mononuclear cells [PBMCs], and isolated monocytes from diabetes patients must be separated into studies with and without stimulation.

TNF-K, IL-6, and IL-8 concentrations in individuals with type 1 and 2 diabetes have been investigated without stimulation..

Diabetes patients had higher levels of TNF-K, IL-6, and IL-8 than non-diabetic controls. [62] [63] [64]

In one investigation, the IL-1 secretion by PBMCs in response to lipopolysaccharide [LPS] was reduced in diabetes [type 1 and 2] PBMCs, whereas the TNF-K response was the same as that of control cells in diabetic [type 1 and 2] PBMCs.

Another research indicated that DM type 1 patients' monocytes generated lower levels of IL-1 and IL-6 in comparison to healthy individuals. There was a clear indication that the reduced output in diabetes cells following stimulation with LPS was due to a genetic defect. [65] Studying the excretion of cytokines by nondiabetic individuals' peripheral blood mononuclear cells (PBMCs) at varying glucose concentrations According to one piece of research TNF-K and IL-6 were raised in nondiabetic monocytes exposed to varying glucose concentrations without being activated. [67]

Immunity innate to the cells

PMNs\sChemotaxis

Type 1 and type 2 diabetes patients' PMNs had significantly reduced chemotaxis than did healthy controls. 68 and 69

Adherence

The adhesion of diabetic PMNs in vitro without stimulation has been reported in a variety of methods, with varying degrees of agreement. Despite this, there were no differences in PMNs between diabetic and nondiabetic patients after stimulation.

There was no correlation between adherence and blood glucose or haemoglobin A1c levels. [70]

After the hyperglycemia was reversed, only a small fraction of DM type 1 and DM type 2 patients with untreated hyperglycemia had an increase in the reduced adhesion of PMNs to nylon fibre columns. [71]

Phagocytosis

Diabetic patients' PMNs demonstrated a lower phagocytosis capability compared to that of healthy individuals. HbA1c levels were lower in individuals with normal phagocytosis than in those with impaired phagocytosis [better regulation]. [72]

The killing ability of diabetes PMNs is lower than that of non-diabetic PMNs. It was shown that diabetic PMNs had a decreased ability to destroy Staphylococcus aureus in all studies including this pathogen. Macrophages / Monocytes

The phagocytosis ability of diabetes monocytes was not significantly affected by plasma from healthy controls, despite the poor chemotaxis and phagocytosis of diabetic monocytes.

A Dendritic Cells [Dcs]

These cells, called dendritic cells (DCs), function as bridges between the body's innate and adaptive immune systems by conveying antigens to the immune system. [74]

Type 1 and type 2 diabetes both have lower DC counts, according to some research. [75]

T2DM patients with poor metabolic control exhibited a lower number of myeloid and plasmacytoid DCs compared to healthy controls. The risk of opportunistic infections increases as a consequence. [76]

Reduced DC counts were less obvious but still significant in the case of good glycemic control, particularly for myeloid DC1 [mDC1] cells, showing that diabetic women with poor glycemic control [HbA1c >7 percent] have fewer circulating plasmacytoid DCs [pDCs] than diabetic women with good glycemic control [HbA1c 7 percent] or healthy women. [77]

Hyperglycemic medium and hyperglycemic sera from T2DM patients have been shown to inhibit monocyte growth and activation in vitro. NK cells

A kind of innate lymphocyte, known as NK cells, is capable of identifying and destroying virus-infected and tumor-infected cells. T2DM contains an increased number of NK cells, however the vast majority of these cells are damaged.

It is possible that the increased glucose transporter type 4 [GLUT4] in diabetic NK cells increases the risk of colon cancer in diabetics. [79]

The activating receptors NKG2D and NKp46 were discovered to be reduced in T2DM patients' NK cells, as well as their ability to degranulate. As HbA1c levels rise, NKG2D expression falls, indicating that chronic hyperglycemia is responsible for NK cell dysfunction.

Hyperglycemia also causes NK cells to die by increasing the expression of genes involved in the unfolded protein response (UPR). Cells of the Lymph Node [Ilcs]

Compared to healthy individuals, diabetes patients have an increased amount of ILC1s in their blood and fat tissue.

There is a correlation between the frequency of circulating ILC1s and a number of blood tests, including fasting plasma glucose, haemoglobin A1c, the homeostasis model assessment of insulin resistance (HOMAIR), serum free fatty acids (FFAs), and the adipose tissue insulin resistance index. [81]

Patients with high levels of ILC1 have a greater chance of developing type 2 diabetes (T2DM). [82]

In obese individuals, ILC1s present in adipose tissue are thought to be responsible for the development of tissue fibrosis and diabetes via the production of interferon-y. [83]

Patients with diabetic kidney disease had significantly increased amounts of ILC2s, as well as IL-4, IL-5, and IL-13 blood cytokine levels, which are all associated with disease severity. [84]

Anti-Adaptive Immunity B Cells.

The non-enzymatic glycation process results in covalent sugar adducts with various proteins when blood glucose levels are elevated. Immunoglobulins [Igs] may be affected in a number of ways, including changes in their structure and function. In diabetics, Igs have a greater molecular mass than in healthy individuals.

As a consequence, in people with this condition, vaccinations that stimulate humoral immunity may be less effective. Diabetes patients who are immunised with influenza [flu] vaccinations have normal or even greater levels of flu-specific antibodies compared to healthy persons, according to studies. Defective glycated antibodies, on the other hand, are less effective in neutralising viruses, increasing infection risk. [87]

More than a few studies have shown that T2DM patients' T-cell functions are impaired. T helper and cytotoxic T-cell activation was greater in obese diabetics compared to nonobese diabetics [88]. [89]

Despite this, PBMCs from obese diabetes individuals generated lower amounts of IL-2, IL-6, and TNF- when stimulated with phytohemagglutinin [PHA]. [90].

Diabetes patients had reduced pathogen-specific memory T-helper responses and fewer CD4+ T cells in response to stimulation with Streptococcus pneumonia. Increased susceptibility to infection and a higher incidence of infectious diseases in T2DM patients may be linked to a reduction in mitochondrial DNA activity. [92]

People with COVID-19 are more likely to have diabetes than the general population. When infected with SARS-CoV-2, diabetics are more likely to be admitted to the hospital, have more severe pneumonia, and die earlier than non-diabetics. Innate and humoral immunity can be compromised by long-term chronic hyperglycemia. As a result, the development of acute respiratory distress syndrome is more likely to occur in people with diabetes because of the low-grade chronic inflammatory condition. Pancreatic damage caused by SARS-CoV-2 might aggravate hyperglycemia and potentially lead to diabetes in previously healthy individuals.

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