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RELATIONSHIP BETWEEN RISKS OF MICROBIAL INFECTION, GENETIC PREDISPOSITION, IMMUNODEFICIENCY AND COMPLICATIONS OF DIABETES MELLITUS PANDEMIC

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ABSTRACT

In general, infectious diseases are more prevalent and/or severe in diabetic mellitus patients, Increased morbidity is possible. Immune dysfunction is preferred in a hyperglycemic environment (such as: damage to neutrophil function, depression of the antioxidant system, and humoral immunity), micro- and macroangiopathies, neuropathy, decline in urine antibacterial activity, urinary dysmotility and gastrointestinal, and a higher number of medical interruptions, all of which lead to a higher incidence of infections in diabetic patients.Both systems and organs are affected by the infections. Some of these concerns, such as: foot infections, rhinocerebralmucormycosis, malignant external otitis and gangrenous cholecystitis, are more common with diabetics, In addition to the elevated morbidity, infectious mechanisms can be the primary sign of diabetes mellitus (DM)/or the triggers for diseaserelated complications including: diabetic ketoacidosis and hypoglycemia, to avoid hospitalizations, deaths, and treatment costs, influenza vaccines and anti pneumococcal are recommended.

KEYWORDS: Diabetes Mellitus,Complications, Pandemic,Costs,Genetic Predisposition,Immune Response, Microbial Infection

Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic condition characterized by hyperglycemia as a result of insufficient insulin action, insulin secretion, or both , DM is associated with relatively specific of long term complications caused by persistent hyperglycemia, affecting a variety of body organs, especially the nerves, eyes , and kidneys, as well as a higher risk of cardiovascular disease, such as:myocardial infarction, Angina pectoris, peripheral artery disease, stroke, and congestive heart failure are all examples of cardiovascular disease caused by DM complications. (1,2). as Figure(1)

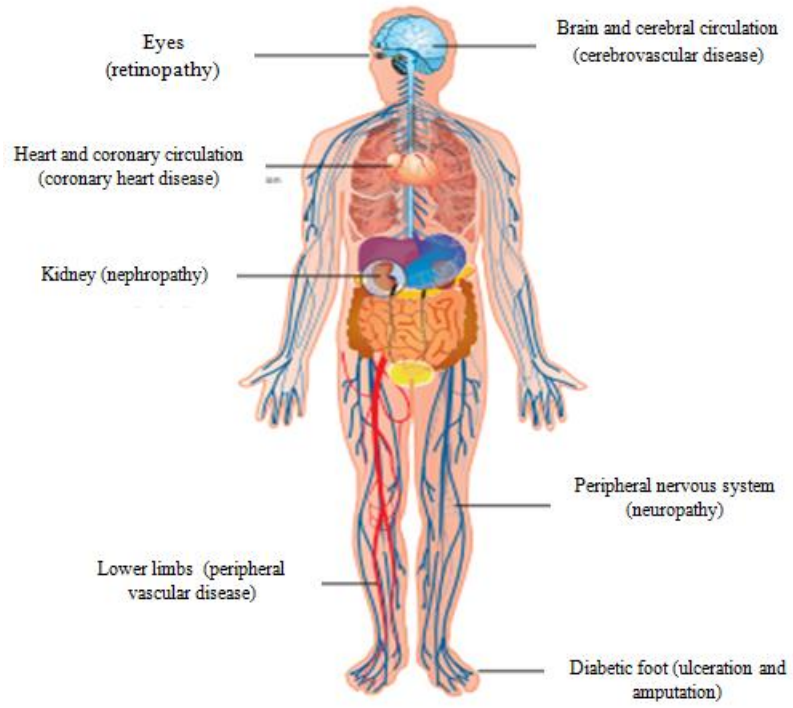

Figure 1: The Most Severe Diabetic Complications (3)

According to the World Health Organization, all forms of DM have increased exponentially over the last few decades all over the world, The number of people with DM increased from 108 million (4.7%) in 1980 to 425 million (8.5%) in 2017, and it'sprojected to reach 629 million by 2045 (3,4) Figure (2)

Diagnosis of Diabetes Mellitus (DM)

long-term levels of blood glucose (HbA1C proportion)[HbA1C refers to the fraction of glycated hemoglobin A1c and is the quantification of beta-N-1-deoxy fructosyl component of hemoglobin in blood,and an indicator of glycaemia over a long period of time (approximately 3 months)] ,fasting plasma glucose, random plasma glucose, a more detailed method for measuring the glycaemia levels is a two-hour plasma glucose value after a 75 g oral glucose tolerance test (OGTT),also allows for the detection of Impaired Fasting Hyperglycemia (IFG) and Impaired Glucose Tolerance (IGT),can all be used to diagnose DM (5,6). (Table 1)

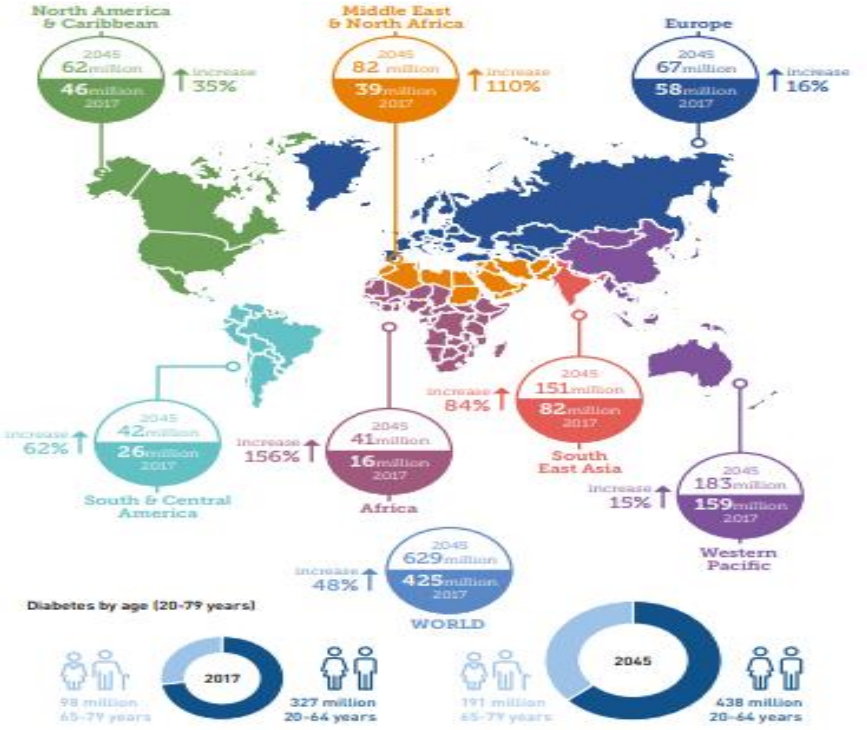

Figure. 1: Number of People with DM Worldwide and by Country in 2017 and 2045. (With Permission from the International Federationof Diabetes.) [3]

Table 1: Diagnosis Criteria of Normaligt, IFG, and DM.Adapted From(7,8)

Item		Venous plasma glucose Concentration (mmol/L)
Normal	Fasting	**< 6.1**
	2 hour during OGTT	**< 7.8**
IGT	Fasting	**<7.0**
	2 hour during OGTT	**7.8-<11.1**
IFG	Fasting	**6.1-<7.0**
DM	Fasting	**≥ 7.0**
	2 hour during OGTT	**≥ 11.1**

The IFG and IGT are two different initial states that predispose to diabetesand are thus referred to as prediabetes,The term "prediabetes" refers to a blood glucose level that is higher than normal fasting blood glucose levels but lower than the diagnostic level for DM (7).These (IFG and IGT) must be considered as risk factors for cardiovascular disease and diabetes rather than clinical entities in and of themselves, Obesity (especially visceral or abdominal obesity) , dyslipidemia (high triglycerides and/or low HDL cholesterol), and hypertension are all linked to IFG and IGT,(8).

Classifications of DM

Diabetes can be divided into a groups of metabolic disorders characterized by hyperglycemia caused by insulin secretion, insulin action, or both, Long term damage, and dysfunction of eyes, kidneys, blood vessels, nerves, and heartare all associated with chronic hyperglycemia Nerves and the heart are two of the most important organs in the human body (9,10):-

1. Type 1 diabetesmellitus(T1DM)

This type is caused by the loss of beta cells in the pancreas and is associated with ketoacidosis, This form of diabetes, also known as "insulin dependent diabetes" or "juvenile onset diabetes," is responsible for 5 -10% of all diabetes cases, It includes cases where beta cell destruction is caused by an autoimmune process as well as cases where the cause of beta cell destruction is unknown (1,8).

2. Type 2 diabetes (T2DM)

This formof diabetes, also known as"noninsulin dependent diabetes" or "adult onset diabetes," is responsible for 90–95 % of all diabetes cases can range from a predominant secretory defect with insulin resistance to a predominant insulin resistance with relative insulin deficiency These people do not need insulin therapy to survive, at least at first, and sometimes during their lives. Differentiating between T1DM and T2DM diabetes is important because treatment methods vary, but it can be complicated in some cases at the time of diagnosis (8,9).

3. Gestational diabetes (GD)

Is a form of diabetes diagnosed during the second or third trimester of pregnancy that isn't obvious, pregnant womens' diabetes is diagnosed T2DM ,who develop diabetes during the first trimester (11).

4. Other types of DM

Include a wide range of relatively rare disorders, Types of diabetes that are primarily genetically defined, or diabetes that is related to other diseases or drug use (12).

Pandemic of Diabetes Mellitus and Costs in Healthcare

Diabetes mellitus (DM) strikes people when they are at their most prosperous, slowing economic growth, reducing life expectancy in the elderly, and rising costs of healthcare, DM is one of the top ten causes of death, accounting for over 80% of premature NCD deaths (along with major NCDs such as cardiovascular, respiratory, and cancer disease, Insulin dependent diabetics began to live longer lives after the advent of insulin, but long term complications grew, and T1DM became a chronic disease (13).

T2DM affects 87–91% of diabetics in developing countries, T1DM affects 7–12%, and other forms of diabetes affect 1–3% of diabetics, there are 425 million people with diabetes worldwide in the age group of 20–79 years old in 2017, By 2045, the population is estimated to reach 629 million , Nearly half of diabetics (49.7%) go undiagnosed, and 352 million people have IGT, accounting for 7.3 percent of adults aged 20 to 79, IGT is expected to affect 532 million (8.3% of adults) by 2045 in the same age group. Any type of hyperglycemia in pregnancy affected 21.3 million live births in 2017(13,14 ,15).

Diabetes is responsible for nearly 5 million deaths each year in people aged from 20 to 99 Diabetes mellitus is prevalent in Europe, with rates ranging from 2.9 percent in Ireland to about 10% in Portugal and Bosnia-Herzegovina , Diabetes mellitus is more common in cities than in rural areas (10.2% vs. 6.9%) and urbanization is increasing, particularly in Asia and Africa (14)

The Pearl River Delta in China experienced the most rapid urbanization in human history, a rural region transformed into the world's largest city, with a population of over 40 million people. Over 3 million people in Italy have T2DM, and 1 million have undiagnosed hyperglycemia (ISTAT, 2013), T1DM is now five times more common in Finland than it was 60 years ago, in children with diabetes have a lower genetic risk than they did previously ,Australia, along with

Scandinavia and Sardinia, is a high-incidence country for T1DM (16).

Global healthcare spending on people with diabetes mellitus was reported to be USD 850 billion in 2017 ,the cost in the United States of diagnosed DM was 327 billion USD (including 90 billion USD in lost productivity), and DM treatment accounts for one out of every four dollars spent on healthcare , Cost has risen by 26% in the last five years. The average annual cost per diabetic subject in Lombardy (Northern Italy) was 3300 Euro. Hospitalizations accounted for 54 percent of total costs, with medications accounting for 32 percent and outpatient claims accounting for 14 percent (15,17).

Genetic Predisposition to T1DM and T2DM

T1DM and T2DM are polygenic diseases, meaning that they are caused by a combination of genes. Single gene disorders leading to beta cell or other defects are rare types of DM (about 1% of cases)(18).T1DM has a well-established genetic basis, with more than 60 known genes accounting for 80% of its heritability, the DQB1 gene, which encodes the beta chain of the Class II DQ molecule responsible for antigen presentation, is the primary disease risk determinant in the human leukocyte antigen (HLA) system. Its alleles, when combined with neighboring DRB1and DQA1gene variants, form the DR-DQ haplotypes, which classified as risk ,defensive or neutral, In white people, the heterozygous variation of the two susceptibility haplotypes DRB1*03-DQA1*0501-DQB1*0201/DRB1*0401-DQA1*0301-DQB1*03 (DR3 DQ2/DR4-DQ8 in terms of serological specificity) represents the highest risk disease , and is related to about 50% of disease heritability, The haplotype DR15-DQ6 is defensive, HLA associations can vary depending on ethnicity (19)

Beta cell specific autoantibody patterns, are also related to HLA Class II haplotypes , GADA are most common in patients with the HLA DQ2-DR3 haplotype, whereas DR4-DQ8 patients have insulin and IA-2 autoantibodies, With increasing age at diagnosis, heritability decreases,Other predisposing gene variants have been identified outside of the HLA region by genome wide association (GWAS) studies such as INS, IL27, PTPN22, IFIH1 , Insulin expression in the thymus, modulation of T-cell activation, and innate virus immunity are all examples of genes involved in immune function and likely pathogenic pathways, As a result, a genetic score that incorporates measurements of HLA and non HLA loci can be used to help predict the risk of T1DM (20,21) .

In T2DM,Having a diabetic parent raises the risk of developing diabetes by 30–40 %. More than 200 genomic regions have been implicated in the predisposition to T2DM in GWAS studies (22,23). The interplay between insulin sensitivity, appetite control, adipose storage, and beta cell failure is controlled by genetic and environmental factors in T2DM.28 Genes work byregulating a variety of aspects,such as: the insulinmediatedglucose uptake in skeletal muscle which is regulated by TBC1D4 gene, the ability to generate new adipocytesand the regulation of gene expression in these cells such asPPARG, IRS1, KLF14 genes, lipoprotein lipas-mediated lipolysis (24). Insulin secretion is hampered by beta cell dysfunction or a lack of beta cell growth such asABCC8, KCNJ11 People with diabetes-predisposing gene variants are more likely to have a weakened immune system, A genetic score integrating measurements of several loci, similar to that used to assess T1DM genetic risk, would be useful in assessing T2DM genetic risk (25).

Immune Response Deficiency

The pathogenesis of immune dysfunction in diabetes mellitus has already been the subject of extensive research, Hyperglycemia and diabetic acidosis impair phagocytic mechanisms such as leukocyte chemotaxis and adherence, Complement promotes phagocytosis and the opsonization of non-self microorganisms by neutrophils and macrophages in the antibody-mediated beta cellular immune system. The second signal for B-lymphocyte activation and antibody

production is induced by complement activation products. In fact, only a few studies have found that DM patients have a C4 deficiency (26) .

Not only the complement system, but also the inflammatory cytokine network, has been discovered to be out of control. Increased glycation in DM patients has been linked to decreased secretion of IL-1 and IL-6 by mononuclear cells and monocytes, according to some studies (27). Elevated glucose levels have also been shown to inhibit myeloid cell production of Interleukin-10(IL10), as well as T-cell production of Interferon gamma (IFN-γ)and tumor necrosis factor(TNF)-α , Glycation will also minimize the expression of class I MHC on the surface of myeloid cells, decreasing cell immunity (28).

During hyperglycemia, the movement of polymorphonuclear and mononuclear leukocytes, chemotaxis, and phagocytic activity are all reduced. This hyperglycemic state often affects antimicrobial activity by inhibiting the enzyme glucose-6 phosphate dehydrogenase (G6PD), which increases polymorphonuclear leukocyte apoptosis while decreasing transmigration through the endothelium. Certain studies have shown that when the glycated hemoglobin (HbA1c) level is less than 8.0 % , CD4+T-lymphocytes' proliferative activity and their antigen response is not impaired Immunoglobulin glycation is proportional to the increase in HbA1c in diabetic patients, and this can harm the antibodies' biological function ,However, the clinical significance of these findings is unclear, since in people with diabetes, antibody responses to vaccination and common infections are sufficient (29).

Major Microbial Infections and DM

Some researchers believe that the variations in infection risk factors between diabetic and non diabetic patients are due to non controlled studies, Most experts, however, come to the conclusion that there is clinical evidence pointing to a higher prevalence of infectious diseases in people with diabetes. (30, 31).

1. Microbial Infections ssociated with systemic disease

TuberculosisSpp

Is a form of *tuberculosis*associated with Respiratory tract that affect About 9 million new cases of *tuberculosis* were diagnosed in 2009, with 1.7 million people dying from the disease, a Patients with diabetes are more likely to develop *tuberculosis* than people without the disease, According to some research, people with diabetes are more likely to develop multi-resistant tuberculosis, and treatment failures and death are more common in these people(32)

Helicobacter Pylori

*Helicobacter pylori*caused Gastritis, andthe association between DM and *Helicobacter pylori* infection is debatable, while some studies have linked some virulent strains of H. pylori to neuropathy, microalbuminuria, and macroangiopathy in DM2 patients, there appears to be no connection between *H. pylori* infections and these DM complications. (33)

Candida Albicans

candidiasis of Oral and esophageal is the most common causative agent , It is pathogenesis is linked to a variety of factors that enhance its virulence, with extracellular enzymes like proteinase and phospholipase being especially significant, Candidiasis may show itself in a number of ways, including median rhomboid glossitis or central papillary atrophy, denture stomatitis, atrophic glossitis, angular cheilitis, and pseudomembranous candidiasis , the diagnosis is clinical in nature.In the case of esophageal candidiasis, however, an endoscopy is necessary (34).

Salmonella Enteritidisand Campylobacter

The main pathogens are *Campylobacter* and *Salmonella enteritidis*in emphysematous cholecystitis is more frequent to develop in males with DM, the clinical presentation is similar to that of uncomplicated cholecystitis such as: right upper quadrant abdominal pain, fever, and vomiting), Peritonitis does not normally manifest itself clinically, Crackles can be detected when palpating the abdomen and are related to a bad prognosis, the presence of gas within the gall bladder, which can be seen on a radiograph or a computerized tomography scan, is used to make the diagnosis. (35).

Hepatitis B ,CandEnteroviruses

Hepatitis B virus (HBV) infects about 350 million people worldwide, With the availability and widespread use of the anti-HBV vaccine, this number is expected to decrease ,the research on the correlation between T2DM and HBV has been inconsistent, Blood glucose irregularities have been identified by some investigators, but not by others (36).

Hepatitis C virus (HCV) is a global public health concern that affects over 170 million people worldwide, with the number predicted to grow due to the lack of a vaccine to prevent it, around 50–80 % of these patients develop a chronic infections, which puts them at a higher risk of developing cirrhosis , Several studies from various countries have shown that 13–33 %t of HCV patients have DM, the bulk of which is type 2 diabetes mellitus (T2DM) (37).

Enteroviruses are found all over the world and are primarily transmitted via the feces–oral route. human enterovirus, a Poliovirus, human enterovirus B (including the six Coxsackie B virus serotypes), echovirus D, and echovirus C are the five forms.Several epidemiological and clinical studies have suggested that enteroviruses, especially Coxsackie B4 and B3 viruses, play a role in the development of type 1 diabetes mellitus in genetically predisposed people, Anti enterovius antibodies, capsid protein VP1, and enterovirus RNA were found in small intestine biopsies, blood, and autopsy pancreas specimens of people with type 1 diabetes mellitus, suggesting a temporal association between T1DM and enterovirus infection peaks, The function of enterovirus in the pathogenesis of T1DM can be explained by a number of mechanisms (38), 1) persistent infections for pancreatic beta cells, which causes cell damage and the release of sequestered antigens, triggering an autoimmune response , 2) molecular mimicry (partial sequence homology) between the GAD65 (Glutamic Acid Descarboxilase) , the 2C viral protease , the IA2 protein and the VP1 viral capsid protein ,3) Autoreactive T- cells are activated by bystanders, and 4) thymus infection However, a causal relationship must still be identified.

2. Microbial Infection Associated With Skin and Soft Tissue

Infections of Foot

The most severe chronic complications of diabetes are foot infections, which are one of the leading to hospitalization and frequently result in osteomyelitis, amputation, and death,about 60% of all infected ulcers have *Staphylococcus aureus* and *Staphylococcus epidermidis* isolated, but *streptococci*, *Enterococci,* and enterobacteria are less common,while the anaerobic bacteria are present in 15% from infected ulcers, Infection in a freshly acquired superficial ulcer is likely to monomicrobial owing to aerobic Gram positive cocci including staphylococci, but in a long period of ulceration and increased depth are same to raise the chances of the wound being polymicrobially contaminated and resistant species,(39,40).

Necrotizing Fasciitis

Fast and progressive necrosis of the subcutaneous tissue and fascia characterizes necrotizing fasciitis, resulting in fulminant local tissue death, systemic toxicity, and microvascular thrombosis symptoms. In about 40% of the cases, there is a risk of death , fever and extreme local pain are the first signs, accompanied by areas of skin necrosis and small ulcers that is drain a colorless fluid and have an unpleasant odor, (41).

fasciitis in people with diabetes mellitus is typically polymicrobial, with little anaerobic and many aerobic microorganisms, furthermore, type I fasciitis is caused by an anaerobic microorganism in combination with little or more facultative aerobic microorganisms, whereas type II fasciitis is due to a group A streptococcus with or without staphylococci involvement (42)

Fournier Gangrene

A fasciitis that affects the male genitalia is known as Fournier gangrene*E. coli* , the more common etiologic agents, *Klebsiella sp*., *E. coli*, and other bacteria ,the etiology may also be Proteus sp., *Peptostreptococcus*, polymicrobial, and Clostridium are involved, aerobic or anaerobic Up to 70% of patients with this infections have DM , Streptococci, Bacteroides, Bacteroide, It is primarily affects the scrotum, but it may also affect the prostate , Contrary to common opinion, the penis, perineum, and abdominal wall are all related. The testicles are generally spared, contrary to common opinion (43)

3. Microbial Infections for Head and Neck

Invasive external otitis and rhinocerebralmucormycosis are the two most dangerous head and neck infections in diabetics, An inflammation of the external auditory canal that spreads to the base of the skull and surrounding areas is known as invasive external otitis, the etiologic agent is commonly Pseudomonas aeruginosa, and it mostly affects elderly diabetics (44)

The symptoms include hearing loss, torrhea, and excruciating pain, Osteomyelitis of the skull base and cranial nerve involvement are possible, In half of the cases, facial paralysis occurs, Magnetic resonance imaging is the most effective diagnostic tool, Periodontitis is a chronic inflammatory condition marked by the development of a periodontal pocket, connective tissue loss, and alveolar bone resorption, which can lead to tooth loss in some cases, It's four times more common in people with diabetes, and it's the sixth most common DM complication, Insulin resistance is initiated or spread by periodontitis, which worsens glycemic regulation (45,46)

4. Microbial infections for Urinary tract

Urinary tract infections (UTIs) are more common in people with diabetes, and they can lead to complications and/or severe consequences, Inadequate glycemic regulation, DM length, diabetic microangiopathy, recurrent vaginitis, impaired leukocyte activity, anatomical and functional defects of the urinary tract are the major risk factors for UTI in people with diabetes , (47,48)

Asymptomatic bacteriuria is more common in women with diabetes, but evidence on the natural history of this disease in women with diabetes is mixed, Some research find that pyelonephritis progresses, although others found that this does not result in severe complications, As a result, regular antibiotic therapy for asymptomatic bacteriuria in diabetic women is still debatable ,Individuals with DM are 4–5 times more likely to experience acute pyelonephritis, The majority of infections are caused by *E. coli* or *Proteussp* , Except for the bilateral renal involvement, the clinical appearance is close

to that of non diabetic individuals, People with diabetes are also more likely to experience complications including perinephric and/or renal abscesses, and renal papillary necrosis, emphysematous pyelonephritis (EP) , Emphysematous pyelonephritis (EP) is identified by renal parenchymal necrosis and the presence of gas in the collection system or perinephric tissues, It's most common in women with diabetes mellitus.,the most common pathogens are *E. coli* and *Enterobacteraerogenes,* followed by *Proteus sp.,Klebsiella sp*., *Streptococcus sp*. and *Candida* (49).

The first signs and symptoms include fever, chills, mass , nausea, vomiting and flank pain, Crackles are less common in the flank or thigh, Gas in the urinary tract may be detected using abdominal computerized tomography, Infections caused by fungi, especially Candida, are more common in DM. ,It may be difficult to tell the difference between infection and colonization. Infection is indicated by urinary symptoms or pyuria , Fungal cystitis can lead to the development of "fungal balls," which can block the urinary tract Diabetics are more likely than non diabetics to develop emphysematous cystitis, this condition is define by the presence of gas in the bladder cavity and penetration of the bladder wall cause by bacterial infections that produce carbon dioxide., *E. coli* is the most commonly encountered pathogen, followed by *Klebsiella, Proteus, Enterobacter,* and *Candida*, Women are impacted more than men, (48,49).

5. Other Microbial infection

Viruses

In 2007, the human immunodeficiency virus (HIV) infected approximately 33 million people. Because of advancements in diagnosis and care, a growing number of patients are experiencing chronic conditions, such as diabetes, the increased risk of DM is linked to HIV infections / or its treatment, insulin resistance is the key factor for implicated in the pathogenesis of diabetes in HIV patients, Insulin resistance is caused by high levels of inflammatory cytokines, which affect glucose tolerance and cause T2DM. Recently, some patients have developed autoimmune T1DM as a result of immune regeneration while on highly active antiretroviral therapy (HAART) (48,49).

CONCLUSIONS

Infectious diseases(ID) are more common in people with diabetes mellitus . The major pathogenic mechanisms are: increased virulence of certain pathogens in a hyperglycemic environment; decreased interleukin output in response to infection; reduced phagocytic activity and chemotaxis , immobilization of polymorphonuclear leukocytes; gastrointestinal and urinary dysmotility, glycosuria. most diseases for example: rhinocerebralmucormycosis, malignant external otitis, and almost always affect diabetics, gangrenous cholecystitis, Furthermore, Infectious diseases in people with diabetes can cause metabolic problems including hypoglycemia, ketoacidosis, and coma, in addition to being potentially more serious. Because of their effect on the reduction of respiratory infections, the number of deaths, and the amount and duration of hospitalizations due to respiratory tract diseases, the recommendation of mandatory immunization with influenza vaccines and anti pneumococcal is important,More research is needed to better understand the immunopathogenic mechanisms that link diabetes and infections, as well as to develop strategies to increase vaccination coverage among diabetic mellitus patients

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