Infections in patients with diabetes mellitus: A review of pathogenesis

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ABSTRACT

In general, infectious diseases are more frequent and/or serious in patients with diabetes mellitus, which potentially increases their morbimortality. The greater frequency of infections in diabetic patients is caused by the hyperglycemic environment that favors immune dysfunction (e.g., damage to the neutrophil function, depression of the antioxidant system, and humoral immunity), micro- and macro-angiopathies, neuropathy, decrease in the antibacterial activity of urine, gastrointestinal and urinary dysmotility, and greater number of medical interventions in these patients. The infections affect all organs and systems. Some of these problems are seen mostly in diabetic people, such as foot infections, malignant external otitis, rhinocerebral mucormycosis, and gangrenous cholecystitis. In addition to the increased morbidity, infectious processes may be the first manifestation of diabetes mellitus or the precipitating factors for complications inherent to the disease, such as diabetic ketoacidosis and hypoglycemia. Immunization with anti-pneumococcal and influenza vaccines is recommended to reduce hospitalizations, deaths, and medical expenses.

Key words: Diabetes mellitus, immunization, infections, vaccines

INTRODUCTION

Diabetes mellitus (DM) is a clinical syndrome associated with deficiency of insulin secretion or action. It is considered one of the largest emerging threats to health in the 21st century. It is estimated that there will be 380 million persons with DM in 2025.\(^1\) Besides the classical complications of the disease, DM has been associated with reduced response of T cells, neutrophil function, and disorders of humoral immunity.\(^2-4\) Consequently, DM increases the susceptibility to infections, both the most common ones as well as those that almost always affect only people with DM (e.g. rhinocerebral mucormycosis).\(^4\)

Such infections, in addition to the repercussions associated with its infectivity, may trigger DM complications such as hypoglycemia and ketoacidosis.

This article aims to critically review the current knowledge on the mechanisms associated with the greater susceptibility of DM for developing infectious diseases and to describe the main infectious diseases associated with this metabolic disorder.

MATERIALS AND METHODS

The MEDLINE and LILACS databases were searched for articles published between 1999 and 2011, using the following keywords in various combinations: “diabetes mellitus,” “infections,” “immunization,” and “vaccines.” Bibliographic search included consensus papers, editorials, original articles, and review articles written in English, Spanish, and Portuguese. The articles were initially selected on the basis of their titles and abstracts. Articles published in languages other than the selected ones, articles without abstract, and those articles whose titles were not relevant to the purpose of this review were excluded.

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**Diabetes Mellitus and Infections: Physiopathology**

The main mechanisms associated with the interface DM and infections are depicted in Figure 1.

**Complement**

The complement system is one of the main mechanisms responsible for the humoral immunity. It consists of serum and surface proteins whose main functions are to promote the opsonization and phagocytosis of microorganisms through macrophages and neutrophils and to induce the lysis of these microorganisms. Moreover, complement activation products provide the second signal for B-lymphocyte activation and antibody production.

Although some studies have detected a deficiency of the C4 component in DM,[5,6] this reduction of C4 is probably associated with polymorphonuclear dysfunction and reduced cytokine response.[2,5]

**Inflammatory cytokines**

Mononuclear cells and monocytes of persons with DM secrete less interleukin-1 (IL-1) and IL-6 in response to stimulation by lipopolysaccharides.[2,4] It appears that the low production of interleukins is a consequence of an intrinsic defect in the cells of individuals with DM.[2,7] However, other studies reported that the increased glycation could inhibit the production of IL-10 by myeloid cells, as well as that of interferon gamma (IFN-γ) and tumor necrosis factor (TNF-α) by T cells. Glycation would also reduce the expression of class I major histocompatibility complex (MHC) on the surface of myeloid cells, impairing cell immunity.[8]

**Antibodies**

Glycation of immunoglobulin occurs in patients with diabetes in proportion with the increase in HbA1c, and this may harm the biological function of the antibodies.[4] However, the clinical relevance of these observations is not clear, since the response of antibodies after vaccination and to common infections is adequate in persons with DM.[4]

**Major Infections Associated with Diabetes Mellitus**

Some investigators claim that the differences in the risk factors for infection between diabetic and non-diabetic patients result either from non-controlled studies or biased studies (e.g. persons with DM have frequent medical appointments which may increase the probability of being diagnosed with other diseases). However, most researchers conclude that there is clinical evidence pointing to the higher prevalence of infectious diseases among individuals with DM.[2,3,10] Table 1 summarizes the major infections associated with DM.

**Respiratory infections**

Respiratory tract infections are responsible for a significant number of medical appointments by persons with DM compared to those without DM.[4,11-16]

**Streptococcus pneumoniae and influenza virus**

The most frequent respiratory infections associated with DM are caused by *Streptococcus pneumoniae* and influenza virus.[9,15] Persons with DM six times more likely need hospitalization during influenza epidemics than non-
Diabetes is also a common coexisting condition and a risk factor for complications in patients with H1N1 (pandemic influenza virus) infection. The American Diabetes Association (ADA) and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommend anti-pneumococcal and influenza vaccination for people with DM, as shown in Tables 2 and 3, respectively. The World Health Organization recommends vaccination against the H1N1 virus, which is a single-dose vaccine, to minimize the virus-related morbidity and mortality.

These vaccines reduce the number of respiratory infections, the number and length of hospitalizations, the deaths caused by respiratory tract infections, and the medical expenses related to influenza and pneumonia. Despite these benefits, the vaccination coverage in persons with DM remains inadequate.

**Tuberculosis**

In 2009, approximately 9 million new cases of tuberculosis were diagnosed and 1.7 million persons died from this infection. Patients with diabetes are at higher risk of contracting tuberculosis than individuals without DM. Some studies have reported that persons with DM are more likely to develop multi-resistant tuberculosis and that treatment failures and death are more frequent in these patients. In addition, tuberculosis infection and treatment (rifampicin increasing the metabolism of oral antidiabetic drugs) may complicate the glycemic control.

It is suggested that DM depresses the immune response (impairing chemotaxis, phagocytosis, and antigen presentation in response to Mycobacterium tuberculosis infection and affecting T-cell function and proliferation) facilitating infection and progression to symptomatic disease.

The association of these two diseases poses a major burden to the health public system, especially in the developing countries where tuberculosis is one of the most important causes of bacterial infection and the prevalence of type 2 DM is increasing. Therefore, routine screening of patients with tuberculosis for DM and patients with DM for tuberculosis should be implemented.

**Urinary infections**

Urinary tract infections (UTIs) are more prevalent in individuals with DM and may evolve to complications and/or serious manifestations. The main risk factors for UTI in DM are: inadequate glycemic control, duration of DM, diabetic microangiopathy, impaired leukocyte movement, and bacteriuria.

### Table 1: Major infections associated with diabetes mellitus

| Respiratory infections | Strep, Streptococcus pneumoniae | Influenza | H1N1 | Tuberculosis | Asymptomatic bacteriuria | Fungal cystitis | Empysematous cystitis | Bacterial pyelonephritis | Empysematous cystitis | Perinephric abscess | Gastrointestinal and liver infections | H. pylori infection | Oral and esophageal candidiasis | Emphysematous cholecystitis | Hepatitis C | Hepatitis B |
|------------------------|--------------------------------|----------|------|-------------|-------------------------|----------------|--------------------|----------------------|--------------------|----------------|-----------------------------|----------------|--------------------------|-----------------|-------------|-------------|
| Urinary tract infections | Asymptomatic bacteriuria | Fungal cystitis | Empysematous cystitis | Bacterial pyelonephritis | Emphysematous cystitis | Perinephric abscess | Gastrointestinal and liver infections | H. pylori infection | Oral and esophageal candidiasis | Emphysematous cholecystitis | Hepatitis C | Hepatitis B |
| Skin and soft tissue infections | Necrotizing fasciitis | Fournier’s gangrene | Head and neck infections | Invasive external otitis | Rhinocerebral mucormycosis | Other infections | Human immunodeficiency virus |  |

### Table 2: Influenza vaccination in patients with diabetes mellitus

| Age group | Dosage (ml) | Number of doses | Route |
|-----------|-------------|-----------------|-------|
| 6–35 months | 0.25 | 2 doses at the first time* | IM |
| 3–8 years | 0.50 | 2 doses at the first time* | IM |
| ≥9 years | 0.50 | 1 dose annually | IM |

*Children 6 months through 8 years of age receiving influenza vaccine for the first time should receive two doses administered at least 1 month apart.

### Table 3: Pneumococcal vaccination in patients with diabetes mellitus

| Age at first dose (months) | Primary scheme | Boosters |
|--------------------------|----------------|----------|
| 2–6 | 3 doses (2/4/6 months) | 12–15 months of age |
| 7–11 | 2 doses (0/2 months) | 12–15 months of age |
| 12–23 | 2 doses (0/2 months) | None |
| ≥24 | 2 doses (0/2 months) | None |

Pnc7, 7-polyvalent conjugate vaccine (pneumococcal conjugate vaccine); Pn23, 23-polyvalent polysaccharide vaccine (pneumococcal vaccine)
function, recurrent vaginitis, and anatomical and functional abnormalities of the urinary tract.\cite{6,25,29}

**Asymptomatic bacteriuria**

Although women with DM have greater prevalence of asymptomatic bacteriuria,\cite{25,27,30} the data on the natural history of this condition in women with DM are conflicting. Some studies reported progression to pyelonephritis,\cite{28,30} whereas other suggested that this does not lead to serious complications.\cite{11,25,31} Thus, the routine recommendation of antibiotic therapy for asymptomatic bacteriuria in diabetic women remains controversial.\cite{16}

**Bacterial pyelonephritis**

Acute pyelonephritis is 4–5 times more common in individuals with DM.\cite{20} Most infections are caused by *Escherichia coli* or *Proteus* sp.\cite{9} The clinical presentation is similar to that of non-diabetic individuals, except for the bilateral renal involvement.\cite{6,12} Additionally, persons with DM are at increased risk for complications such as perinephric and/or renal abscesses, emphysematous pyelonephritis (EP), and renal papillary necrosis.\cite{9,12,32}

**Emphysematous pyelonephritis**

EP is characterized by necrosis of the renal parenchyma with the presence of gas in the collecting system or in the perinephric tissues.\cite{30,36} It is most commonly observed in DM women.\cite{16,25,32,36}

*E. coli* and *Enterobacter aerogenes* are the most frequent pathogens, followed by *Klebsiella* sp., *Proteus* sp., *Candida* and *Streptococcus* sp.\cite{9,32,35}

Fever, chills, mass and flank pain, nausea, and vomiting are the first symptoms.\cite{27} Crackles in the flank or thigh are less frequent.\cite{16,32,35,37} Abdominal computerized tomography allows the identification of gas in the urinary tract.\cite{9,16,32,35,36-40}

**Fungal cystitis**

Fungal infections are more common in DM, particularly those caused by *Candida*.\cite{28,41} The distinction between infection and colonization can be difficult. The presence of urinary symptoms or pyuria suggests infection.\cite{32} Fungal cystitis may result in the formation of “fungal balls” which may complicate as urinary tract obstruction.\cite{28}

**Emphysematous cystitis**

Emphysematous cystitis affects persons with DM more frequently than non-diabetics.\cite{26,40,42,43} It is characterized by the presence of gas in the bladder cavity and infiltration of the bladder wall due to infection by bacteria that produce carbon dioxide.\cite{44} The most frequent pathogen is *E. coli*, followed by *Enterobacter*, *Proteus*, *Klebsiella*, and *Candida*.\cite{32}

Women are more affected than men.\cite{26,40,44} Computerized tomography is the standard diagnostic method.\cite{45}

**Perinephric abscess**

The main etiologies of renal and perinephric abscesses are enteric gram-negative bacilli (predominantly *E. coli*) or polymicrobial infection.\cite{45,47} Around one-third of perinephric abscesses occur in persons with DM.\cite{16,46,47}

The initial clinical manifestations are fever, backache, dysuria, and/or polyuria.\cite{47} A palpable mass may be present.\cite{42} In case of perirenal suppuration, the overlying skin may show inflammatory reaction.\cite{48} In individuals with DM, the clinical presentation is non-specific. Therefore, the diagnosis is usually late, contributing to worse prognosis. This diagnosis should be considered in patients with acute pyelonephritis that does not get better after antimicrobial therapy.\cite{45}

**Gastrointestinal and liver infections**

The regularity of gastrointestinal motility and sensitivity are important mechanisms of defense against infections.\cite{32} Chronic hyperglycemia contributes to increase the risk of gastrointestinal infectious processes.\cite{32,49}

**Gastritis caused by Helicobacter pylori**

The association of DM and infection by *Helicobacter pylori* is controversial. Although some studies showed that some virulent strains of *H. pylori* are related to macroangiopathy, neuropathy, and microalbuminuria in patients with DM2, there is apparently no relationship between *H. pylori* infection and these DM complications.\cite{49,53}

Some data indicate a possible association of *H. pylori* infection with coronary insufficiency and/or cerebral occlusive vascular disease in adults with DM.\cite{51} Another consequence of this infection is the increase in insulin requirements in children with DM1.\cite{51}

The efficiency of *H. pylori* eradication is lower in persons with DM, whereas the re-infection rates are seen to be higher.\cite{50,51,54}

**Oral and esophageal candidiasis**

The most common etiological agent is *Candida albicans*.\cite{4,55} Its pathogenesis is related to a combination of factors that increase its virulence, with emphasis on the production of extracellular enzymes such as proteinase and phospholipase.\cite{55} Candidiasis manifests in different ways: median rhomboid glossitis or central papillary atrophy, atrophic glossitis, denture stomatitis, pseudomembranous candidiasis, and angular cheilitis.\cite{55} The diagnosis is eminently clinical. However, in case of esophageal candidiasis, endoscopy is needed.\cite{55}
Emphysematous cholecystitis
The emphysematous cholecystitis is more frequent in males with DM.[32] The main pathogens are *Salmonella enteritidis* and *Campylobacter*. The clinical presentation is not different from that of non-complicated cholecystitis (e.g. right upper quadrant abdominal pain, vomiting, and fever).[3] Clinical signs of peritonitis are usually not observed. Crackles can be felt on abdominal palpation, being associated with a worse prognosis.[8] The diagnosis is made by the detection of gas inside the gall bladder, demonstrated in radiograph or computerized tomography scan.[32]

Hepatitis C
Hepatitis C virus (HCV) is a major public health problem affecting more than 170 million people worldwide and this figure is expected to increase due the lack of a vaccine to prevent it.[44] Approximately 50–80% of these patients develop a chronic infection and have a greater chance to progress to cirrhosis.

Several studies, from different countries, have reported that 13–33% of patients with HCV infection have diabetes, mostly type 2 diabetes mellitus (T2DM),[35] compared with the prevalence of 4–10% for non-HCV control population.[58] These data suggest that patients with HCV are 3 times more likely to develop DM than individuals who are HCV negative. Therefore, T2DM is considered an extrahepatic manifestation of this infection.[57]

Patients with HCV who develop T2DM have a more severe liver disease and increased fibrosis compared to non-diabetic HCV patients.[59] Possible explanations are that in individuals with a genetic predisposition to T2DM, the HCV infection could cause (1) impairment of beta-cell responsiveness as a result of a direct viral effect, mostly the genotype 1 or 4,[59] and/or (2) liver damage leading to an abnormal glucose metabolism and insulin resistance.[57]

Early screening for T2DM should be instituted in all patients with HCV, especially if they have other risk factors for diabetes, and screening for T2DM should be performed in areas of high HCV prevalence.

Hepatitis B
About 350 million people are infected by the hepatitis B virus (HBV) worldwide.[60] This number is expected to decrease with the availability and widespread use of the anti-HBV vaccine.

The studies on the relationship between HBV and T2DM are not consistent. Some investigators have reported blood glucose abnormalities,[61] while others have not.[62] Lao et al.[63] reported an independent association between HBV infection and gestational diabetes. Further studies are needed to clarify this questionable association.

However, HBV infection outbreaks have been reported among diabetic patients who share a blood glucose meter without cleaning and disinfecting between uses, associated with limited awareness of the high risk for HBV transmission during fingerstick blood glucose monitoring.[64]

Enteroviruses
Enteroviruses are largely distributed in the world and are mainly transmitted by the fecal–oral route. They are classified into five species: poliovirus, human enterovirus A, human enterovirus B (including the six Coxsackie B virus serotypes), echovirus C, and echovirus D.

Several epidemiological and clinical studies have supported the role of enterovirus, especially Coxsackie B4 and B3 virus, in the development of T1DM in genetically predisposed individuals.[4] Such association is supported by the description of a temporal relationship between the occurrence of T1DM and peaks of enterovirus infections and by the detection of anti-enterovirus antibodies, enterovirus RNA, and capsid protein VP1 in blood, small intestine biopsies, and autopsy pancreas specimens of individuals with T1DM.[65]

Various mechanisms can explain the role of enterovirus in the pathogenesis of T1DM:[65,66] (1) persistent infection of pancreatic beta cells provoking cell damage and release of sequestered antigens inducing an autoimmune response; (2) molecular mimicry (partial sequence homology) between the 2C viral protease and the GAD65 (Glutamic Acid Descarboxilase) and between the VP1 viral capsid protein and the IA2 protein; (3) bystander activation of autoreactive T cells; (4) thymus infection; and (5) loss of regulatory T cells. However, a causative correlation still needs to be established.

Skin and soft tissue infection
Persons with DM are more predisposed to skin and soft tissue infections such as folliculitis, furunculosis, and subcutaneous abscesses. These infections may break out during the course of the disease or may be the first sign of DM presentation,[67,68] and can also be more severe in these populations.[4,32,67]

Foot infection
Foot infections are the most important chronic complications of DM, being one of the most common causes of hospitalization and often resulting in amputation, osteomyelitis, and death.[45,67,69,70]
The clinical signs of infections are very protean and poor, often leading to delayed diagnosis.[71] The diabetic foot infections are usually divided into moderate or “non-limb threatening” and serious or “limb-threatening.”[32,79,72] Moderate infections are defined as superficial, with cellulitis less than 2.0 cm in the largest diameter, without evidence of serious ischemia, systemic toxicity, or bone and/or articular involvement. Serious infections are defined as deep ulceration, with cellulitis equal to or greater than 2.0 cm in the largest diameter, with evidence of serious ischemia, systemic toxicity, or bone and/or joint involvement.[72]

These infections can be monomicrobial or polymicrobial. *Staphylococcus aureus* and *Staphylococcus epidermidis* are isolated from around 60% of all the infected ulcers. Enterococci, streptococci, and enterobacteria are less frequent, and 15% of the infected ulcers have strict anaerobic bacteria.[70]

Infection in a very recently acquired superficial ulcer is likely to be monomicrobial due to aerobic Gram-positive cocci, such as staphylococci, while a long duration of ulceration and increased depth are likely to increase the chances of the wound, yielding both polymicrobial growth and resistant organisms.[70]

Simple clinical assessments are predictive of bone involvement, such as size and depth of ulcer. Ulcers larger or deeper than 2 cm² are more likely to be associated with underlying bone infection.[16,32,71] It is worth stressing that imaging evaluation can be normal in the beginning of the infection, since radiological abnormalities are either observed 10–20 days after the beginning of the infectious process or when 40–70% of the bone is lost.[16,32] Thus, the most sensitive tests are scintigraphy and magnetic resonance imaging.[16]

**Necrotizing fasciitis**

Necrotizing fasciitis is characterized by fast and progressive necrosis of the fascia and subcutaneous tissue, causing fulminant local tissue destruction, microvascular thrombosis, and systemic signs of toxicity. Mortality occurs in approximately 40% of the cases.[9,73-76]

The initial symptoms are fever and intense local pain, followed by areas of skin necrosis with small ulcers that drain a colorless fluid and have unpleasant smell.[16,32] Air in the soft tissues can be better detected by radiograph.[32] The most affected sites are thorax, abdominal wall, extremities, perineum, and groin.[74-76]

In DM, fasciitis is typically polymicrobial, with one anaerobic and many aerobic microorganisms.[16] Type I fasciitis is caused by the combination of an anaerobic microorganism with one or more facultative aerobic microorganisms, and type II fasciitis is caused by a group A streptococcus with or without the involvement of *staphylococci.[73,74]*

**Fournier gangrene**

Fournier gangrene is a fasciitis that affects the male genitalia. The most common etiologic agents are *E. coli, Klebsiella sp.*, *Proteus sp.*, and *Peptostreptococcus.[77,78]* The etiology can also be polymicrobial, involving *Clostridium*, aerobic or anaerobic streptococci, and *Bacteroides.[32,78]*

Up to 70% of the patients with this infection have DM.[29,32,77] It usually involves the scrotum, but can be extend to the penis, perineum, and abdominal wall.[9,16,29,78] Contrary to the general belief, the testicles are usually spared.[77]

**Head and neck infections**

The two most serious head and neck infections in diabetic persons are invasive external otitis and rhinocerebral mucormycosis.[12]

**Invasive external otitis**

Invasive external otitis is an infection of the external auditory canal that can extend to the skull base and adjacent regions.[9,16,79] It often affects elderly diabetic individuals and the etiologic agent is usually *Pseudomonas aeruginosa.[16,79]*

Excruziating pain, otorrhea, and hearing loss are the characteristics.[9] Skull base osteomyelitis and cranial nerve involvement may occur. Facial paralysis occurs in 50% of the cases.[16] The best diagnostic method is the magnetic resonance imaging.[16]

**Rhinocerebral mucormycosis**

Mucormycosis is a rare opportunistic and invasive infection caused by fungi of the class Zygomycetes.[80,81] The genus most commonly associated with human infections is the *Rhizopus*, followed by *Mucor* and *Cunninghamella.*[82]

This infection occurs in approximately 50% of the cases in individuals with DM due to the greater availability of glucose to the pathogen that causes mucormycosis, the decrease in serum inhibitory activity against the *Rhizopus* in lower pH, and the increased expression of some host receptors that mediate the invasion and damage to human epithelial cells by *Rhizopus.[32,79,82]*

The mucormycosis can be acute and chronic.[80-82] The classical triad is characterized by paranasal sinusitis, ophthalmoplegia with blindness, and unilateral proptosis with cellulitis.[16,80] Facial or eye pain and necrotic wound of the palate of the nasal mucosa may occur. Black necrotic eschar in the nasal cornets is a characteristic sign.[16,85,82]
Periodontitis

Periodontitis is a chronic inflammatory disease characterized by the formation of a periodontal pocket, loss of connective tissue, and alveolar bone resorption, which may sometimes result in tooth loss. It is four times more common in persons with DM and is considered the sixth most common complication of DM. Increased risk of common infections in diagnosis, at the onset, and during HAART therapy. An increased risk of developing diabetes is related to the HIV itself or its treatment. Insulin resistance is the main mechanism implicated in the pathogenesis of diabetes in HIV patients. Insulin resistance results from high levels of inflammatory cytokines that impair glucose tolerance, leading to the development of T2DM. More recently, some patients were reported to develop autoimmune T1DM after immune restoration during highly active antiretroviral therapy (HAART).

Risk factors for DM in HIV patients are: high viral burden, low CD4 count, longer duration of HIV infection, advancing age, male gender, lower socioeconomic class, and accumulation of visceral fat. Diabetes is fourfold more frequent in HIV patients on HAART. The protease inhibitors cause insulin resistance by interfering with the GLUT-4 mediated transport and by inhibiting the peroxisomal proliferator activated receptor which increases the release of fatty acids and induces insulin resistance. The nucleoside reverse transcriptase inhibitors also contribute to the insulin resistance.

Patients with HIV should be screened for diabetes at diagnosis, at the onset, and during HAART therapy. An oral glucose tolerance test is recommended to assess the insulin resistance. The treatment of DM in HIV poses some limitations. For example, although metformin is the drug of choice, its use may not be tolerated by cachexic patients or by those with lypoatrophy. The side effects of thiazolidinediones (e.g. higher cardiovascular morbidity, osteoprosis) may prevent their use in HIV patients with diabetes. Glinides and sulfonylureas may not be effective due to insulin resistance. Therefore, insulin is the drug of choice for the HIV-associated diabetes.

Other infections

Human immunodeficiency virus

Approximately 33 million people were infected by the human immunodeficiency virus (HIV) in 2007. The improvements in diagnosis and treatment have translated into an increasing number of patients developing chronic complications including DM. The increased risk of developing diabetes is related to the HIV itself or its treatment. Insulin resistance is the main mechanism implicated in the pathogenesis of diabetes in HIV patients. Insulin resistance results from high levels of inflammatory cytokines that impair glucose tolerance, leading to the development of T2DM. More recently, some patients were reported to develop autoimmune T1DM after immune restoration during highly active antiretroviral therapy (HAART).

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Diabetes is fourfold more frequent in HIV patients on HAART. The protease inhibitors cause insulin resistance by interfering with the GLUT-4 mediated transport and by inhibiting the peroxisomal proliferator activated receptor which increases the release of fatty acids and induces insulin resistance. The nucleoside reverse transcriptase inhibitors also contribute to the insulin resistance.

Conclusions

Infectious diseases are more prevalent in individuals with DM. The main pathogenic mechanisms are: hyperglycemic environment increasing the virulence of some pathogens; lower production of interleukins in response to infection; reduced chemotaxis and phagocytic activity; immobilization of polymorphonuclear leukocytes; glycosuria, gastrointestinal and urinary dysmotility. Some infections almost always affect only diabetic persons, such as malignant external otitis, rhinocerebral mucormycosis, and gangrenous cholecystitis. In addition to being potentially more serious, infectious diseases in DM may result in metabolic complications such as hypoglycemia, ketoacidosis, and coma. The recommendation of compulsory immunization with anti-pneumococcal and influenza vaccines is essential because of their impact on the reduction of respiratory infections, the number and length of hospitalizations and the number of deaths related to respiratory tract diseases.

More research is needed for clarification of the immunopathogenic mechanisms linking DM and infections and to develop strategies to improve vaccination coverage for diabetic patients.

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