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Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Infections and diabetes: Risks and mitigation with reference to India

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ARTICLE INFO

Article history:

Received 16 September 2020

Received in revised form

18 September 2020

Accepted 19 September 2020

Keywords:

Diabetes
Hyperglycemia
Infection
COVID-19
Tuberculosis
Vaccination

ABSTRACT

Background and aims: The link between diabetes and increased risk of infectious disease has long been recognized, but has re-entered sharp focus following the COVID-19 pandemic.**Methods:** A literature search was conducted in PubMed for articles in English on diabetes and infection. **Results:** Diabetes predisposes to infections through alterations in innate and acquired immune defenses. Outcomes of infection are worse in people with uncontrolled diabetes, and infection can worsen hyperglycemia in hitherto well controlled diabetes (bidirectional relationship). Diabetes does not increase the risk of infection with COVID-19 per se, but predisposes to severe disease and poor outcomes. COVID-19 has also been linked to deterioration of glycemic control as well as new-onset diabetes.**Conclusions:** Clinicians caring for people with diabetes should be aware of the increased risk of infections in this population, as well as the possibility of worsening hyperglycemia. A holistic approach with frequent monitoring of blood glucose levels and appropriate titration of medications, along with close attention to nutritional status, is essential to ensure the best possible outcomes.

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1. Introduction

Infectious disease is an important, yet oft-neglected corollary of uncontrolled diabetes mellitus. In the pre-insulin era, most deaths among individuals with type 2 diabetes and many among type 1 diabetes occurred as a result of uncontrolled infection. It is a matter of concern that even today, infections continue to cause significant morbidity and mortality in patients with diabetes, notwithstanding the recent advances in antihyperglycemic and antimicrobial therapeutic options.

In this short review, we will review the mechanisms underlying increased susceptibility to infection in diabetes and briefly discuss the clinically relevant infections found in patients with diabetes, with particular reference to the ongoing COVID-19 pandemic. Indian situation has been highlighted whenever data are available.

2. Search strategy

We searched PubMed for original and review articles in English

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<https://doi.org/10.1016/j.dsx.2020.09.022>

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published, using the following keywords: diabetes and infection, hyperglycemia COVID-19, tuberculosis, vaccination, infections, and diabetes in India, from 2000 till September 2020.

3. Why do patients with diabetes have an increased risk of infections?

The relationship between diabetes and infection has been known for long and has been traditionally considered as bidirectional (Fig. 1) [1]. Uncontrolled diabetes affects almost all components of immunity:

1. Dysregulated innate immunity including defective neutrophil and macrophage function [2].
2. Abnormal complement function, which may be related in part to defects in neutrophil function and cytokine responses [3].
3. Defects in T-cell responses [4].
4. Defective humoral (antibody-mediated) immunity [5].

In addition, the widespread vasculopathy typical of long-standing uncontrolled diabetes interferes with the body's ability to combat infection by limiting the ingress of immune cells as well as antimicrobial factors, and by promoting tissue necrosis and gangrene. Certain features of the hyperglycemic milieu contribute

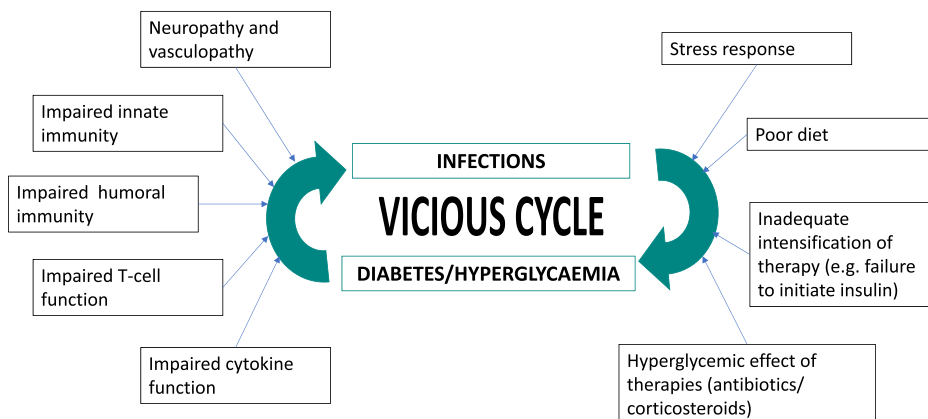


Fig. 1. Bidirectional relationship between diabetes/hyperglycemia and infection.

to the growth of specific micro-organisms (e.g. ketosis promoting the growth of fungi causing mucormycosis).

The infections met with in diabetes patients can be broadly classified into two categories.

1. Infections that are common in the non-diabetic population, that also affect people with diabetes, often with more severe clinical presentation and worse outcomes.
2. Infections that are peculiar to individuals with diabetes and virtually unknown in the normal population.

4. Common infections in individuals with diabetes

These include respiratory infections, genitourinary tract infections and skin and soft tissue infections (Table 1). In a series of 380 patients with diabetes and infections attending a tertiary care centre in North India, the most commonly encountered infections were those of the soft tissues (42.8%), respiratory tract (30.2%) and genitourinary tract (28.4%). Infection of more than one site was present in 5.3% of patients [6]. Diabetes has been shown to increase the risk of lower, but not upper respiratory tract infections [7].

Tuberculosis (TB) is a common comorbidity of diabetes, particularly in developing countries. India faces a double burden with the highest number of TB patients, and the second highest number of individuals with diabetes, living within its borders. The relationship between TB and diabetes is bidirectional; individuals with diabetes are more likely to contract TB, and individuals with diabetes are more likely to have diabetes compared to the general population.

[8]. The greater risk of contracting TB in diabetes, as well as reactivation of latent TB, is postulated to be due to a combination of susceptibility to infection with oxidative stress and increased tissue inflammation [8]. A recent systematic review on the co-prevalence

of TB and diabetes in low and middle-income countries found that diabetes was found in 1.8–45% of individuals diagnosed with TB, and that 0.1–6% of individuals with diabetes had TB [9]. TB in diabetes has certain peculiar characteristics that make diagnosis and management difficult (see Box 1) [10].

Genitourinary infections found in patients with diabetes include urethritis, vaginitis, cystitis, and prostatitis. Common causative organisms are Gram negative bacteria such as *E. coli* and *Klebsiella* and fungi such as *Candida*. In Indian patients with diabetes and UTI, the most common organisms isolated were *E. coli* (64.6%), *Klebsiella* (12.1%) and *Enterococcus* (9.9%) [11]. Infection with extended spectrum beta-lactamase producing *E. coli* was found to be more frequent in individuals with diabetes. Also, nearly 30% of individuals with positive urine culture were found to be asymptomatic. However, current guidelines state that asymptomatic bacteriuria need not be treated, even among patients with diabetes [12].

Use of sodium-glucose cotransporter-2 inhibitors (SGLT2i) for management of hyperglycemia has been associated with increased risk of genital mycotic infections [13]; cystitis and upper urinary tract infections are less common but can occasionally occur [14].

Skin and soft tissue infections found in patients with diabetes include furuncles, carbuncles, and cellulitis. In India, more than 60% of all skin and soft tissue infections have been shown to be associated with *Staphylococci* [6]. Infection is also an important component of the Diabetic Foot Syndrome. Most cases of diabetic foot infection have been shown to be polymicrobial in nature, with predominance of Gram-negative organisms [15–17]. Prevalence of antimicrobial drug resistance was also found to be higher among patients with diabetes, which could be attributed, at least partially, to the production of biofilms by the causative organisms [18].

The antimicrobial management of these conditions does not differ significantly from that in the population without diabetes.

Table 1
Infections prevalent in patients with diabetes.

Common infections	<ul style="list-style-type: none"> • Respiratory infections (viral and bacterial including tuberculosis) • Genitourinary infections
Uncommon infections peculiar to diabetes	<ul style="list-style-type: none"> • Skin and soft tissue infections (furuncles, carbuncles, cellulitis) • Malignant otitis externa • Rhinocerebral mucormycosis • Emphysematous cholecystitis • Emphysematous pyelonephritis • Renal papillary necrosis • Necrotising fasciitis (including Fournier's gangrene)
Diabetic foot infections	<ul style="list-style-type: none"> • Associated with diabetic neuropathy and peripheral vascular disease

Box 1

Diabetes and tuberculosis (Refs.8–10,39-45)

Magnitude of the problem.

- 75 million individuals with diabetes in India
- 2.2 million new cases of TB in India every year

Co-prevalence.

- 30–60% of individuals with TB have diabetes
- 2–5% of individuals with diabetes have TB
- Bidirectional screening is indicated: all patients with TB should be screened for diabetes and vice versa

Peculiarities of TB in diabetes.

- Relative paucity of physical signs
- More extensive caseation and cavitation
- Minimal pleural involvement
- Hemoptysis more common

Issues in management.

- Longer course of treatment may be needed
- Lower likelihood of sputum conversion
- Increased risk of treatment failure, relapse and death
- TB can worsen glycemic control
- Issues with polypharmacy and compliance
- Rifampicin can alter metabolism of oral antidiabetic agents, reducing efficacy
- INH can worsen peripheral neuropathy

Achievement and maintenance of tight glycemic control, most often requiring the use of intensive insulin therapy, is key to improving outcomes.

5. Diabetes and COVID-19

COVID-19 is an acute, predominantly respiratory viral illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). From studies conducted in China, Europe, and the U.S., it appears that individuals with diabetes are not at higher risk of infection with SARS-CoV2 compared to the general population [19,20] (Box 2). However, it is clear that they do tend to have worse outcomes, with respect to development of more severe illness and mortality risk, than individuals without diabetes [21]. While mortality due to COVID-19 has been lower in south Asian countries such as India, the sheer number of individuals with diabetes in this region represents a huge population at high risk of adverse outcomes due to this infection [22,23]. As individuals with diabetes tend to be older and to have higher burden of cardiometabolic risk factors such as obesity and hypertension (as well as cardiovascular disease per se), it is likely that their increased risk of adverse outcomes is mediated, to a large extent, through these comorbidities than by diabetes per se [24]. Recently, there have been reports of new-onset diabetes following infection with SARS-CoV2, mainly from the U.S. [25], but increasingly from elsewhere in the world as well. New-onset hyperglycemia during COVID infection can have multiple causes—weight gain following disordered diet and exercise during lockdown, mental stress, and unwarranted use of dexamethasone

Box 2

DIABETES AND COVID-19 (Refs.19–26, 37–38, 60)

Magnitude of the problem.

- 420 million people with diabetes worldwide (75 million in India)
- 28 million infections with COVID worldwide as of September 2020 (4.4 million in India)

Effect of diabetes on COVID.

- Diabetes per se not a risk factor for contracting COVID infection
- Severe disease and adverse outcomes more likely in individuals with diabetes
- Poor outcomes may be linked to other comorbidities such as older age, obesity and hypertension, more frequent among people with diabetes
- Poor long-term (pre-infection) diabetes control, admission hyperglycemia and inpatient hyperglycemia linked with poor outcomes

Effect of COVID and its Treatment on diabetes.

- COVID infection can worsen diabetes control
- New onset diabetes has been reported with COVID
- Some treatments used for COVID treatment (e.g. steroids) can exacerbate hyperglycemia

Social aspects.

- Adverse effect of pandemic and consequent lockdowns on routine diabetes care. This is likely to exacerbate diabetes control and also add new patients of diabetes to already high numbers.
- Patients unable to exercise regularly, access healthy diet and procure medications promptly. This will increase morbidity and even mortality.

for mild to moderate cases of COVID [26]. It is also likely that the novel SARS coronavirus has a direct diabetogenic potential by way of its effects on the pancreas. The angiotensin converting enzyme 2 (ACE2) receptor, by means of which SARS-CoV2 enters target cells, is also present on the pancreatic beta-cell [27]. Infection of the beta cell may lead to acute impairment of insulin secretion or even destruction of the beta cell, as has been reported for human herpesvirus infection in Africa [28].

In individuals with pre-existing diabetes, the current COVID pandemic and the public health/governmental responses to it are also likely to impact glycemic control in significant ways. Lack of accessibility to testing and care during lockdowns, increased snacking and reduced physical activity are likely to worsen diabetes control, and predispose patients to complications [29], although such deterioration has not been found in all studies [30].

6. Rare infections peculiar to patients with diabetes

- **Malignant otitis externa** refers to Pseudomonas infection of the external acoustic meatus ad middle ear.

- **Rhinocerebral mucormycosis** is infection of the nasal cavity and orbit by fungi such as *Rhizopus*, *Mucor* and *Absidia*.
- **Emphysematous pyelonephritis** refers to infection of the renal parenchyma by gas-forming micro-organisms such as *E. coli*.
- **Renal papillary necrosis** is a complication of UTI in diabetic patients characterized by necrosis and sloughing off of the renal papillae.
- **Emphysematous cholecystitis** is inflammation of the gall bladder due to infection by gas-forming micro-organisms.
- **Necrotising fasciitis** is an uncommon infection of soft tissue caused by various combinations of Streptococci, Staphylococci, and anaerobes. Necrotising fasciitis of the perineum is termed **Fournier's gangrene**.

A high index of suspicion is required for the diagnosis of most of these conditions. Treatment involves, in addition to specific antimicrobial agents, early and aggressive surgical intervention wherever indicated. The prognosis for many of these conditions is poor, even with prompt treatment.

7. Effect of hyperglycemia and glycemic control on infections

While the deleterious effects of uncontrolled hyperglycemia on infection have been well characterized, there is less information available on whether controlling hyperglycemia can have beneficial effects on infection prevention and control [31].

7.1. Uncontrolled hyperglycemia increases hospitalization and morbidities of infections

Analysis of patients with type 1 and type 2 diabetes enrolled in primary care in England have shown a clear increase in long-term risk of infection with increasing HbA1c [32]. In a population-based study from Denmark, individuals with HbA1c of 10.5% and above had hazards ratio of 1.64 for infections requiring hospitalization, compared to individuals with HbA1c between 5.50 and 6.49% [33].

7.2. Hyperglycemia and morbidity and mortality due to COVID19

During the ongoing COVID pandemic, attempts have been made to link the severity of disease outcomes in COVID-19 with the levels of background glycemic control, as well as the glucose levels at admission and during the course of hospitalization. Higher HbA1c at hospitalization, indicating poor long-term glycemic control, has been associated with higher risk of in-hospital death due to COVID, although this has not been replicated in all studies [34]. Patients with higher blood glucose levels at admission tended to have the most florid lesions on chest imaging and were more likely to require ICU admission and intubation and to die compared to those who had lower blood glucose levels [35]. In-hospital hyperglycemia was associated with worse clinical outcomes among patients with COVID studied in China and the U.S [36,37]. These findings reinforce the need for ensuring tight glycemic control in patients with diabetes during the current pandemic, and also for the maintenance of euglycemia in patients who are hospitalized for COVID-19. In this context, it should be remembered that some medications used for the treatment of severe COVID (particularly corticosteroids) have the potential to raise blood glucose levels, and that the antidiabetic drug regimen will need to be appropriately titrated in patients receiving these treatments [21]. Even in the absence of these treatments, infection with SARS-COV2 has been associated with extremely high insulin requirements among patients with diabetes, and the development of hyperglycemic crises in some cases [38].

7.3. Hyperglycemia and treatment failure and relapse in TB

The presence of diabetes is associated with increased risk of treatment failure, relapse, and death in patients with TB [39]; similar results have been reported from India as well [40]. The role of tight glycemic control in improving treatment outcomes in TB remains controversial [41]. A study from China showed that treatment outcomes were worse among those with suboptimal glycemic control [42]. Similarly, Mahishale et al. [43] showed that optimal glycemic control resulted in 88% reduction of sputum non-conversion at 2 months of treatment compared to poor glycemic control. However, Nandakumar et al. [44] found no correlation between diabetes control and TB treatment outcomes in their study conducted in Malappuram district of Kerala. In this context, it is interesting to note that recent studies have shown an association of poorly controlled diabetes with better outcomes in individuals with low body-mass index; this needs confirmation in larger studies [45].

7.4. Effect of tight glycemic control on infections

Maintenance of tight glycemic control during the peri- and postoperative period has been found to be associated with a lower incidence of surgical site infections in patients with diabetes [46,47]. Even though maintenance of tight glycemic control has been long considered one of the cornerstones of diabetic foot management, there is little evidence by way of randomized controlled trials to suggest that foot ulcer outcomes are improved by this approach [48]; such trials are urgently needed, considering the global magnitude of the problem of diabetic foot. In a retrospective study of more than 7300 patients with COVID-19 from China, well controlled blood glucose (defined as glycemic variability between 3.9 and 10 mmol/l) was associated with significantly lower mortality compared to higher blood glucose variability (>10 mmol/l) [49].

8. Diet and nutrition in patients with diabetes and infections

The role of diet has often been overlooked while managing infections in patients with diabetes. Some general points can be summarized from available studies:

- Severe infection is a hypercatabolic state and any diet plan for patients with infection should take this into account, ensuring adequate intake of protein and micronutrients to promote healing. This is particularly relevant in the Indian context, where the baseline protein intake is extremely low. Particularly in patients with diabetes and TB without hepatic or renal insufficiency, it is recommended that proteins should be the major source of energy [50].
- Supplementation of micronutrients for 6 months has been shown to reduce the incidence of common infections (respiratory, skin, and urogenital) in patients with diabetes [51]. A recent review [52] on the role of micronutrient supplementation in diabetic foot ulcers concluded that while there was some evidence to support the role of Vitamins A, C, D and E, and zinc in ulcer healing, the level of evidence was not strong enough to support any recommendations for routine supplementation with these nutrients. In patients with risk of limb ischemia and/or hypoalbuminemia, supplementation with arginine, glutamine and betahydroxy methyl butyrate has been shown to improve foot ulcer healing [53].
- Supplementation of vitamin D has been shown to improve the proportion of sputum smear and culture conversion in patients with active pulmonary TB (with or without diabetes) [54].

Table 2
Recommendations for vaccination in individuals with diabetes [57–59].

Vaccine	Recommendation
Pneumococcus	<ul style="list-style-type: none"> Children should be vaccinated with 13-valent pneumococcal conjugate vaccine (PCV13) before the age of 2 years People with diabetes aged 2–64 years should receive 23-valent pneumococcal polysaccharide vaccine (PPSV23). Booster dose is needed after age 65
Influenza	<ul style="list-style-type: none"> Annual vaccination with influenza vaccine (preferably quadrivalent vaccine) is recommended for all people 6 months of age and above
Hepatitis B	<ul style="list-style-type: none"> Administer a 2- or 3-dose series of hepatitis B vaccine, depending on the vaccine, to unvaccinated adults with diabetes ages 18 through 59 years Consider administering a 3-dose series of hepatitis B vaccine to unvaccinated adults with diabetes ≥ 60 years of age.
Other vaccines	Should be administered as appropriate for age

D. Similarly, vitamin D deficiency was associated with an increased risk of testing positive for COVID-19, raising the possibility that supplementation of this vitamin could reduce the risk of COVID infection; however, it should be noted that this study was not restricted to individuals with diabetes [55].

Recently, consensus guidelines have been published for balanced nutrition in the time of the COVID pandemic [56]. These can be summarized as follows.

- Individuals not infected with COVID, or those with mild to moderate disease, consume a balanced diet rich in vegetables, fruit, legumes, nuts, and whole grain as well as egg and lean meat wherever applicable.
- Intake of probiotic-rich food is encouraged, and hydration should be maintained particularly when febrile.
- Saturated fat and processed food should be avoided, as should extreme “fad” diets.
- The diet should provide at least 1 g of protein per kg body weight per day in older persons and should contain adequate amounts of micronutrients such as Vitamins A, C, and D, zinc, and selenium.
- In severely ill patients, these nutritional requirements should be met by way of oral supplementation wherever possible, with enteral and parenteral supplementation being reserved for the most severely ill individuals who cannot tolerate oral intake.

9. Vaccinations in patients with diabetes

As individuals with diabetes represent a vulnerable subgroup of the population with respect to susceptibility to infection, preventing these infections by means of vaccination assumes paramount importance. In addition to all routine immunisations recommended for the general population, the American Diabetes Association provides additional recommendations for the use of pneumococcal, influenza and hepatitis B vaccines in individuals with diabetes [57]. Attempts have been made to formulate similar recommendations for India also [58,59] (Table 2).

In this context, it should also be noted that the nationwide lockdowns imposed in India and other countries to combat the spread of the COVID-19 pandemic have had an adverse impact on the coverage of infection control and immunization programs directed against other communicable disease; these countries should gear up to face a recrudescence of many of these hitherto controlled infections in the near future [60].

10. Conclusions

Infectious disease continues to take a heavy toll of the population with diabetes even in the present day. The increased susceptibility of the individual with diabetes to infection has recently returned to sharp focus with the advent of the COVID-19 pandemic, reiterating the need for achieving tight control of hyperglycemia

and managing comorbidities appropriately in this population from the time of diagnosis of diabetes. Also, there are certain unusual infections that appear to be exclusively found in patients with diabetes; the clinician dealing with patients with diabetes should be ever alert to the possibility of these infections, as prompt diagnosis may mean the difference between life and death in many cases.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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