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Review Article

Diabetes and bacterial infection

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Abstract

People with diabetes are at increased risk of infection and are worried about biological agents such as bacteria. Particularly, foot infections, urinary tract infections, pneumonia, and skin diseases are due to bacterial infections that make diabetic patients suffer from clinical difficulties. Although antibiotics, one of the bacterial therapies, have been used, the emergence of multidrug-resistant bacteria is now in demand for alternative therapies. Although, many studies reported that antibiotic-resistant for bacterial infections and their rate have increased significantly in the diabetic patient population. Still, there is no report that directly compares the prevalence of antibiotic-resistant infections in diabetes types. In this review, we described the diverse types of diabetes with their bacterial infection and the reported resistance. Generally, diabetic patients are susceptible to vancomycin-resistant enterococcal infections, extended-spectrum β-lactamase-producing intestinal bacteria, carbapenem-resistant intestinal bacteria, and unfermented gram-negative bacilli. Thus, early detection of diabetes and prompt treatment are important to control chronic infections in diabetic patients.

Abbreviations

CDC: Centers for Disease Control; WHO: World Health Organization; US: United States; MRSA: Methicillin-Resistant S. Aureus; HIV/AIDS: Human Immunodeficiency Virus/Acquired immunodeficiency syndrome; FDA: Food and Drug Administration; ADA: American Diabetes Association; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; IGT: Improved Glucose Tolerance; GBD: Global Burden of Disease; IGRA: Interferon Gamma Emission Measurement; AMR: Antimicrobial resistance; UTI: Urinary Tract Infection; HbA1c: Hemoglobin A1c; ICAM-1: Intercellular Adhesion Molecule 1; TB: Tuberculosis.

Introduction

Diabetes has traditionally been considered a 'rich disease' that is found primarily among the elderly in developed countries. However, diabetes is now affecting all levels of society and is becoming a rapidly growing problem in poor communities. The World Disease Burden Survey estimated 1.4 million deaths related to diabetes consequences worldwide in 2016 [1], which is an increase of 31% from 2006. In 2019, there were 437.9 million types 2 diabetic patients worldwide, with an age-standardized prevalence of 5,282.9 per 100,000 population, which reflects an increase of 49% from 1990 [2].

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Furthermore, the number is expected to rise to 669 million by 2045 [3].

In general, people with diabetes have an increased risk of infection, and worse outcomes are known to be diabetic foot infection, Urinary Tract Infections (UTI); especially from *E. coli*, streptococcus pneumoniae, cellulitis, streptococcal species common causes including Candida, mucor invasive mold infections, and frequent skin infections [4,5]. Other than the difficulty in treating infections in diabetic patients due to their diminished circulation that restricts immune cells and the right concentration of antibiotics to the infected area, remarkably, antimicrobial drug resistance implies a great therapeutic challenge. On the other hand, it is a significant economic burden on health providers due to the increased number of diabetic patients and the severity of the infectious multi-resistant bacteria complication [6].

Centers for Disease Control (CDC) and World Health Organization (WHO) have declared antibiotic resistance a threat to public health [7-9]. The CDC estimates that antibiotic-resistant infections have resulted in higher than 2.8 million antibiotic-resistant infection cases, and at least 35,000 deaths, thus resulting in a $55 billion loss or more in the United States (US) each year [9,10]. Moreover, according to the British government's review of antibiotic resistance in 2016, the estimated number of infections is 2 billion, the estimated cost of infection is $100 trillion, and the number of deaths is estimated at 10 million by 2050 [11]. in 2019, there were an assessed 4·95 million (3·62-6·57) passings related to bacterial/ antimicrobial resistance counting 1·27 million (95%) passings attributable to antimicrobial resistance [12].

Classification of diabetes

It should be noted that assigning a type of diabetes to an individual often relies on the conditions at the time of diagnosis and additional tests and that many patients with diabetes do not easily fit the same grade. The following table 1 shows the current classification of diabetes by the WHO and the American Diabetes Association (ADA) [13,14]. In addition, the table includes four clinical and physiological classes: type 2 diabetes mellitus (T2DM), type 1 diabetes mellitus (T1DM), gestational diabetes, and other specific types of diabetes caused by distinct reasons. T2DM is the most common type of diabetes, accounting for approximately 90% of all cases of diabetes worldwide [6]. While T1DM is caused by an autoimmune disease that destroys the beta cells that produce insulin from the island of the pancreas. T1DM is therefore characterized by insufficient production of insulin and the inability of the body to fully react to insulin, which is defined as insulin deficiency .

Risk factors of diabetes

With the rapid increase in the prevalence of diabetes in recent decades, the environment and lifestyle have become increasingly important in the development of the disease. Table 2 demonstrated a summary of the modifiable and non-modifiable hazards of T2DM, a disease caused by complex interactions between environmental and genetic factors [15].

Inadequate glycemic control increases the risk of diabetes infection. Frequent studies have revealed an impaired host defense against pathogens in diabetic patients when they assessed diabetes-related mechanisms [16-18].

Current trend and perspective of diabetes

As Table 3 shows the world population of diabetes from the age of 20 to 79 (2017), this figure worldwide is expected to rise to 629 million by 2045 [6,19]. Nearly half (49.7%) of people with diabetes and 352 million patients with improved glucose tolerance (IGT) reached 7.3% of adults aged 20 to 79. By 2045 the number of people with IGTs in the same age group is expected to be 53 million (8.3% of adults). Around the world, between the ages of 20 and 99, about 5 million deaths each year are attributed to diabetes. In developed countries, 87 to 91% of people with type 2 diabetes, 7 to 12% with type 1 diabetes, and 1 to 3 percent of people with diabetes have distinct types of diabetes [3]. Therefore, it is obvious that the prevalence of diabetes substantially intensifies with age.

Table 1: An etiological classification of diabetes mellitus, adapted from WHO [13], and the American Diabetes Association [14].

Type	Pathophysiology
Type 1	Results from β-cell destruction, usually lead to absolute insulin deficiency
• Autoimmune	
• Idiopathic	
Type2	
•Predominantly insulin resistance	May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance
• Predominantly insulin secretory defects	
Other specific types	Results from other causes include genetic defects in β-cell function; genetic defects in insulin action; diseases of the exocrine pancreas; endocrinopathies; drug or chemical induced; infections
Gestational diabetes	Diagnosed during pregnancy (encompasses gestational impaired glucose tolerance and gestational diabetes mellitus)

Table 2: Modifiable and non-modifiable risk factors for type 2 diabetes (adapted from the International Diabetes Federation: a consensus on type 2 diabetes prevention) [15].

Modifiable risk factors	Non-modifiable risk factors
Overweight and obesity (Central and total)	Age
Sedentary lifestyle	Sex
Adverse diet/dietary factors	Ethnicity
Smoking	Family history of type 2 diabetes
Intrauterine environment	History of gestational diabetes
Hypertension/use of antihypertensive medication	
Serum cholesterol	
Triglycerides	
Previously identified glucose intolerance	

Table 3: World: adults with diabetes in 2017 and projected figures for 2045 [6].

Population data	2017	2045
Total world population	7.5billion	9.5 billion
Number of people with diabetes (18-99 years)	451 million	693million
Number of deaths due to diabetes (> 20 years)	5.0 million	_

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Studies have recommended that the environment and lifestyle in childhood have a significant impact on the risk of T2D in adulthood. Therefore, there is a need to focus on prenatal and early fetal nutrition. For T1D, although it is currently possible to treat the disease, there are no effective and safe interventions to prevent it. Moreover, several studies indicate that lifestyle interventions, intensive lipid and blood pressure monitoring, and glycemic control are cost-effective ways to control diabetes and are important factors in reducing the risk of diabetes and its associated complications. It is a global crisis affecting the economies and health status of all nations, the economic growth and lifestyle changes are the most important reasons for the increasing prevalence of diabetes.

Diabetes and specific infections

It is commonly known that people with diabetes, such as diabetes foot infection, urinary tract infection (especially *E. coli* infection), streptococcus pneumonia, Candida and mucor invasive fungal infection, cellulitis (the common cause of streptococcal species) and surgical sites, have increased the risk of infection and have worse consequences [4,5].

Tuberculosis is the main culprit of disease and death worldwide and is estimated to be 1.2 million cases in 2017 [1]. Diabetes can triple the risk of developing tuberculosis which is further associated with an increased risk of tuberculosis death or failure to treat tuberculosis. The Global Burden of Disease (GBD) group reported that diabetes accounts for about 10.6% of people who are HIV-negative compared to tuberculosis mortality [20]. More than half of the world's tuberculosis patients are in 30 countries as of 2020, and there are 8 countries described for two-thirds of the new cases which are China, India, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa. [1,21]. Moreover, the dual burden of TB and diabetes for patients is in adults with an age between 20 to 79 years in the following 5 countries: China with 114 million patients, India with 73 million patients, Indonesia with 10 million patients, the Philippines with 3.7 million patients, and Pakistan with 7.5 million patients [22]. In a country with a double burden of tuberculosis and diabetes, two-way checkups are urgently needed as the incidence of diabetes continues to rise and the prevalence of tuberculosis continues. There is evidence that the presence of clinical tuberculosis causes high blood pressure and affects the response to clinical results and treatment [23]. Blood testing to diagnose tuberculosis would be highly desirable, but currently, the Interferon Gamma Emission Measurement (IGRA) that is examined with blood does not have sufficient sensitivity and specificity for this purpose. Screening people with tuberculosis diabetes is even more difficult because they depend on questionnaires for symptoms following chest X-rays. Tuberculosis can complicate diabetes management and worsen glycemic control. In particular, some drugs used to treat tuberculosis interact with drugs used to treat diabetes. Both diseases have significant health and economic impacts on individuals and their families. As previously mentioned, untreated latent tuberculosis infection can lead to tuberculosis disease. Tuberculosis can lead to illness and death if left untreated. However, people with either latent tuberculosis infection or tuberculosis disease can be effectively treated. Therefore, it is highly recommended that patients diagnosed with TB should be screened for diabetes and contrariwise.

On the other hand, people with diabetes have a twelve-fold increased risk of melioidosis, and over half of all cases of melioidosis have diabetes, especially T2D [24]. The greatest increased risk for infection in people with diabetes is a 12-fold increased risk and is seen for the grossly under-recognized tropical fatal disease melioidosis, which is caused by the Gram-negative bacterium *Burkholderia pseudomallei* [25,26].

Additionally, studies in developed countries have shown that people with diabetes have a high rate of infection from different bacteria and a threefold higher risk of Enterobacteriaceae bacteremia. [27,28].

Moreover, some bacterial species are reported more often concerning diabetes such as *Staphylococcus aureus*, this bacterium is a risk factor for invasive infections in diabetic patients [29]. *S. aureus*, the most common cause of tropical inflammation, is an infection of skeletal muscles characterized by intramuscular abscess common in the tropics, accounting for 1 to 4% of acute hospitalization [30]. Long-term diabetes, suboptimal glycemic control, and complications of diabetes, including kidney disease, further increased the risk of *S. aureus* infection. There is a great need to improve care for people with diabetes, including better infection control in patients with co-morbidities.

Also, a link between salmonella infection and diabetes has also been reported. The retrospective application of 134 cases of salmonella infection, including 38 cases of *Salmonella Typhi* infection that cause Typhoid fever, showed that 34% of adults aged 50 had diabetes [31]. It has been announced that diabetes is related to an increase in the risk of infection with *S. enteritis* after exposure to the U.S. hospital outbreak [32]. Another cause of Typhoid fever than *Salmonella enterica* serotype *Typhi* is Rickettsia group *Orientia Tsutsugumush*i. This fever is also known as Scrub typhus, which has been an independent risk factor for more serious diseases in prior research on *eschar-positive scrub typhus* [33,34].

Diabetes is a problem that needs to be revealed which bacteria are much more susceptible to and have worse consequences than other bacteria. *M. tuberculosis* and *B. pseudomallei* are considered bacteria of diabetic-associated infections that are mostly intracellular bacteria [35]. In addition, damage to blood cell function or adaptation to T cell immunity of diabetes can cause increased susceptibility to intracellular pathogens. One of the things we should not overlook is that diabetes is linked to antimicrobial resistance (AMR). The condition of diabetes is related to the increase in drug resistance in tuberculosis, including multi-drug-resistant tuberculosis [36,37] [30,31]. Besides tuberculosis, people with diabetes are overindulgent in cohorts with multi-drug-resistant infections. What is important is that the growth rate of AMR will have a greater impact on people with diabetes in the future. Their risk of infection adds to the need for health interventions.

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Common infections and resistance to antimicrobial drugs

Due to impaired defenses and disease complications, people with diabetes are prone to new infections and recurrences. Uncommon life-threatening infections are more frequent in people with diabetes than in people without diabetes such as necrotizing soft tissue infection, emphysematous pyelonephritis, emphysematous cholecystitis, malignant otitis, and perioperative infection. While pediatric infections occur in 25% of diabetic patients and occur in peripheral blood circulation disorders.

Diabetes is associated with the risk of blood flow infections and sepsis obtained in communities and hospitals [38,39,43,44]. Causes the change of congenital immune response and acquired immune response after recovery from sepsis continues, increasing immune function disorder, chronic inflammation, and microbial persistence, and infection in this vicious cycle can worsen blood sugar management [40]. Table 4 summarizes the common infections of diabetic patients.

Staphylococcus aureus, *Streptococcus*, *Enterococcus*, *Enterobacteriaceae*, and *Pseudomonas* are the most common pathogens in South Korea as well [42,43]. In Saudi Arabia, a total of 134 pathogens were separated from 126 patients. The most common Gram-negative pathogens were *Pseudomonas aeruginosa* (15.6%) and *Klebsiella spp.* (6.7%). On the other hand, the most common Gram-positive bacteria were *Staphylococcus aureus* (35%) and *Streptococcus* (8.9%) [44]. There is a different distribution of pathogens that commonly infect diabetic patients based on the geographical region. However, a recent meta-analysis found that *Staphylococcus aureus* was the most commonly identified organism in diabetics, of which 18% were MRSA, and the other widespread organisms were *Pseudomonas*, *E. coli*, and *Enterococcus* [45].

Diabetic patients with UTI (76.2%) patients were most commonly have the following pathogens: *Escherichia coli* followed by *Klebsiella pneumonia* [46,47]. Aerobic urinary tract infection was detected in urine in the combined urinary tract infection, with the formation of gases in the urinary tract, such as kidney, sour, ureter, and light, and *Escherichia coli* (n=6), *Klebsiella* (n=1), and *Proteus* (n=1) in patients with Emphysematous pyelonephritis diabetes [48]. As a unique case, a 46-year-old patient with a neurogenic disorder caused by insulin-dependent diabetes and kidney deficiency describes a clinical case with complaints about UTI, including fever, chili, dysentery, and reinstatement. After the urine culture test, it was confirmed that the Vitek-2 system was for *Sphingomonas paucimobilis* (*S. paucimobilis*), an *aerobic Gram-negative* bacterium [49]. For diabetic patients with UTI, a higher level of HbA1c causes bacteremia and septicemia [25].

Candida skin infections occur around the skin in wet, warm areas, and when the body is fat, the disease has a complex

Table 4: Common infectious events in people with diabetes [41].

Body site	infection	Etiologic agent(s)
Head and neck	Periodontal disease Mucormycosis (zygomycosis) Endophthalmitis Malignant otitis externa	Oral commensals, *Porphyromona gingivalis, Tannerella forsythia, Treponema denticola, Rhizopus* spp., *Mucor* spp., *E. coli, K. pneumoniae, P. aeruginosa, Aspergillus* spp., and other fungi.
Respiratory tract	Pneumonia and bronchopneumonia	*S. pneumoniae, S.aureus, K.pneumoniae,* and other Gram-negative *bacilli.*
		Legionella spp.
		Influenza virus
	Tuberculosis	*M. Tuberculosis* complex.
Urinary tract	Urinary tract infection: cystitis, urethritis, pyelonephritis, complications	*E. coli, Klebsiella* spp., and other *enterobacteria.*
		Acinetobacter spp.
		P. aeruginosa.
		S. agalactiae.
		Candida albicans, other yeasts.
Intra-abdominal compartment	Hepatic and intra-abdominal abscesses	*K. pneumoniae*
	Cholecystitis	*Enterobacteriaceae: E. coli,* other species.
		Obligate anaerobic bacteria: *Bacteroides fragilis, Clostridium perfringens.*
Skin and subcutaneous tissues	Intertrigo	*Candida* spp.
	Skin lesions	*Varicella-Zoster* virus.
	Cellulitis	*S. aureus.*
		S. pyogenes.
	Superficial mycoses and onychomycosis	Dermatophytes.
Soft tissue, bones, joints	Necrotizing fasciitis	*S. pyogenes; S. aureus, Enterobacteriaceae.*
		Obligate anaerobic bacteria: *Bacteroides* spp., *Clostridium perfringens.*
		Vibrio spp.
		Aeromonas spp.
		Salmonella spp.
		Enterococcus spp.
	Diabetic foot	*S. pyogenes, S. aureus,* Gram-negative bacilli, anaerobic bacteria, fungi.
	Osteomyelitis, septic arthritis	*S. aureus, M. tuberculosis* complex.
Bacteremia and sepsis	Community-acquired and hospital-acquired	*E. coli, S. aureus, Streptococcus pneumoniae, Enterobacteriaceae, enterococci, Pseudomonas aeruginosa, Candida albicans,* other agents.

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system to detect surrounding pH that causes metabolic reactions that allow attachment, growth, and intrusion as microbial metabolites increase the skin pH, causing obvious infection (vitaminosis). Diabetes patients with higher pH levels in intertriginous areas are particularly susceptible to candidiasis [50]. In addition, the adhesion of *Candida. Albicans* to vaginal epithelial cell lines and cells have been shown to increase at higher glucose concentrations. At the same time, ICAM-1 expression in cells was also increased [51].

To a lesser extent, *Chryseobacterium* species are gaining importance as emerging opportunistic nosocomial pathogens. Limited availability of clinical data necessitates reporting of such isolates [52]. A case of the closed carotid artery in *Scedosporium apiospermum* fungus, central skull base osteomyelitis, and finally in 48-year-old diabetic patients was reported [53]. The first case of mycotic aneurysms of the intrapetrous carotid artery by *Pseudomonas aeruginosa* was reported in diabetic people, presenting high-grade bacteremia and otorrhagia [54].

Drug-resistant organisms and diabetes

In the US, only the MRSA (methicillin-resistant *S. aureus*) infection, is described as having more deaths than HIV/AIDS and tuberculosis combined [55]. After the discovery of antibiotics, a drug called the antibiotic pipeline was introduced steadily. However, the speed at which bacteria are resistant to antibiotics has reduced commercial interest in the research and development of new compounds. There were 16 new antibiotics approved by the US Food and Drug Administration (FDA) from 1983 to 1987. The number was constantly downgraded, and six new antibiotics were approved between 2010 and 2016 [56]. At the end of the line, the antibiotic's carbapenem line is often designated as the "last resort" due to its adverse health effects.

Table 5 shows a common drug-resistant phenotypic prevalence rate (from the 1st day 2015 survey conducted in 53 countries) [57] in which germs are isolated from patients diagnosed with infections worldwide. Drug resistance is especially prevalent in the diabetic patient group, as people with diabetes are more exposed to antibiotics than people without diabetes. The prevalence of MRSA was similarly high in both groups of diabetic and non-diabetics. In contrast, the prevalence of common resistive phenotypes; carbapenem-resistant (CarbaR), production of extended-spectrum β-lactamases (ESBL), Gram-negative nonfermenting rods (GNNF), and vancomycin-resistant enterococci (VRE), in diabetic patients was more pronounced. Therefore, early diagnosis and rapid treatment of infection are particularly important for people with diabetes, including surgical separation, when necessary.

Table 5: Prevalence of drug-resistant isolates in adult inpatients diagnosed with bacterial infection worldwide and in Europe and in Asia (1-day survey, the year 2015) compared with adult non-diabetic and diabetic inpatients at a single hospital (Varese, Italy, the year 2017) [57].

	Prevalence of drug-resistant bacterial isolates (%)				
	MRSA	VRE	ESBL-enterobacteria	CarbaR enterobacteria	CarbaR GNNF bacilli
World, *n* = 6750	5.3	1.1	8.1	1.2	2.6
Europe, *n* = 3981	5.3	1.6	14.8	0.9	6.7
Diabetic inpatients, Varese, *n* = 518	33.8	3.5	16.7	2.9	45.6
Non-Diabetic inpatients, Varese, *n* = 6540	34.1	2.9	13.2	1.8	32.4

Common resistance phenotypes: CarbaR, carbapenem-resistant; ESBL, production of extended-spectrum β-lactamases; GNNF, Gram-negative nonfermenting rods; MRSA, methicillin-resistant S. aureus; VRE, vancomycin-resistant enterococci.

Complications of diabetes favor infection

Complications of diabetes mellitus confer an additional risk for infection. Vascular pathology and reduced perfusion, autonomic neuropathy, and sensory neuropathy that implies reduced sensitivity to painful stimuli and repeated trauma, urinary retention, reduction of sweating, and alterations of gastrointestinal mobility and absorption. Other diabetes, Mellitus-related conditions include increased body mass, dyshidrosis dehydration and superficial skin infections (especially at body folds), infection of foot ulcer [58], and people with diabetes are exposed to risks of infection associated with semi-invasive or invasive procedures (e.g., dialysis, surgery, general hospital assistance). Insulin injections, even if sporadically, may aid subcutaneous infection. In diabetic patients, intensive monitoring and antidiabetic pharmacotherapy should be considered. Physicians treating patients with diabetes should be more aware of the increased risk of infection and the potential for exacerbating hyperglycemia. A universal approach that includes frequent monitoring of blood glucose levels and appropriate adjustment of medications, along with close attention to nutritional status, is essential to achieve the best possible results. It is alarming that despite recent advances in hypoglycemic and antibiotic treatment options, infections remain to cause significant morbidity and mortality in people with diabetes.

Conclusion

All together considered that people with diabetes had a significantly greater rate of infections, as well as increased vulnerability to lower respiratory tract infections, urinary tract infections, bacterial skin, mucous membrane infections, and wound infections. Surgical site infections, foot infections, and urinary tract infections especially from *E. coli*, *streptococcal pneumonia* and *cellulitis* (a common cause of *streptococcal* species), *Candida*, and *mucus-invasive fungal* infections, are known to have an increased prevalence in diabetic patients than non-diabetic ones. People with diabetes are highly at risk of infection and have worse outcomes compared to non-diabetes [4,5]. Nowadays, it is well known that diabetes is most susceptible to, and adversely affected by, *M. tuberculosis* [1,20], and gram-negative bacteria *Burkholderia pseudomallei* [59]. Moreover, damage to the blood cell function or adaptation of T cell immunity of diabetes can cause increased susceptibility to intracellular pathogens such as *S. aureus* [29], *Salmonella* [32], and *Scrub typhus* [33], which are reported in many cases.

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One of the things we should not overlook is that diabetes is linked to AMR. This condition of diabetes is related to the increase in drug resistance in TB including multi-drug-resistant tuberculosis [36,37]. Furthermore, the number of published results indicate that diabetic patients are more susceptible to vancomycin-resistant *enterococci*, extended-spectrum 1-lactamase-producing *enteropathic* bacteria, carbapenem-resistant intestinal bacteria, and non-fermented gram-negative bacilli than non-diabetic patients, with similar appearance of *S. aureus* infection [41]. Therefore, early detection of diabetes mellitus and rapid treatment of infections are especially important and should be monitored regularly.

Author contributions

Conceptualization, T.K., Y.H., Y.L., H.J., J.K., and S.K.; supervision, S.K.; funding acquisition, H.J., and S.K.; writing original draft, T.K., J.K., and S.K.; writing review and editing, T.K., and S.K. All authors have read and agreed to the published version of the manuscript.

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