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EC MICROBIOLOGY
Review Article

Immunodeficiency in Diabetic Patients

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Received: August 05, 2020; **Published:** September 29, 2020

Abstract

Introduction: Patients who have diabetes mellitus (DM) are more susceptible to infections than those without DM. Due to the defects seen in the immunity, the course of the infections and increased prevalence of infections are seen more in this group. Cellular and humoral immunity show disturbances. Diabetic polymorphonuclear cells and diabetic monocytes/macrophages also tend to show decreased functions. Higher glucose environment tends to attract certain microorganisms causing infections that affect multiple organs and organ systems, eventually leading to morbidity and mortality of the patients.

Aim of the Work: The review summarizes the physiopathology, associated mechanisms that make DM patients susceptible to developing infections, and major infections seen with diabetes mellitus.

Methodology: This article is a comprehensive review of PUBMED from the year 1999 to 2017.

Conclusion: Novel treatment options and methods to prevent infectious diseases in diabetic patients can be better understood if proper knowledge about immune dysfunctions during hyperglycemia is known. This can, in turn, improve the outcome of treatment of these infectious diseases.

Keywords: *Type 2 Diabetes; Immunity; Immune Dysfunction; Hyperglycemia*

Introduction

Deficiency of insulin secretion or action or both causes the clinical syndrome of Diabetes mellitus (DM). It is a metabolic disorder where hyperglycemia is seen as a result of the defect of insulin action [1]. One of the largest developing threats in today's century is considered to be DM [2]. Auto-immune mediated pancreatic beta-cell destruction, which leads to insulin deficiency is the primary cause of Type 1 diabetes. Beta-cell autoantibodies are usually present in this type [3,4]. Type 2 diabetes is seen in a patient with insulin resistance where there is an increased glucotoxicity, lipotoxicity, endoplasmic reticulum-induced stress, and apoptosis which could progressively destroy the beta cells [2,4]. Pathogenesis of type 2 diabetes shows beta-cell autoantibodies, a combination of peripheral insulin resistance and dysfunctional secretion of insulin by pancreatic beta cells [2,5].

Reduced response of T cells, neutrophil function, and disorders of humoral immunity are also seen in diabetes apart from the increased susceptibility to infections. Infections in diabetic patients show a more complicated course and further trigger complications associated with DM, like hypoglycemia and ketoacidosis [2].

Methods

We conducted a thorough systematic search on scientific database including PubMed search engine and Google Scholar for all studies discussing immune system dysfunction and abnormalities associated with diabetes mellitus. All relevant available full articles between 1999 and 2017 were reviewed and included. The terms used in the search were: immune system dysfunction, diabetes mellitus, immunodeficiency, and human immunodeficiency virus.

Risk of infections

An increased risk of infection among diabetic patients compared with general population is evidenced in a large number of studies. However, the magnitude of this risk is uncertain. One matched cohort study based on the Canadian electronic medical record-based sur-

veillance system found an increased odd of infection among patients with diabetes (22 percent on insulin) compared with matched control after controlling for potential confounders; adjusted odds ratio 1.21, 95% CI 1.07-1.37.6 Diabetes mellitus was associated particularly with higher incidence of skin and soft tissue infections followed by genitourinary, gastrointestinal, and respiratory infections. On the other hand, the study found no association between DM and head and neck, musculoskeletal, and viral infections. Another retrospective cohort study has examined the incidence rate ratio (IRR) among 5863 patients with type 1 DM and 96,930 patients with type 2 diabetes mellitus using a large primary care database in England. When compared with age, sex, and practice-matched controls, the incidence rate ratio was 1.66 and 1.47 for type 1 and type 2 respectively [7]. In contrast to previous study, the IRRs were highest for bone and joint infection in both type 1 and type 2 diabetes mellitus. For type 1 diabetes mellitus, IRRs were also high for endocarditis, meningitis, and sepsis. Candidiasis, sepsis, and cellulitis were highly associated with type 2 diabetes mellitus. A study from Netherland has examined the number of infection in 193 patients treated for type 2 DM during a two-year period has found a mean of 2.4 (± 1.9) infections per patient during that period [8].

Most, but not all studies correlate the risk of infection in diabetes mellitus with hyperglycemia or lack of adequate control.9 Particularly, a strong association between diabetes mellitus and postoperative hyperglycemia with surgical site infections (SSIs) were reported.9,10 As an example, diabetes mellitus was significantly associated with SSI (OR 1.3, 95 % CI 1.2-1.4) in a multivariable logistic regression study of 49,817 patients undergoing major vascular surgery [11]. Moreover, postoperative hyperglycemia was the sole independent risk factor for SSI among 1561 patients undergoing general and vascular surgery after multivariate adjustment for other factors, such as age, emergency status, American Society of Anesthesiologists preoperative classification score, and operative time [12]. The study's retrospective design, the absence of postoperative glucose level measurements on approximately a quarter of the patients, and the lack of association between hyperglycemia and SSI among vascular surgery patients limit confidence in the study results. However, many observational data are generally consistent with these findings, another prospective study that included 1000 patients undergoing cardiothoracic surgical procedures has also reported an increasing association between the level of postoperative hyperglycemia and the risk of SSI [10]. Accordingly, evidence from several studies has suggested that adequate glucose control during the operative and perioperative period can reduce the risk of postoperative infections following cardiac surgery [13]. One meta-analysis of 4 randomized trials and 6 cohort studies has concluded that glycemic control with a continuous insulin infusion to maintain glucose levels ≤200 mg/dL lowers the rate of SSI following cardiac surgery when compared with subcutaneous insulin [13]. In addition to increased risk of infection, patients with diabetes mellitus have worse outcomes with infections such as bacteremia and endocarditis [14].

Pathophysiology

A summarization of the major mechanisms associated with the infections are shown below [2].

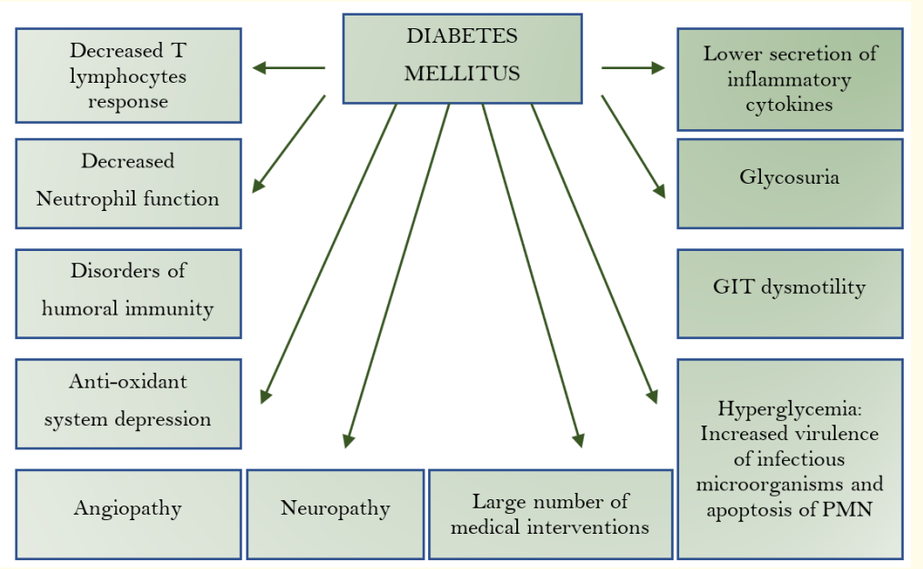

Figure 1: *Pathophysiology of infections associated with DM [2].*

Complement

This system has serum and surface proteins, which causes opsonization and phagocytosis of microorganisms with macrophages and neutrophils, which lyses these microorganisms. It also activates the B-lymphocyte and causes antibody production [2]. The reduction of the CD4 cells could be associated with reductions in cytokine response and polymorphonuclear dysfunction [15].

Inflammatory cytokines

The interleukin-1 (IL-1) and IL-6 secreted in response to the lipopolysaccharides stimulation is less due to an intrinsic defect in the cells of DM patients. There is also evidence that an increase in glycation can hinder the production of IL-10 by myeloid cells and that of interferon-gamma (IFN-γ) and tumor necrosis factor (TNF)-α by T cells [7]. Glycation also reduces the expression of class I major histocompatibility complex (MHC) on the myeloid cell's surface, which can impair cellular immunity [17].

Polymorphonuclear and mononuclear leukocytes

Hyperglycemia causes decreased mobilization of polymorphonuclear leukocytes, chemotaxis, and phagocytic activity. The antimicrobial function is blocked by the hyperglycemic environment due to the inhibition of glucose-6-phosphate dehydrogenase (G6PD), increased apoptosis of polymorphonuclear leukocytes, and reduced polymorphonuclear leukocyte transmigration via the endothelium [16]. In animal study, the level of macrophage inflammatory protein 2 (a mediator of lung neutrophil recruitment) was significantly decreased in diabetic compared with control mice [18]. The deficiency causes a delay in neutrophil recruitment in the lungs. Nevertheless, diabetic mice with a scalp bacterial infection had more than two-fold induction of genes that directly or indirectly induce apoptosis compared with controls [19]. Hence, blocking apoptosis allows for a significant improvement in wound healing and bone growth.

Another suggestion is that hyperglycemia impairs opsonophagocytosis by diverting nicotinamide adenine dinucleotide phosphate from superoxide production into the aldose reductase-dependent polyol pathway [20].

Antibodies

The biological function of the antibodies may be harmed by the glycation of immunoglobulin that increases the HbA1c in diabetic patients. However, it was also seen that the antibodies' response after vaccination and to common infections is normal in these patients [7].

Vascular insufficiency

Patients with diabetes mellitus commonly develop vascular disease. The mechanisms by which vascular insufficiency increases the risk of infection include local tissue ischemia that in turn enhances the growth of microaerophilic and anaerobic organisms. Simultaneously, this lead to depression of the oxygen-dependent bactericidal functions of leukocytes. In addition, vascular disease related to diabetes may impair the local inflammatory response and the absorption of antibiotics.

Sensory peripheral and autonomic neuropathy

Peripheral neuropathy is a common complication of diabetes mellitus. Minor local trauma associated with peripheral neuropathy may result in skin ulcers that in turn lead to diabetic foot infections. The condition is complicated by the fact that skin lesions in such patients are often either unnoticed or ignored until infection occurs. Autonomic neuropathy in diabetic patient may lead to urinary retention and stasis. This predispose these patient to urinary tract infections.

Increased skin and mucosal colonization

Some data suggest that patients with diabetes, especially dependent on daily insulin, often have asymptomatic nasal and skin colonization with bacteria as *S. aureus*. Furthermore, analysis of National Health and Nutrition Examination Survey (NHANES) data demonstrate that diabetic patients colonized with *S. aureus* are more likely to have a methicillin-resistant *S. aureus* isolate than a susceptible one; the odds ratio was 2.6 (95% CI 1.1-6.1) [21]. Colonization with *S. aureus* could predispose in turn to cutaneous or incisional staphylococcal infections as well as transient bacteremia; the latter may lead to infection at distant sites. Additionally, DM patients have commonly mucosal colonization with *Candida albicans*. Poor glycemic control in women with diabetes increases the risk of vulvovaginal candidiasis than control women [22]. In particular, women with type 2 diabetes appear more prone to non-albicans *Candida species* [23].

Organism-specific factors

There are several organism-specific factors that predispose diabetics to infection. Glucose-inducible proteins promote adhesion of *Candida albicans* to buccal or vaginal epithelium. This adhesion is believed to impair phagocytosis, increasing the virulence of the organisms [24]. Ketone reductases associated with diabetes mellitus increase the risk of mucormycosis caused by *Rhizopus* species. The mechanism is based on the fact that these organisms thrive in high glucose; this conditions are typically present in diabetic patients with diabetic ketoacidosis [25].

Diabetic patients are also at increased risk of acquiring melioidosis in endemic areas. Nevertheless, DM is considered the single most common risk factor in patients who develop this infection. One of multiple explanations for this tendency is that macrophages, which are the main defense mechanism against the incriminated *Burkholderia pseudomallei*, are impaired in diabetic patients [26]. Glyburide treatment has shown to be associated with reduced mortality in patients with melioidosis through reduces bacterial dissemination of *B. pseudomallei* in an experimental mouse model [27].

Uropathogenic Escherichia coli have a specific contribution in morbidity of diabetic patients. Advanced glycation end products (AGEs) accumulate in these patients over time. In animal study, AGEs facilitate the binding of *Escherichia coli* isolates to the bladder urothelium, which is believed to elucidate the higher susceptibility of patients with DM to lower urinary tract infections with this organism [28].

Common infections associated with diabetes mellitus

Literature has shown that infectious diseases are seen higher in individuals with diabetes as opposed to individuals without [2,7].

Respiratory tract infections

Common infections are associated with Streptococcus pneumoniae and influenza virus. Anti pneumococcal and influenza vaccination have been recommended for DM patients by the American Diabetes Association (ADA) and the Centers for Disease Control and Prevention (CDC). The WHO has recommended a single-dose vaccine to reduce the mortality and morbidity against the H1N1 virus. Tuberculosis is

also seen higher in diabetic patients, and they are more susceptible to develop multi-resistant tuberculosis, where treatment failures and mortality are more. The treatment for TB can complicate glycemic control as the medicines can increase the metabolism of oral antidiabetic drugs. Depression in the immune response where chemotaxis, phagocytosis, and antigen presentation in response to Mycobacterium tuberculosis infection is impaired in turn affecting the T-cell function and proliferation is seen in DM cases with tuberculosis, which can progress to symptomatic disease [1,9].

Urinary infections

Lack of adequate glycemic control, duration of DM, diabetic microangiopathy, impaired leukocyte function, recurrent vaginitis, and anatomical and functional abnormalities of the urinary tract can increase the risk of UTI in DM. Asymptomatic bacteriuria in DM can progress to pyelonephritis in certain cases [2].

Acute pyelonephritis has a prevalence of 4 - 5 times more in individuals with DM. Apart from Bilateral renal involvement, the clinical presentation is similar to that in non-diabetic patients [7].

Perinephric and/or renal abscesses, emphysematous pyelonephritis (EP) and renal papillary necrosis are the additional complications that DM patients have a risk for [2,7].

Skin and soft tissue infections

Folliculitis, furunculosis and subcutaneous abscesses are common skin and soft tissue infections seen in DM individuals. These infections can occur during the course of the disease or could be the first sign of it [7]. Infections on foot are a common chronic complication of DM, which can further lead to amputation, osteomyelitis, or death. the clinical signs appear late due to which delay in diagnosis is seen [2].

Three distinct stages of foot infection are:

- Localized infection (infection in the ulcer bed with or without purulent discharge and surrounding erythema).
- Spreading infection (Apart from the local signs of infection spreading erythema, edema, lymphangitis, and lymphadenitis will be seen).
- Severe infection (Ulcers with extensive soft tissue infection, bluish discoloration suggesting lack of oxygen leading to gangrene) [10].

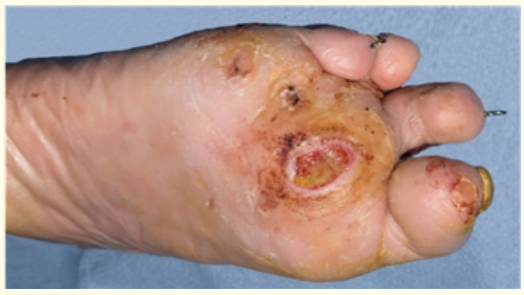

Figure 2: *Infection in ulcer bed with mild surrounding erythema [10].*

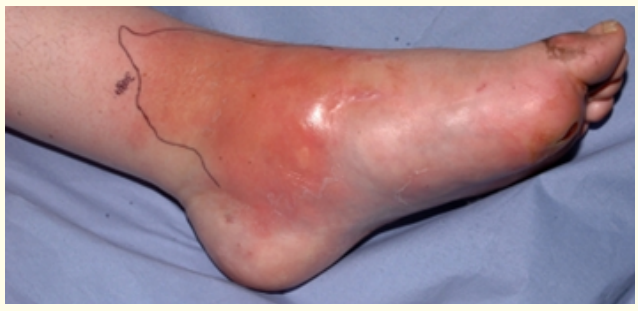

Figure 3: *Total confirmed COVID-19 cases in Feb 20-2020 [19].*

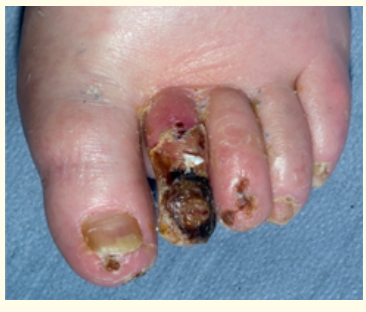

Figure 4: *Infective necrosis of second toe [10].*

Necrotizing fasciitis, which is the fast and progressive necrosis of the fascia and subcutaneous tissue and Fournier gangrene - fasciitis that is affecting the male genitalia, are also seen. Invasive external otitis and rhinocerebral mucormycosis are two of the serious head and neck infections seen in diabetic individuals. Periodontitis, a chronic inflammatory disease of the gums are four times more commonly seen in diabetic patients. It destroys the supporting structures of the teeth, which are the periodontal ligament and alveolar bone [11].

Gastrointestinal and liver infections

Gastrointestinal motility and sensitivity are important in defense against infections. Oral and esophageal candidiasis caused by *Candida albicans* is commonly seen due to the production of extracellular enzymes such as proteinase and phospholipase. Literature also shows DM individuals who have increased susceptibility to Gastritis caused by Helicobacter pylori and other infections by enteroviruses [2,11].

Conclusion

The prevalence of infectious diseases is commonly seen in individuals with DM. Increased virulence to certain pathogens seen in a hyperglycemic environment, polymorphonuclear leukocytes immobilization, decreased interleukin production to respond to an infection, dysmotility seen in the urinary and gastrointestinal tracts, decrease in the chemotactic and phagocytic activity are some of the key pathogenic mechanisms.

Infections like malignant external otitis, rhinocerebral mucormycosis, and gangrenous cholecystitis almost certainly affect only diabetic patients. Some infections can also cause major metabolic complications like hypoglycemia, diabetic ketoacidosis, and coma. Mandatory immunization with anti-pneumococcal and influenza vaccines is recommended because it can help reduce the respiratory infections, the frequency and time of hospitalizations, and the mortality related to respiratory infections.

Bibliography

1. American Diabetes Association. "Standards of medical care in diabetes-2016: summary of revisions". *Diabetes Care* 39.1 (2016): S4-S5.

2. Casqueiro J., *et al.* "Infections in patients with diabetes mellitus: A review of pathogenesis". *Indian Journal of Endocrinology and Metabolism* 16.1 (2012): S27.

3. Mishra M and Fomusi Ndisang J. "A critical and comprehensive insight on heme oxygenase and related products including carbon monoxide, bilirubin, biliverdin and ferritin in type-1 and type-2 diabetes". *Current Pharmaceutical Design* 20.9 (2014): 1370-1391.

4. Petersen M C., *et al.* "Regulation of hepatic glucose metabolism in health and disease". *Nature Reviews Endocrinology* 13.10 (2017): 572.

5. Ndisang J F., *et al.* "Insulin resistance, type 1 and type 2 diabetes, and related complications 2017". *Journal of Diabetes Research* (2017).

6. Abu-Ashour W., *et al.* "Diabetes and the occurrence of infection in primary care: a matched cohort study". *BMC Infectious Diseases* 18 (20018): 67.

7. Carey IM., *et al.* "Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study". *Diabetes Care* 41 (2018): 513.

8. Bartelink ML., *et al.* "Infections in patients with type 2 diabetes in general practice". *Diabetes Research and Clinical Practice* 40 (1998): 15.

9. Martin ET., *et al.* "Diabetes and Risk of Surgical Site Infection: A Systematic Review and Meta-analysis". *Infection Control and Hospital Epidemiology* 37 (2016): 88.

10. Latham R., *et al.* "The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients". *Infection Control and Hospital Epidemiology* 22 (2001): 607.

11. Wiseman JT., *et al.* "Predictors of surgical site infection after hospital discharge in patients undergoing major vascular surgery". *Journal of Vascular Surgery* 62 (2015): 1023.

12. Furnary AP., *et al.* "Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures". *The Annals of Thoracic Surgery* 67 (1999): 352.

13. Boreland L., *et al.* "The effectiveness of tight glycemic control on decreasing surgical site infections and readmission rates in adult patients with diabetes undergoing cardiac surgery: A systematic review". *Heart Lung* (2015): 4.

14. Haug JB., *et al.* "Bloodstream infections at a Norwegian university hospital, 1974-1979 and 1988-1989: changing etiology, clinical features, and outcome". *Clinical Infectious Diseases* 19 (1994): 246.

15. Geerlings SE and Hoepelman AI. "Immune dysfunction in patients with diabetes mellitus (DM)". *FEMS Immunology and Medical Microbiology* 26.3-4 (1999): 259-265.

16. Peleg AY., *et al.* "Common infections in diabetes: pathogenesis, management and relationship to glycaemic control". *Diabetes/Metabolism Research and Reviews* 23.1 (2007): 3-13.

17. Price CL., *et al.* "Methylglyoxal modulates immune responses: relevance to diabetes". *Journal of Cellular and Molecular Medicine* 14.6b (2010): 1806-1815.

18. Amano H., *et al.* "Impairment of endotoxin-induced macrophage inflammatory protein 2 gene expression in alveolar macrophages in streptozotocin-induced diabetes in mice". *Infection and Immunity* 68 (2000): 2925.

19. Al-Mashat HA., *et al.* "Diabetes enhances mRNA levels of proapoptotic genes and caspase activity, which contribute to impaired healing". *Diabetes* 55 (2006): 487.

20. Mazade MA and Edwards MS. "Impairment of type III group B Streptococcus-stimulated superoxide production and opsonophagocytosis by neutrophils in diabetes". *Molecular Genetics and Metabolism* 73 (2001): 259.

21. Graham PL., *et al.* "A U.S. population-based survey of Staphylococcus aureus colonization". *Annals of Internal Medicine* 144 (2006): 318.

22. Donders GG. "Lower Genital Tract Infections in Diabetic Women". *Current Infectious Disease Reports* 4 (2002): 536.

23. Ray D., *et al.* "Prevalence of Candida glabrata and its response to boric acid vaginal suppositories in comparison with oral fluconazole in patients with diabetes and vulvovaginal candidiasis". *Diabetes Care* 30 (2007): 312.

24. Hostetter MK. "Handicaps to host defense. Effects of hyperglycemia on C3 and Candida albicans". *Diabetes* 39 (1990): 271.

25. Ferguson BJ. "Mucormycosis of the nose and paranasal sinuses". *Otolaryngologic Clinics of North America* 33 (2000): 349.

26. Hodgson KA., *et al.* "Altered macrophage function is associated with severe Burkholderia pseudomallei infection in a murine model of type 2 diabetes". *Microbes Infect* 13 (2011): 1177.

27. Wiersinga WJ., *et al.* "Melioidosis". *The New England Journal of Medicine* 367 (2012): 1035.

28. Ozer A., *et al.* "Advanced glycation end products facilitate bacterial adherence in urinary tract infection in diabetic mice". *Pathogens and Disease* (2015): 73.

29. Restrepo BI., *et al.* "Cross-sectional assessment reveals high diabetes prevalence among newly-diagnosed tuberculosis cases". *Bulletin of the World Health Organization* 89 (2011): 352-359.

30. Edmonds M. "The treatment of diabetic foot infections: focus on ertapenem". *Vascular Health and Risk Management* 5 (2009): 949.

31. Preshaw PM., *et al.* "Periodontitis and diabetes: a two-way relationship". *Diabetologia* 55.1 (2012): 21-31.

32. El-Zayadi A and Anis M. "Hepatitis C virus induced insulin resistance impairs response to anti-viral therapy". *World Journal of Gastroenterology* 18 (2012): 212-224.

33. Stanley TL and Grinspoon SK. "GH/GHRH axis in HIV lipodystrophy". *Pituitary* 12 (2009): 143-152.

34. Dube MP. "Disorders of glucose metabolism in patients infected with human immunodeficiency virus". *Clinical Infectious Diseases* 31 (2000): 1467-1475.

35. Brown TT., *et al.* "Anitretroviral therapy and the prevalence and incidence of diabetes in a multicenter AIDS Cohort study". *Archives of Internal Medicine* 165 (2005): 1179-1184.

36. Hertel J., *et al.* "A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity". *Journal of Biological Chemistry* 279 (2004): 55147-55152.

37. Lee GA., *et al.* "The effects of HIV protease inhibitors on carbohydrate and lipid metabolism". *Current Infectious Disease Reports* 6 (2004): 471-482.

38. Woerle HJ., *et al.* "Mechanisms for the deterioration in glucose tolerance associated with HIV protease inhibitor regimens". *Diabetes* 52 (2003): 918-925.

39. Fleishman A., *et al.* "Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults". *The American Journal of Physiology-Endocrinology and Metabolism* 292 (2007): E1666-E1673.

Volume 16 Issue 10 October 2020