Diabetes and Infections: Which is the Fuel?

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1 Introduction

There is a strong relationship between diabetes (DM) and infection. Infections can elicit diabetes or make glycaemic control difficult. On the other hand; experimental models viruses appear capable of both accelerating as well as decelerating the immunological processes leading to type 1 diabetes (T1 DM). Many infections are more common in diabetic patients with increased severity and complications. In this chapter we will discuss some of the infections that can trigger development of DM as well as the commonly encountered infections that a diabetic patient may have.

2 Diabetogenic Infections

Infection is a common trigger for many inflammatory diseases including but not only; rheumatoid arthritis, heart attacks, late-onset asthma, and Crohn's disease. Diabetes also is due to an aberrant overactive immune system exactly like the previously mentioned inflammatory diseases. Autoimmunity plays an important role in development of all types of diabetes. Type 1 diabetes is classified as either autoimmune (immune mediated or T1 DM A) or idiopathic (T1 DM B). The autoimmune type is due to a chronic autoimmune selective destruction of the pancreatic islet beta cells that leads to a marked insulin deficiency. Islet autoimmunity was also observed in adult phenotypic type 2 diabetes (T2 DM) patients. Numerous recent publications note a significant proportion of physician-diagnosed T2 DM in youth with evidence of pancreatic autoimmunity. This clinical phenomenon of antibody positivity in phenotypic T2 DM in youth, is referred to as "type 1.5 diabetes" (T1.5 DM), "double diabetes," "latent autoimmune diabetes in youth" (LADY), or "hybrid diabetes" (Badaru & Pihoker, 2012). This autoimmune-mediated DM is controlled by multiple susceptibility genes that can be modulated by various environmental factors. The role of previous viral infection to the development of T1 DM in humans is controversial. The link between T1 DM and viral infection was first noted from the epidemiological studies. Many viruses have also been shown to affect the development of DM in laboratory animals. Viruses have been appeal to explain the increasing prevalence of DM, seasonal variation in onset, and enhanced susceptibility of transplant populations (Tirabassi et al., 2010). Infections (especially viruses) in presence of genetic associations; may trigger the autoimmune disease process leading to DM or accelerate the already initiated disease process.

The infection can induce diabetes by different mechanisms (shown in Figure 1) including:

- Direct destruction of beta cells (e.g. parotitic pancreatitis).
- Molecular mimicry: microbial antigens share homologies with host antigens (e.g. Cytomegalovirus and Epstein-Barr virus).
- Increased processing and presentation of autoantigens during infection or epitope spreading which make the beta cells a target of the immune system and enhances autoimmunity.
- Increasing inflammation and the secretion of inflammatory cells such as cytokines.
- Increase insulin requirement during infection
- Increase insulin resistance.
Figure 1 showed the mechanisms of infection induced diabetes. (1- virus, 2- Antigen presenting cell, 3- T cell receptor, 4- Activation of T cell, 5- Activated CD4+ T cell, 6- Self peptides (B-cell), 7- Pancreatic β-cells, 8- Direct viral destruction of beta cells, 9- Defective Insulin secretion, 10- β-cell autoantigens and molecular mimicry, 11- Insulin receptors, 12- Insulin resistance).

2.1 Viral Infections

2.1.1 Enteroviruses

Enteroviruses are a genus of Picornaviridae family of viruses and are associated with several human and mammalian diseases. There are over 70 serotypes of enterovirus have been isolated from man and they are originally classified into five groups; polioviruses, Coxsackie A viruses (CA A1-A24), Coxsackie B viruses (CB B1-B6), echoviruses and, enterovirus. Most of the enterovirus infections are symptomatic, especially in young children, but when they do cause clinically overt disease, they can cause a wide range of disorders and can involve many of the body systems. Enteroviruses infections are one of the main environmental triggers of T1 DM and they are one of the most well studied environmental factors in relation to T1 DM sero-epidemiology, histopathology, animal studies, and in vitro experiments. Gamble et al were the first to report the possible link between T1 DM and enteroviral infection (Gamble et al., 1969).
Higher rates of enterovirus infection (particularly with coxsackievirus B-4), defined by detection of enterovirus IgM, IgG, or both, viral RNA with reverse transcription polymerase chain reaction (RT PCR), and viral capsid protein, have been found in patients with DM at diagnosis compared with controls. Prospective studies have also shown more enterovirus infections in children who developed islet autoantibodies, subsequent DM, or both; as well as a temporal relation between infection and autoimmunity. The relation between enterovirus infection and DM is not consistent across all studies, and the subject remains controversial. Furthermore, in animal models viral infections might also protect from DM. A systematic review of coxsackie B virus serological studies did not show an association with T1 DM. Yeung et al showed an association between T1 DM and enterovirus infection, with a more than 9 times the risk of infection in cases of DM and three times the risk in children with autoimmunity. However, causal relation between infection and T1 DM was not possible to determine (Yeung et al., 2011). Stene et al showed that approximately 8% of the children progressing to T1 DM had enteroviral RNA in their serum few months prior to diagnosis. They found that the presence of enterovirus RNA in serum to be a highly significant predictor of progression to clinical T1 DM. The enterovirus infection may be one of many factors that can accelerate progression to DM, e.g., through nonspecific activation of autoreactive T-cells. Also enterovirus viral infection may be able to induce insulin resistance sufficient to precipitate clinically overt DM. The most frequently implicated serotype, was coxsackievirus B4 which is responsible for 2.4% of the enterovirus infectious episodes. However, there may be differences within serotypes because enteroviruses are known to mutate rapidly (Stene et al., 2010).

Enterovirus infection may cause β-cell damage and release of β-cell antigens taken up by antigen-presenting cells; activate the innate immune system; enhance the secretion of interferon-α, and perhaps up regulate the major histocompatibility complex molecules on β-cells. The “fertile field hypothesis” proposes that different viruses may increase the risk of DM in susceptible time windows after an infection, while outside this window a similar viral infection would be resolved with no further consequences for the host (Von Herrath M 2009). Enterovirus infections are more frequent during the 6-month period preceding the appearance of the first diabetes-associated autoantibodies. Enteroviral infection may also be implicated in the pathogenesis of fulminant T1 DM which results from accelerated β-cell failure and is characterized by the rapid onset of severe hyperglycemia and ketoacidosis, with subsequent poor prognosis. In such case; enterovirus initiates co-expression of interferon-γ and CXCL10 in β-cell. CXCL10 secreted from β-cell activates and attracts autoreactive T-cells and macrophages to the islets via CXCR3. These infiltrating autoreactive T-cells and macrophages release inflammatory cytokines including interferon-γ in the islets, not only damaging β-cell but also accelerating CXCL10 generation in residual β-cell and thus further activating cell-mediated autoimmunity until all β-cells have been destroyed (Tanaka et al., 2009).

Coxsackie B 4 virus (CVB4) is the most common enteroviral strain observed in pre-diabetic and diabetic individuals. RNA of CVB could be detected in blood from patients at the onset or during the course of T1 DM with enhancement of the cellular immune response directed against CVB antigens in patients with T1 DM after the onset of the disease. The evidence of the CVB4 in development of T1 DM is supported by isolation of one CVB4 strain from the pancreas of a deceased diabetic child; CVB4 strain obtained from diabetic rats are able to induce diabetes after inoculation in another mice; detection of CVB4 antigens in pancreatic tissue specimens from T1 DM patients; and the ability of enterovirus isolates obtained from newly diagnosed T1 DM patients to infect and induce destruction of human islet cells in vitro (Elshebani et al., 2007). CVB4 infection of islet cells induces strong inflammation mediated by natural killer (NK) cells within the islets with possible cytolysis of β-cells and release of autoantigens
which activate strong immune responses. Poliovirus is one of the enteroviruses that are able to directly infect of β-cells through targeting β-cells via surface molecules such as the poliovirus receptor and integrin αvβ3. Infections by viruses that target β-cells and promote strong inflammation within the islets may thus represent the initial step in the induction of autoimmunity (Filippi & von Herrath 2008). Elevated IgA antibodies to enterovirus were observed in some patients with fulminant T1 DM which may indicate that recurrent enterovirus infection may be a triggering role in development of fulminant T1 DM. Maternal enterovirus infections during pregnancy may increase the risk of offspring developing T1 DM during childhood. Boys of enterovirus IgM-positive mothers have approximately 5 times greater risk of developing DM as compared to boys of IgM-negative mothers. This observation suggests that gestational enterovirus infections may be related to the risk of offspring developing T1 DM in adolescence and young adulthood. Diabetes was also observed in some cases as early as 3 years of age and a case of neonatal DM with evidence of maternal enterovirus infection during pregnancy were also been reported. Maternal enterovirus infection is a significant risk factor for the development of DM in boys, but not in girls. This finding suggests that boys may be more susceptible to the diabetogenic effect of enteroviruses than girls during the prenatal period. Boys might be more susceptible to enterovirus infections, possibly due to the weaker immune system (Elfving et al., 2008). T1 DM associated HLA-DR alleles (DR3 and DR4) have been associated with a stronger humoral response to enterovirus antigens compared to HLADR2. (Sadeharju et al., 2003)

2.1.2 Congenital Rubella

Rubella virus has been thought to cause T1 DM, but it was conclusively associated with congenital rubella syndrome. Rubella virus has the ability to multiply in the pancreas in susceptible population. Experimental congenital rubella infection in rabbits caused histological changes in the beta-cells of the pancreatic islets similar to those found in mice made diabetic by the M variant of the encephalomyocarditis virus (Menser et al., 1978). Congenital rubella syndrome (CRS) increased the risk of DM in the second and third decades of life indicating the possibility of an extensive time lag with an increased incidence of insulin-dependent DM (IDDM) in patients with CRS. Patients with CRS are at increased risk for IDDM if they have the same genetic and immunologic features seen in classic IDDM, namely the presence of HLA DR3 and the absence of HLA DR2 and if they have high prevalence of islet cell cytotoxic or surface antibodies (ICSA). This also may indicate that the genes controlling the susceptibility to T1 DM are necessary for the development of glucose intolerance in CRS patients (Ginsberg-Fellner et al., 1985).

2.1.3 Mumps

Mumps virus is a paramyxovirus which has affinity for the pancreatic cells. The development of DM as a sequel of mumps pancreatitis has been reported in the literature since many decades (Harris, 1899). In most cases, symptoms of DM developed within 1-8 weeks after an infection. Several reports have discussed the relationship between mumps infection and the onset of autoimmune T1 DM with both clinical and epidemiological evidences showed the close relation between apparent or in-apparent mumps infection and DM. In vitro studies have suggested that cytokines released by mumps virus-infected beta cells may lead to an immune response against the beta cells which eventually leading to complete loss of beta cell function. The findings could suggest the presence of an association between fulminant T1 DM and mumps virus infection (Goto et al., 2008). Genetic factors may also contribute to the development of fulminant T1 DM. Imagawa et al. reported that DR4-DQ4 haplotype is frequent in fulminant T1 DM (Imagawa et al., 2005).
2.1.4 Rotavirus

Rotaviruses is dsRNA Reoviridae; responsible for a significant number of childhood gastroenteritis. It has been implicated as one of the viral triggers of diabetes-associated autoimmunity. The reason for this implication was because of demonstration of sequence analogies between T-cell epitopes within the islet antigens GAD 65 (56 kDa isofrom of glutamic acid decarboxylase) and IA-2 (islet antigen-2) and rotavirus protein, suggesting potential cross-reactivity mechanisms. Rotavirus was also able to grow in monkey pancreatic islets in vitro. Honeyman et al reported that DM associated autoantibodies appeared in their study children concomitantly with a rise in rotavirus IgG antibody titre. Rotavirus also can change the permeability and cytokine balance in the intestinal mucosa, and may thereby enhance autoimmunity. Rotavirus gastroenteritis can initiate cytokines induced severe epithelial dysfunction that commonly associates with the disease. While the cytokine IFN-γ affects the permeability at tight junctions in the mucosa, TNF-α and IFN-γ, produced excessively during a rotavirus infection, are directly toxic to, e.g. human colonic epithelial cells (Honeyman et al., 2000). On the other hand, Blomqvist et al and Makela et al could not provide any evidence supporting an association between rotavirus infections and T1 DM or the presence of T1 DM-associated autoantibodies in young children. They failed to support the hypothesis that rotaviruses are important triggers of β-cell autoimmunity in young children at increased genetic risk for T1 DM (Blomqvist et al., 2005 and Makela et al., 2006). Therefore, it can be concluded that the role of rotavirus in the aetiology of T1 DM is unconfirmed (Coppiters et al., 2012).

2.1.5 Measles

Measles virus is one member of paramyxoviridae family. Measles infections generally occur in childhood, but infections in adolescence and adulthood can lead to major complications. Type 1 diabetes is among the various systemic disorders which have been associated with measles, with varying strengths of association. The Swedish Childhood DM Study showed significantly higher rate of T1 DM in children who developed DM among those not vaccinated against measles. The study hypothesized that measles vaccine could have a protective effect, and measles infection could have a diabetogenic effect (Blom et al., 1991). Onal et al described a previously healthy 28 years old woman who developed T1 DM complicated with ketoacidosis following measles virus infection. Serological tests revealed significant elevation of the measles IgM and IgG titers (Onal et al., 2012). However, a study done by Ramondetti et al showed that there was no statistical significance between the incidence of measles cases and DM rates which make the association between measles and T1 DM to be unclear (Ramondetti et al., 2012).

2.1.6 Cytomegalovirus

Cytomegalovirus (CMV) is a member of the Herpesviridae family which commonly infect humans of all ages and reaches most of the population. It has a unique capacity to remain latent in tissues after recovery of the host from an acute infection. Infection with cytomegalovirus is one of the environmental factors implicated in the development of T1 DM, although the association remains unproven. Some clinical studies relate human CMV to the development of T1 DM in humans. The CMV specific viral genome was found in 22% of diabetic patients, correlating with the presence of islet cell autoantibodies in their serum. Molecular mimicry could be involved in CMV-induced diabetes by inducing islet cell autoantibodies. In addition, a CD4 T cell clone reactive to GAD65 is able to cross-reacts with a peptide of human CMV major DNA-binding protein (Alba et al., 2005). Pak et al showed strong correlation between CMV genome and islet cell autoantibodies detected in diabetic patients suggests that persistent CMV infections
may be relevant to pathogenesis in some cases of T1 DM (Pak et al., 1988). The study done by Hjelmesæth et al., supported the hypothesis that asymptomatic CMV infection is associated with increased risk of new-onset post-transplant DM, and suggests that impaired insulin release may involve one pathogenetic mechanism (Hjelmesæth et al., 2004). The same findings were supported by the study of Zanone et al which showed that the association of T1 DM to cytomegalovirus infection and linked the increased risk of new onset post-transplantation DM to the associated CMV infection (Zanone et al., 2010). On the other hand; Aarnisalo et al observed no association between perinatal CMV infection and progression to T1 DM. They showed that perinatal CMV infections are not associated with early serological signs of β-cell autoimmunity or progression to T1 DM in children with diabetes risk-associated HLA genotype (Aarnisalo et al., 2008).

2.1.7 Influenza B

Influenza B virus is a member of Orthomyxoviridae family and is one of the viruses implicated in pathogenesis of fulminant T1 DM especially for class II HLA. A number of case reports described occurrence of fulminant T1 DM after infection with Influenza B virus. Sano et al described a 64 years old Japanese man who developed fulminant T1 DM following infection with influenza B virus (Sano et al., 2008). Feng et al. also reported development of fulminant T1 DM in a 45-year-old Chinese woman who was heterozygous for HLA-DR7-DQ2 and HLA-DR9-DQ9. Yasuda et al., reported occurrence of fulminant T1 DM with thrombocytopenia after influenza vaccination in a 54 years old man with HLA genotypes consistent with susceptibility to fulminant T1 DM. However, lack of well organized studies makes the role of Influenza B virus in development of fulminant T1 DM still unproven.

2.1.8 Epstein-Barr Virus

Epstein-Bar virus (EBV) is a member of the Herpesviridae family. It has been implicated in the aetiology of autoimmune diseases including autoimmune diabetes. A temporal link between EBV infection and the onset of T1 DM has been reported in a rare number of cases but without a strong association between EBV infection and development of T1 DM. However, some evidence suggests that EBV could trigger T1 DM by a mechanism of molecular mimicry. An 11 amino acid sequence in the Asp-57 region of the HLA-DQw8 beta chain is repeated 6 times in the EBV-BRF4-encoded epitope (Alba et al., 2005). Some individuals who carry this sequence (GPPAA) in their HLA-DQ molecule present antibody reactivity to this epitope in EBV. As reported by Parkkonen F et al; two out of seven individuals who had acute EBV infection produced antibodies against an EBV-derived peptide (GPPAAGPPAAGPPAA). These two cases also contracted T1 DM immediately after the infection. This phenomenon may have potential importance in EBV-induced abnormalities, although cross-reactivity against DQ molecules could not be demonstrated in this study (Parkkonen et al., 1994). Further investigation is needed to confirm a relationship between EBV and T1 DM.

2.1.9 Hepatitis C Virus (HCV)

HCV is a member of Flaviviridae family. Several studies from different parts of the world have reported that HCV infection may contribute to the development of DM, and higher prevalence of T2 DM has been observed in patients with HCV infection than in those with other forms of chronic hepatitis. Allison et al. were the first to link viral hepatitis C to DM in 1994. They did a retrospective study included 100 cirrhotic patients listed for transplantation. They reported that the prevalence of T2 DM was higher in patients
with HCV-associated cirrhosis than in cirrhotics with other underlying liver diseases (Allison et al., 1994). HCV infection is more closely related to DM than HBV infection. In a study done by Rouabhia et al.; there was a higher prevalence of DM in patients with HCV infection (39.1%) than in those with HBV infection (5%), and DM occurred at an early stage of hepatic disease. However, other factors such as metabolic syndrome, family history of DM and increased transaminases seem also to be important risk factors for the development of DM (Rouabhia et al., 2010). Mehta et al found an increased prevalence of T2 DM among persons with HCV infection who were at least 40 years of age (Mehta et al., 2000). The mechanisms by which HCV induces increased insulin resistance and the risk for development of DM has not been completely understood. Liver fibrosis progression has long been considered responsible for the appearance of insulin resistance and T2 DM in patients with chronic liver diseases. The mechanism through which HCV is associated with insulin resistance involves interference with insulin signalling, direct viral effects, pro-inflammatory cytokines, and suppressors of cytokine signalling. Excessive tumor necrosis factor alpha (TNF-α) released in HCV-infected patient’s response may mediate the induction of insulin resistance. Other potential mechanisms that have been proposed include the development of insulin resistance as a consequence of elevated iron stores or fatty liver disease, both of which are associated with HCV infection. However, other studies showed that HCV infection was only associated with abnormal glucose tolerance (either impaired glucose tolerance (IGT) or frank DM) in obese participants (Howard et al., 2007).

2.1.10 Hepatitis B (HBV)

HBV is one of the hepadanviridae family. There is a lower risk of DM in HBV infection which could be explained by two factors: (1) HBV infection has been controlled in most developed countries, with active HBV vaccination programme; the occurrence of chronic HBV and its complications in these countries is very low; and (2) The disease progression is rather fast in HBV infection and therefore very few patients reach the level of cirrhosis and thus DM frequency is lower in this population (Naing et al., 2012).

2.1.11 Human Immune Deficiency Virus (HIV)

HIV is one of the Retroviridae family. The association between HIV infection and DM is poorly understood and complicated by the differential prevalence of risk factors for DM in HIV infected persons compared with HIV uninfected persons. While HIV infection itself is not associated with increased risk of DM, increasing age, HCV co-infection and body mass index (BMI) have a more profound effect upon the risk of DM among HIV infected persons. Further, long term anti-retroviral (ARV) treatment also increases risk (Butt et al., 2009).

2.1.12 Possible Role of Other Viruses

Many other viruses had some circumstantial evidences of their role in development of DM like hepatitis A virus, varicella zoster virus, and polio virus. However, scientific evidence still needed to prove this relationship. There are also many other viruses that can induce DM in animals like Kilham rat virus, Bovine viral diarrhoea-mucosal disease virus, Encephalomyocarditis virus, Mengovirus, Mouse hepatitis virus, Lactate dehydrogenase virus and Ljungan virus. These viruses are usually used to induce experimental diabetes.
2.2 Bacterial Infections

2.2.1 Helicobacter Pylori (H. pylori)

*H. pylori* is a gram-negative, spiral-shaped pathogenic bacterium that colonizes in the gastric mucosa and causes chronic gastritis, peptic ulcer disease, and/or gastric malignancies with a prevalence rate of about 30% in developed and up to 80% in developing countries. *H. pylori* infection has been positively related to DM prevalence in many studies (Lutsey *et al.*, 2009). *H. pylori* infection may cause dyslipidemia, because of the elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-c), lipoprotein Lp(a), apolipoprotein apo-B, triglyceride concentrations and decreased levels of high-density lipoprotein cholesterol (HDL-C) and apolipoprotein apoA-1 concentration in the blood. In addition, plasma levels of cholesterol and LDL-c were significantly higher in *H. pylori* positive patients with ischemic stroke compared to *H. pylori* positive patients (Scharnagl *et al.*, 2004; and Kamada *et al.*, 2005). This change in lipid profile toward an atherogenic direction is due to the action of pro-inflammatory cytokines, such as IL-1 and IL-6, INF-α, and TNF-α. *H. pylori* infection can promote platelet activation and aggregation and increase various proatherogenic factors including homocysteine, which is a risk factor for T2 DM, obesity, and CVD. It also can increase reactive oxygen free radicals and increases circulating concentrations of lipid peroxides, also associated with DM and CVD. Finally, *H. pylori* infection influences the apoptosis. This may play an important role in development of metabolic syndrome, and insulin resistance; suggesting a possible mechanistic relationship between *H. pylori* and DM (Polyzos *et al.*, 2011). Jeon *et al.* demonstrated in a prospective cohort study that *H. pylori* infection leads to an increased rate of incident DM. They found that the seropositive for *H. pylori* at enrollment were 2.7 times more likely at any given time to develop DM than seronegative individual (Jeon *et al.*, 2012). However a previous study by Xia *et al.* showed that *H. pylori* infection appears not to be associated with DM or upper gastrointestinal symptoms in DM (Xia *et al.*, 2005). However; there is a great need for further studies on the potential causative role of *H. pylori* on DM that could be used to inform effective prevention strategies for DM.

2.2.2 Other Bacteria

The role of other bacteria in pathogenesis of DM is controversial. Bacterial meningitis can induce hyperglycaemic blood glucose levels in majority of patients on admission. Hyperglycemia may be caused by the physical stress reaction, abnormal blood-glucose regulation mechanisms as a result of central nervous system insults, and preponderance of diabetics for pneumococcal meningitis. Patients with DM and bacterial meningitis are at high risk for unfavorable outcome (Schut *et al.*, 2009). Other bacterial infections like scarlet fever or typhoid fever were implicated in development of fulminant T1 DM but still need to be investigated.

3 Diabetes-preventing Infections

Despite that the viruses can be strong inducers of inflammation; the viral infections and other types of infectious diseases would actually prevent T1 DM. According to the “hygiene hypothesis”; viruses invoke immune mechanisms that help in elimination of auto aggressive T-cells attacking the β-cells, ultimately leading to their immediate but temporally limited amelioration. Instead of enhancing immune function and exerting effector functions such as killing of infected cells or inducing interferon production, the viral infection can turn immune responses off through distinct immunoregulatory mechanisms, in-
Involving both the innate and adaptive immune system, that protect against the development of T1 DM. Many of these mechanisms involve the secretion of immune modulatory cytokines such as IL-10, IL-4, or transforming growth factor (TGF)-β (Herrath, 2009). Invariant NKT cells (iNKT cells) are non-conventional T lymphocytes restricted by the CD1d molecule, which presents glycolipid antigens. Many studies have shown the protective role of iNKT cells against the development of autoimmune diseases, including T1 DM. Although iNKT cells inhibit autoimmune responses, they also promote immune responses against viruses. When stimulated; the iNKT cells promptly secrete copious amounts of various cytokines, and they can provide activation/maturation signals to other immune cells such as DCs, NK cells, T cells, and B cells. With certain viral infections; these cells also can promote plasmacytoid DC (pDC) function locally in the pancreatic islets, leading to enhanced type-I IFN production and low viral burden (Nishio et al., 2010 and Diana et al., 2009). So that restoration of efficient regulatory T cell (T reg cell) populations is therefore a promising therapeutic approach to prevent and even cure disease with the ultimate goal is to tackle the disease at its root, to eliminate the cause for T1 DM (Nishio et al., 2010).

Infections with several pathogens such as lymphocytic choriomeningitis virus (LCMV), some enteroviruses, helminths or Salmonella have been shown to significantly decrease DM incidence. Most of the studies were performed in animal models because of the limited availability of relevant human samples in T1 DM research. Pierce et al showed that specific areas in some viral genomes can help to decrease the incidence of autoimmune DM. Autoimmune T1 DM is inhibited in non-obese diabetic (NOD) mice transgenically expressing all early region 3 (E3) genes of the adenovirus genome under control of a rat insulin promoter (RIPE3/NOD). Genes in E3 of the adenovirus genome allow the virus to evade host immune responses by interfering with MHC class I-mediated antigen presentation and TNF-α or Fas-induced apoptosis of infected cells. These findings indicate that all E3 genes must be expressed to inhibit the diabetogenic potential of NOD immune cells. They also demonstrate that the antiapoptotic E3 genes most effectively protect pancreatic β-cells from diabetogenic immune responses (Pierce et al; 2003). Filippi et al showed that viruses that do not inflict damage on β-cells provided protection from T1 DM by triggering immune-regulatory mechanisms. They showed that infection of pre-diabetic NOD mice with Coxsackie virus B3 or LCMV delayed DM onset and reduced disease incidence. This delay was due to transient up-regulation of programmed cell death-1 ligand 1 (PD-L1) on lymphoid cells, which prevented the expansion of diabetogenic CD8+ T cells expressing programmed cell death-1 (PD-1). Reduced T1 DM incidence was caused by increased numbers of invigorated CD4+CD25+ Tregs, which produced TGF-β and maintained long-term tolerance. Full protection from T1 DM resulted from synergy between PD-L1 and CD4+CD25+ Tregs (Filippi et al., 2009).

Not only the viral infection could prevent development of DM but also other microbes may have similar effects. Silva et al showed that immune-stimulation with Q fever complement-fixing antigen (QFA) can prevent the development of autoimmune DM. However, the mechanism whereby QFA protects against DM currently is not known (Silva et al., 2003). Infection, commencing across a wide age range, with a live, attenuated strain of Salmonella typhimurium, will halt the development of T1 DM in the NOD mice. Zaccone et al showed that infection of NOD mice with attenuated, but not killed, Salmonella typhimurium can reduce the incidence of T1 DM, even if infection occurs after the development of a peri-islet pancreatic infiltrate. Functional diabetogenic effector T cells were still present, as demonstrated by the initiation of DM in NOD-scid recipients of transferred splenocytes. High levels of IFN-γ were secreted by splenocytes of infected mice, but there was no evidence of involvement of IL-10 in the protective effect of the infection (Zaccone et al., 2004). The protective mechanism appears to involve the regulation of autoreactive T cells in a manner associated with long lasting changes in the innate immune com-
partment of these mice. The autoreactive T cells priming and trafficking were altered in mice that had been infected previously by *S. typhimurium*. These changes were associated with sustained alterations in patterns of chemokine expression. There was small numbers of dendritic cells from mice that had been previously infected with, but cleared all trace of a *S. Typhimurium*; which were able to prevent the development of DM in the highly synchronized and aggressive cyclophosphamide-induced model. The effects observed on autoreactive T cell trafficking were recapitulated by the immunomodulatory dendritic cell transfers in the cyclophosphamide model (Raine *et al.*, 2006). Ola *et al* showed that the intranasal treatment with the B-subunit of *Escherichia coli* heat labile enterotoxin (EtxB), a protein that binds GM1 ganglioside (as well as GD1b, asialo-GM1 and lactosylceramide with lower affinities), protected NOD mice from developing DM in a receptor-binding dependent manner. Protection was associated with a significant reduction in the number of macrophages, CD4(+) T cells, B cells, and major histocompatibility complex class II (+) cells infiltrating the islets (Ola *et al.*, 2006).

Infection with *Mycobacteria* or immunization of mice with *Mycobacteria*-containing adjuvant was able to prevent DM in NOD mice. Infection of NOD mice with *Mycobacterium avium*, done before the mice show overt DM, resulted in permanent protection of the animals from DM and this protective effect was associated with increased numbers of CD4(+) T cells and B220(+) B cells. The protective effect of *M. avium* infection against DM of NOD mice may be achieved by peripheral deletion of autoreactive T lymphocytes via Fas–FasL. The event may result from molecular mimicry between mycobacterial antigen and pancreatic autoantigens, leading to deletion of lymphocytes reactive to β-cells as a consequence of the immune response directed to *Mycobacteria*, or simply deletion of bystander autoreactive lymphocytes. The regulatory role of Fas up-regulation on activated lymphocytes could then be able to suppress unintended activation of autoreactive clones, thereby protecting against the initiation of the autoimmune aggression of the pancreatic islets of NOD mice (Martins & Aguas; 1999). Bergerot *et al* showed that oral intake of small amounts (2-20 µg) of human insulin conjugated to cholera toxin B subunit (CTB) can effectively suppress β-cell destruction and clinical DM in adult NOD mice. The protective effect could be transferred by T cells from CTB-insulin-treated animals and was associated with reduced lesions of insulitis. Furthermore, adoptive co-transfer experiments involving injection of Thy-1,2 recipients with diabeticogenic T cells from syngeneic mice and T cells from congenic Thy-1,1 mice fed with CTB-insulin demonstrated a selective recruitment of Thy-1,1 donor cells in the peripancreatic lymph nodes concomitant with reduced islet cell infiltration. These results suggest that protection against autoimmune DM can be achieved by feeding minute amounts of a pancreas islet cell autoantigen linked to CTB and appears to involve the selective migration and retention of protective T cells into lymphoid tissues draining the site of organ injury (Bergerot *et al*., 1997).

Helminth infestation can modulate the immune response. Intestinal nematode parasites can produce strong polarized Th2-type responses in mice. Helminth infection can enhance susceptibility to certain infectious diseases, like TB and viral hepatitis but also have protective effects in murine models of asthma, multiple sclerosis, and inflammatory bowel disease. Inoculation of NOD with *Trichinella spiralis*, *Heligmosomoides polygyrus*, or *Schistosoma mansoni* markedly reduced the rate of T1 DM and suppressed lymphoid infiltration in the islets. Injection of whole eggs or soluble antigens from the schistosome egg antigen or the schistosome worm antigen in NOD mice was able to prevent T1 DM. Qian *et al* showed that the *H. polygyrus* strongly reduced the spontaneous onset of DM in NOD mice when given as late as 12 weeks of age and even prevented the much more aggressive Cyp-induced T1 DM in NOD mice. *H. Polygyrus* induced Th2-type response markedly increases in IL-10, FoxP3+ Tregs, and AAMϕs (Liu *et al* 2009). Jiménez *et al* showed that *T. crassiceps* infection protects against Multiple Low Dose
Streptozotocin-Induced DM, independently of the genetic background of the host (Espinoza-Jiménez et al., 2010).

4 Effects of Diabetes on Infections

Individuals with DM can have any infection that affects the general population with more increased risk of mortality and morbidity of a variety of specific infectious complications than in normal population. This increased risk is due to both the effect of DM on the immune system as well as the higher prevalence of pre-existing chronic conditions, such as cardiovascular disease or chronic kidney disease (CKD). The immune abnormalities in DM are due to higher pro-inflammatory pro-coagulant, and anti-fibrinolytic activity, depression of the antioxidant system, and humoral immunity as well as higher expression of pathogen recognition cell-surface receptors. There are also defects in leukocyte function, especially migration, phagocytosis, intracellular killing, chemotaxis; and complement dysfunction due to decreased polymorph nuclear (PMN) membrane fluidity. These changes occur especially with poor glycemic control, and microvascular and macrovascular angiopathy which increase soft tissue and organ infections in diabetic patients. There is also a decrease in the antibacterial activity of urine, gastrointestinal and urinary dysmotility, and greater number of medical interventions in these patients. Peripheral sensory neuropathy may result in unawareness of lower extremity trauma and inadequate attention to minor wounds with increased incidence of infection. The higher mortality of infection in diabetic patients is also due to the increased risk of acute organ dysfunction due to higher chronic disease burden (Yende et al., 2010).

The infections affect all organs and systems. There is an increased frequency and severity of many infections among diabetic patients which include foot infections; rhinocerebral mucormycosis; cystitis; complicated urinary tract infections, including pyelonephritis; intrarenal abscesses; perinephric abscesses; pneumonia; lower-extremity soft tissue infection, including polymicrobial gangrene; emphysematous or gangrenous cholecystitis; and malignant otitis externa. There is also increased carrier state rate of *Staphylococcus aureus* among those patients which raises risk for infection with this organism. There are different risk factors which may act alone or in combination in favour of certain infections. Hyperglycemia is nearly a constant risk factor for most infections. Male sex is a risk factor for emphysematous cholecystitis caused by *Clostridium perfingens* while the female sex is a risk factor for urinary tract infection. Insulin injection is a risk factor for infections with *Staphylococcus aureus*. Angiopathy is a risk factor for polymicrobial soft tissue infection especially with *Streptococci, anaerobes*, and *gram-negative bacteria*. Age is very important risk factor for both pneumonia and emphysematous cholecystitis (Schaberg & Norwood; 2002).

4.1 Respiratory Tract Infections

4.1.1 Effects on Pneumonia

Pneumonia is a major cause of morbidity and mortality among diabetic patients with a higher risk of death following pneumonia than in non diabetics. About 20% of subjects with community acquired pneumonia (CAP) have DM with an increased incidence of pneumonia due to different pathogens in diabetic patients. There is an increase in *S. aureus* caused pneumonia secondary to nasal carriage, particularly among recently hospitalized diabetic patients. There is also increased incidence of pneumonia due to both *gram-negative* organisms and fungi among those patients. Diabetes was present in 69% of patients
with *Escherichia coli* pneumonia. The most frequent respiratory infections associated with DM are caused by *Streptococcus pneumoniae* and influenza virus. Despite that the incidence of pneumococcal infection was virtually identical in diabetic and non-diabetic subjects; however, the diabetic subjects are 15.8-25.6 times more likely to be hospitalized for pneumonia during the first 13 weeks of the influenza season. The relative risk of hospitalization for influenza is 5.7-6.2 times greater in diabetic than non-diabetic subjects. The severity of *Streptococcus pneumonia* and influenza was more aggressive in diabetic patients than that found in the general population. This increased rate of hospitalization may be due to the lower threshold for hospitalization for treatment of complicated pneumonia in diabetic subjects (Bouter *et al*., 1991). Pneumonia was a contributing factor in 25% of the fatal cases of diabetic ketoacidosis. *Klebsiella pneumonia* and *S. aureus* were the most frequent causes. The mortality due to pneumonia and influenza in diabetic patients who were diagnosed at age of 30 years was 1.7 times higher than for non-diabetic subjects. Younger-onset patients with DM (age <30 years) were 7.6 times more likely to die from these infections over an average follow-up period of 8.5 years (Wheat; 1980). The increase in mortality is not only due to an altered immune response, but may be due to worsening of pre-existing cardiovascular and kidney disease (Yende *et al*., 2010).

### 4.1.2 Tuberculosis (TB)

Diabetes is a high risk factor for infection with TB with higher risk for development of multi-resistant TB and that treatment failures and death in diabetic than in non diabetic patients. Tuberculosis developed most frequently in patients with poor glycaemic control. Diabetic patients who needed more than 40 units of insulin per day are twice as likely to develop TB as those using lower doses, thus linking severity of DM with risk of TB (Dooley & Chaisson; 2009). 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 American Thoracic Society includes patients with DM in their list of patients who are considered immunosuppressed enough to require isoniazid for a positive purified protein derivative (PPD). Diabetic TB has been described as an acute, exudative, rapidly caseating disease that progresses to a toxic downhill course. Patients with DM also present with more advanced disease and are more liable to have lower lobe disease. TB infection and treatment also might induce glucose intolerance and complicate the glycemic control i.e. rifampicin increasing the metabolism of oral antidiabetic drugs. Diabetic patients with positive tuberculin reactions who have never been treated should receive isoniazid and pyridoxine for 1 yr regardless of their age or radiographic findings due to potentially greater severity of TB in diabetic individuals (Dooley & Chaisson 2009; Ruslami *et al*., 2010; Wheat; 1980).

### 4.1.3 Influenza and H1N1

Influenza increases frequency of medical consultation, hospitalization, ICU admission, and risk of death in diabetic population. About 14-21% of the hospitalized patients due to influenza A (H1N1) are diabetics. Conversely, the risk of respiratory illness and of hospitalization within 14 days of a diagnosis of influenza in patients with DM may be reduced by oseltamivir.

### 4.2 Urinary Tract Infections

Urinary tract infections are among the more common infection in diabetic patients especially in women. There is higher incidence of urinary tract infections especially in upper tract in diabetic patients than in
non diabetics. Although the majority of urinary tract infections in diabetic patients are asymptomatic, DM also may lead to a predisposition to more severe infections. The most common organisms involved are *E. coli*, followed by other gram-negative bacteria. This increased incidence in DM is due to several predisposing factors. Diabetic neuropathy can cause neurogenic bladder and dysfunction which is probably the most important predisposing factor. The neurogenic bladder causes obstruction of normal urine flow. Obstruction of the lower urinary tract enhances the development of urinary tract infections especially pyelonephritis. Diabetes-associated angiopathy correlates with the increased incidence of urinary tract infection in diabetic patient. The glucosuria and the high concentrations of urinary glucose impair phagocytic function of polymorph nuclear leukocytes. Also the higher rate of urologic procedures and manipulation is also an important predisposing factor in some cases. The common renal infections in diabetic patients include pyelonephritis, renal carbuncles (intra-renal abscesses caused by hematogenous spread of *S. aureus*), renal corticomedullary abscesses, perinephric abscesses, and the rare but devastating emphysematous pyelonephritis. Nosocomial urinary tract infections are also more common in diabetic individuals.

Acute pyelonephritis was found to be four-to fivefold higher in diabetic than in non-diabetic individuals. A possible explanation for this increased rate may be reflected in the studies that show lower urinary tract obstruction. It is associated with risk of bacteraemia, long hospitalization, and mortality especially in elderly diabetics (Kofteridis et al., 2009). However, Rhee et al found that an older age and DM were not found to be independently associated with hospital admission in women with acute pyelonephritis (Rhee et al. 2011). The presence of small vessel disease superimposed on renal parenchymal infection may account for the high incidence of renal papillary necrosis in diabetic persons. Presence of bacteraemia indicates severe infection. Most infections are caused by *Escherichia coli* or *Proteus sp*. The clinical presentation is similar to that of non-diabetic individuals, except for the bilateral renal involvement. Additionally, persons with DM are at increased risk for complications such as perinephric and/or renal abscesses, emphysematous pyelonephritis, and renal papillary necrosis (Peleg et al., 2007).

Emphysematous pyelonephritis (EPN) is a severe necrotizing kidney infection characterized by gas production in or around the kidneys (in perinephric tissue). It is a rare and often life threatening condition that commonly occurs in diabetics and may require life-saving urgent nephrectomy. Over 70% of reported cases have occurred in diabetic patients. The enteric gram-negative bacilli such as *Escherichia coli* and *Enterobacter aerogenes* are the most frequent pathogens, followed by *Klebsiella sp.*, *Proteus sp.*, *Candida* and *Streptococcus* with *E. coli* accounting for 60%. Gas formation in EPN is due to pathogenic bacteria causing mixed acid fermentation in a hyperglycemic environment in tissues that are ischemic. This results in tissue destruction and encourages purulent infection and inhibition of removal of locally produced gas. Fever and flank pain are nearly always present, and a renal mass can be felt in 45% of cases. Crackles in the flank or thigh are less frequent. Abdominal radiographs frequently show mottled lucencies overlying the kidneys. Abdominal computerized tomography allows the identification of gas in the urinary tract. Survival is higher in patients managed with antibiotics plus surgery (67%) than with antibiotic therapy alone (30%). Surgery is recommended for patients who do not improve after a few days of antibiotic therapy (Laway et al., 2012).

Renal carbuncles (intrarenal abscesses) are caused by the hematogenous spread of *S. Aureus* while renal corticomedullary abscesses are intrarenal foci of infection associated with reflux and obstruction caused by the same organisms that typically cause pyelonephritis. Perinephric abscesses may be more common in diabetic patients. DM is present in about one-third of patients with perinephric abscesses. Perinephric abscesses are caused either by the rupture of intrarenal abscesses into tissue surrounding the kidney or by the hematogenous or lymphatic deposition of organisms into that tissue. *E. coli* or other organ-
isms are usually isolated, but a wide variety of organisms, such as *S. aureus*, *fungi*, *anaerobes*, and *mycobacteria*, have been reported. *Staphylococci* cause about 10% of cases. The onset typically is insidious. Symptoms have been present for more than 5 days in the majority of patients with perinephric abscesses compared with only about 10% of patients with pyelonephritis. It should be suspected in patients with urinary tract infections and an abdominal or flank mass or persistent fever after 4 days of antimicrobial therapy. Effective treatment requires surgical drainage of the abscess in addition to specific antibiotics. Papillary necrosis is another important complication of urinary tract infections in diabetic patients. DM has been present in over 50% of patients with papillary necrosis. Papillary necrosis was found to be about five times more frequent in diabetic than non-diabetic individuals. It should be suspected if patients with urinary tract infections responds poorly to antimicrobial therapy or develops renal insufficiency (Casqueiro *et al*.; 2012).

Cystitis emphysematosa is less severe and is usually cured by antibiotics alone. It is characterized by the presence of gas vesicles in the bladder wall. It is associated with infection by *coli form* organisms in patients with glycosuria. A history of pneumoturia may be obtained although the diagnosis is made radiographically. Its course is benign (Schaberg & Norwood; 2002). Asymptomatic bacteriuria (ASB) refers to the presence of bacteria in bladder urine in an asymptomatic individual. It is a significant risk factor for pyelonephritis and renal dysfunction in diabetic patients. The most commonly isolated microorganism was *Escherichia coli*. The duration of DM, high HbA1c, glucosuria and pyuria are risk factors for ASB in diabetic patients. Bacteriuria may be a marker for bladder neuropathy indicating more severe DM. Also; new retinopathy appeared in 21% of diabetic patients with persistent bacteriuria compared with only 4% of diabetic patients whose bacteriuria cleared. It is more in the diabetic women than in diabetic men. Some studies reported progression to pyelonephritis, whereas other suggested that this does not lead to serious complications. Thus, routine recommendation of antibiotic therapy for asymptomatic bacteriuria in diabetic women remains controversial (Casqueiro *et al*.; 2012).

Urinary fungal infections are more common in diabetic patients than non-diabetics; the majority of which are clinically insignificant. Diabetes is present in 20%–90% of patients with *Torulopsis glabrata* urinary tract infections. *Candida* was cultured from the urine of 35% of glycosuric diabetic persons in one study. Both *Candida* and *T. glabrata* can cause cystitis, pyelonephritis, renal or perinephric abscesses, fungus balls, and a clinical picture identical to gram-negative sepsis. Several factors may explain the predisposition of diabetic patients to fungal infections of the urinary tract. Glycosuria has been shown to be important. Yeast is present in the urine of 35% of diabetic patients without glycosuria. Fungal cystitis may result in the formation of “fungal balls” which may cause urinary tract obstruction. Unfortunately, some *Candida* and *T. glabrata* are initially resistant to 5-fluorocytosine and others become resistant during therapy (Segireddy *et al*., 2011).

### 4.3 Gastrointestinal and Hepatic Infections

The regularity of gastrointestinal motility and sensitivity are important mechanisms of defence against infections. Diabetes is responsible for about one quarter of gastroparesis. Both chronic hyperglycemia and gastrointestinal dysmotility contribute to increase the risk of gastrointestinal infectious processes. Common gastrointestinal and liver infection in diabetic patients include; *H. pylori*; oesophageal *candidiasis*; emphysematous cholecystitis; *Hepatitis C*; and *Hepatitis B* infection.
4.3.1 H. Pylori Infection

Many studies evaluated the prevalence of *H. pylori* infection in diabetic patients and the possible role of this infection in their metabolic control. Some studies found a higher prevalence of the infection in diabetic patients and reduced glycemic control while others did not support any correlation between metabolic control and *H. pylori* infection. Infection with *H. pylori* is common in diabetic patients who have inadequate metabolic control as such individuals are colonized by *H. pylori* in the gastric antrum, probably because of chemotactic factors such as tumor necrotic factor (TNF), interleukins-IL1, IL2, and IL8 which are present in gastric epithelium. These cytokines induce a number of changes in the gastric epithelium that promote inflammation and epithelial damage thus leading to increased risk of aberrant repair giving the picture of gastric atrophy or epithelial cell metaplasia. Infection with *H. pylori* is an important factor for diabetes-associated dyspepsia. The role of *H. pylori* infection in diabetic dyspepsia is mainly related to blood glucose concentration. Hyperglycemia may induce infection by *H. pylori* or the silent infection may get reactivated and produce symptoms of dyspepsia in DM (Saluja *et al*., 2002; Devrajani *et al*., 2010).

4.3.2 Oral Eosophageal Candidiási

*Candida albicans* is the most common etiological agent. The increased frequency of oro-esophageal candidiasis is due to both the increase in its virulence and the production of extracellular enzymes such as proteinase and phospholipase. It can be manifested as median rhomboid glossitis or central papillary atrophy, atrophic glossitis, denture stomatitis, pseudomembranous candidiasis, and angular cheilitis. Oesophageal candidiasis needs high suspicion and endoscopy is required (Menezes *et al*., 2007).

4.3.3 Emphysematous Cholecystitis

Emphysematous cholecystitis is a rare but severe infection associated with gas-forming organisms such as *Clostridial* species and other anaerobes. It occurs more frequently in male diabetics. However, nowadays; *Salmonella enteritidis* and *Campylobacter* are the main pathogens. It presented with the same clinical presentation of non-complicated cholecystitis with right upper quadrant abdominal pain, vomiting, and fever. However, patients with this illness are usually more ill and crackles can be felt on abdominal palpation which may denote with a worse prognosis. Clinical signs of peritonitis are usually not observed. The diagnosis is made by the detection of gas inside the gall bladder, demonstrated in radiograph or computerized tomography imaging of the abdomen. Treatment is by a combined surgical intervention and antibiotic therapy (Calvet & Yoshikawa; 2001).

4.3.4 Hepatitis C (HCV)

As mentioned before that infection with *hepatitis C* increases the risk of having DM. About one third of patients with *HCV* infection have DM, mostly T2 DM. Patients with HCV are 3 times more likely to develop DM than individuals who are HCV negative. Association of DM with *hepatitis C* infection increases the severity of the liver disease and degree of fibrosis compared to non-diabetic *HCV* patients. The frequency of DM increased along with pathological staging. The fibrosis score was higher in diabetic *HCV* patients. Liver biopsy specimens of diabetic HCV patients showed higher inflammatory activity defined by histological activity index score than the nondiabetic *HCV* group for moderate and severe stages. Individuals with T2 DM have a higher incidence of liver function test (LFT) abnormalities than individuals who do not have DM (Elhawary *et al*., 2011).
4.3.5 Hepatitis B (HBV)

HBV infection outbreaks have been reported among diabetic patients who received routine finger sticks. Transmission was attributed to the use of shared equipment and lapses in aseptic technique or infection control practices associated with blood glucose monitoring (Perz & Fiore, 2005).

4.4 Skin and Soft Tissue Infections

Diabetes mellitus is associated with increased frequency of skin and soft tissue infections such as folliculitis, furunculosis, and subcutaneous abscesses. Incidence ranges from 20-50%, mostly in T2 DM. The major underlying cause is hyperglycemia and ketoacidosis leading to immune dysfunction. Recurrent furunculosis and folliculitis especially of the back may be the first sign of DM presentation. Pyodermic infections such as impetigo, folliculitis, carbuncles, furunculosis, ecthyma, and erysipelas if present can be more severe and widespread in diabetic patients. Soft tissue infections of the lower extremities and gangrene are among the most dreaded complications associated with DM. Patients with DM clearly have an elevated risk of infected lower-extremity ulceration and subsequent amputation (Lipsky et al., 2010). Fungal skin infection especially mucocutaneous Candida occurs more frequently in diabetic patients, especially those with poorly controlled disease. Candidal infection can be an early sign of undiagnosed DM. Perlèche is a classic sign of DM in children, and localized candidal infection of the female genitalia (vulvovaginitis) has a strong association with DM. It is important to remember that in men, Candida balanitis, and intertrigo (axillary, inguinal web space), can be the presenting signs of DM. Paronychia, onychomycosis and glossitis are also common (Mujtaba, 2009). Association of dermatophyte infection with DM is controversial but recent data shows a statistically significant relationship. Common superficial infections are caused by Trichophyton rubrum, T mentagrophytes, and Epidermophyton floccosum. In diabetic patients, onychomycosis or tinea pedis should be monitored and treated, as it can be a port of entry for infection. This is especially true for patients with neurovascular complications and intertrigo (Hattemn et al.; 2008).

4.4.1 Foot Infection

Diabetic foot infections are common, and serious. They are diverse, and can range from cellulitis of a toe to gangrene of the foot. Diagnostic and treatment strategies are correspondingly varied. Foot ulcers usually occur in patients with sensory polyneuropathy who develop skin breakdown after unrecognized trauma. These infections can be monomicrobial but usually polymicrobial. S. aureus and S. 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. 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 (Nicolau & Stein; 2010). Infection easily occurs in tissue with an inadequate microvascular or macrovascular blood supply. Uncontrolled soft tissue infection can then lead to necrotizing processes and systemic sepsis. The clinical presentations of these infections are very variable and poor, often leading to delayed diagnosis especially with less pain sensation due to diabetic neuropathy. The diabetic foot infections are usually classified into moderate or “non-limb threatening” and serious or “limb-threatening”. 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 (Joseph & Lipsky; 2010). Chronic infection, such as osteomyelitis, can also occur in conjunction with cutaneous ulcers. Treatment of these infections involves a combination of early surgical intervention for debridement or amputation and any necessary vascular repair, antibiotic therapy, and local wound care.

4.4.2 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. About 10-60% of all cases of necrotizing fasciitis occur in patients with DM. It is a life threatening bacterial infection of the soft tissue with spread along facial planes; with a mortality of approximately 40% of the cases. The perenium, trunk, abdomen and upper extremities are most commonly involved. In DM fasciitis; although most cases result from polymicrobial facultative gram negative bacilli such as Escheracia coli and anaerobes such as bacteroids, peptoptreptococcus and clostridium species, approximately 10% cases are monomicrobial often due to streptococcal species. 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. The initial symptoms are fever and intense local pain, followed by areas of skin necrosis with small ulcers that drain a colourless fluid and have unpleasant smell. Degree of pain and toxicity are out of proportion to the severity of the findings. Air in the soft tissues can be better detected by radiograph. Treatment includes urgent surgical debridement and appropriate antibiotics (Shimizu & Tokuda, 2010; Oncul et al., 2008)

4.4.3 Fournier Gangrene

Fournier gangrene is a fasciitis that affects the male genitalia causing fulminant gangrene of the penis and scrotum in young men. It can however occur at any age, women may be susceptible, but the disease predominantly affects men. Up to 70% of the patients with this infection have DM. It usually involves the scrotum, but can extend to the penis, perineum, and abdominal wall. Contrary to the general belief, the testicles are usually spared. It is a life-threatening emergency with a mortality rate of up to 40%. Predisposing factors include DM, alcoholism, intravenous drug use, HIV and malignancy. Fournier's gangrene is caused by normal skin commensals of the perineum and genitalia which act synergistically to cause infection. The most common etiologic agents are E. coli, Klebsiella sp., Proteus sp., and Peptostreptococcus. The etiology can also be polymicrobial, involving Clostridium, aerobic or anaerobic streptococci, and Bacteroides. Treatment involves vigorous antibiotic therapy, surgical debridement and treatment of identified predisposing factors.

4.5 Head and Neck Infections

The two most serious head and neck infections in diabetic patients are invasive external otitis and rhinocerebral mucormycosis. Periodontal infection is also a common infection in diabetic patients.

4.5.1 Malignant Otitis Externa

Malignant otitis externa is a unique infection occurs almost exclusively in diabetic individuals, and usually seen in elderly persons. Recently, however, cases have been described in patients without diabetes. It is
a severe, necrotizing infection of the external auditory canal that can extend to the skull base, adjacent regions, and central nervous system with high morbidity and mortality. It is caused almost exclusively by *Pseudomonas aeruginosa* but rarely by *Aspergillus*. *Pseudomonas aeruginosa* is not a part of the normal flora of the ear. The presence of that organism is thought to be increased in the presence of hot, humid conditions or following irrigation of the ear with non-sterile water. The organism is thought to penetrate the cartilage in the external auditory canal through the naturally occurring fissures of Santorini. A necrotizing cellulitis exacerbated by microvascular disease then occurs. Infection then involves mastoid air cells and the temporal bone. Subsequently, the base of the skull becomes involved. The infection begins insidiously, but it is characterized by a gradually worsening, excruciating pain, purulent discharge associated with a polypoid mass of granulation tissue. Signs of systemic infection such as fever and leukocytosis are absent. The soft tissues around the ear are swollen and tender. A polypoid mound of granulation tissue is seen in the ear canal at the osseus-cartilaginous junction in 90% of patients (Carfrae & Kesser, 2008).

Facial nerve paralysis complicates 50% of cases. Skull base osteomyelitis and cranial nerve involvement may occur. So, paralysis of other cranial nerves indicates extension to the bones of the skull. Meningitis and sigmoid sinus thrombosis are rare complications. Radiographs of the ear and mastoid are usually normal; thus, the diagnosis must be made on clinical grounds. The best diagnostic method is the magnetic resonance imaging. The diagnosis is confirmed by the isolation of *Pseudomonas aeruginosa* from cultures of drainage from the ear in cases in which patients have severe ear pain, with granulation tissue present in the external auditory canal with or without radiographic evidence of disease. Other organisms rarely cause this disease e.g. *Staphylococci* or facultative gram-negative bacilli. *P. aeruginosa* may also be found in the ear canal of patients with uncomplicated otitis externa, culturing pseudomonas is not diagnostic of malignant otitis externa. The predisposition of diabetic patients may be due to the diabetic microangiopathy. Blood vessels in the infected tissues show marked intimal proliferation, leading some to speculate that vascular insufficiency resulting from diabetic microangiopathy may predispose to this infection. Therapy should include debridement and antibiotic therapy. Traditionally, standard therapy has been a combination of extended spectrum penicillin and an aminoglycoside given for 4–8 weeks, depending on the severity of illness. Use of a single drug, such as ciprofloxacin given orally or ceftazidime given intravenously for 6 weeks, has shown success in less severely ill patients. Early initiation of antibiotic therapy and surgical intervention are important for optimal outcomes. Without prompt recognition and therapy, the mortality may approach 40 percent (Rubin & Yu, 1988; Schaberg & Norwood; 2002).

**4.5.2 Rhinocerebral Mucormycosis**

Mucormycosis (also referred to as zygomycosis or phycomycosis) is a rare opportunistic, extremely difficult to treat, invasive and often fatal infectious disease that is usually associated with diabetic ketoacidosis. Mucormycosis is caused by fungi of the class *Zygomycetes*. The genus most commonly associated with human infections is *Rhizopus*, followed by *Mucor, Absidia* and *Cunninghamella*. Several distinct patterns of infection occur, including rhinocerebral infection and invasive pulmonary or gastrointestinal disease. The ubiquitous organisms invade through nasal passages producing black necrotic tissue and black pus. More than 50% of cases with mucormycosis are diabetics. This is because the acidic pH associated with diabetic ketoacidosis decreases the serum inhibitory activity against the *Rhizopus*. Ketosis also impairs the inflammatory response and permits tissue invasion in experimental mucormycosis. Acidosis and high concentrations of glucose increase the growth rate of *phycomycetes*. There is also over
expression of some host receptors that mediate the invasion and damage to human epithelial cells by *Rhizopus* (Liu et al., 2010). Mucormycosis is usually acute but occasionally chronic. Clinical features of this infection are distinctive with classical triad of paranasal sinusitis, ophthalmoplegia with blindness, and unilateral proptosis with cellulitis, bloody nasal discharge, unilateral headache, eyelid swelling, and lacrimation. Facial or eye pain and necrotic wound of the palate and nasal mucosa may occur. Ischemic nasal turbinates become necrotic. Black necrotic eschar in the nasal cornet is a characteristic sign. Jugular tenderness may be present with thrombophlebitis of the internal jugular vein. Paralysis of cranial nerves II-V, seizures, hemiparesis, coma, or other findings of meningoencephalitis appear as a result of vascular thrombosis and extension of the infection through the orbit and cribriform plate to the meninges and brain. Unilateral proptosis, chemosis, and retinal vein engorgement suggest that cavernous sinus thrombosis has occurred. Papilledema and retinal hemorrhages may develop later. Untreated patients frequently die within a week of onset of the infection. Thus, clinicians must be familiar with this rare but life-threatening infection (Severo et al., 2010).

### 4.5.3 Periodontal Infection

Periodontitis ranks sixth among all complications of DM and is four times more common in persons with DM. It 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. DM and periodontitis are common multi-genetic and multifactorial chronic diseases with a higher incidence at increased age. Both of the morbidities negatively affect periodontal health and systemic health, thus affecting the quality of life. There is a bidirectional correlation between DM and periodontitis. Periodontitis starts or disseminates insulin resistance, thus worsening glycemic control. Persistent poor glycemic control has been associated with a greater incidence and progression of gingivitis and periodontitis, producing a vicious circle.

### 4.6 Other Infections

#### 4.6.1 Malaria

Co-occurrence of T2 DM and malaria may have substantial implications. An increased risk for *P. falciparum* infection in persons with DM might become clinically relevant (and microscopically detectable) under several conditions. The impact of semi-immunity on controlling parasitemia may weaken with advancing T2 DM and immune dysfunction as suggested by the observed risk increase with increasing glucose concentration. Conversely, children who lack semi-immunity but have more severe T1 DM may be particularly prone to malaria. Such vulnerability is also conceivable for women with gestational DM whose immune systems are relatively naive with regard to pregnancy-specific *P. falciparum*. Moreover, low-level infections in patients with T1 DM may constitute an unrecognized infectious reservoir in areas where malaria is endemic. The lowered *P. falciparum* prevalence under metformin medication is due to biguanides’ antimalarial efficacy (Danquah et al., 2010; Okell et al., 2009).

#### 4.6.2 Bacteraemia

There is increased morbidity and mortality rate due to bacteremia in the diabetic patients which exceeded that of the non-diabetic patients. In NHDS study (1989 to 1991); the prevalence of bacteremia caused by
S. aureus and enteric organisms in diabetic subjects exceeded that in non-diabetic subjects by a large margin. Bacteremia is found in a 1.9-fold higher proportion of diabetic versus non-diabetic hospitalizations. The greatest difference was seen in the youngest age group (18-44 years, relative frequency = 2.0), with a gradual decline as age increased. However, the improved management of diabetic patients with acute illnesses in recent years may account for the absence of an effect of DM on outcomes in these patients (Leibovici et al., 1991; Peralta et al., 2009).

4.6.3 Surgical Site Infection (SSI)

Surgical site infections continue to constitute a challenge for surgeons. Protocols are now in place to reduce the rate of post operative infection. DM is a known major risk factor for SSI. Complications of DM, specifically peripheral neuropathy, have been shown to increase the risk of developing a post-operative infection. Gram-negative wound infections are three times more frequent in diabetic than in non-diabetic individuals. Postoperative hyperglycemia is the most important risk factor for surgical site infection. Aggressive early postoperative glycemic control should reduce the incidence of SSI (Ata et al., 2010).

5 Effects of Infection on Diabetes

Maintaining good glycemic control is not easy. Infection or an illness such as a cold or flu, for instance, can cause high blood sugars, loss of DM control, and may induce ketoacidosis especially in T1 DM. Infection stimulates the release of stress hormones such as cortisol and adrenaline. Cortisol binds to receptors on the fat cells, liver and pancreas, which increases glucose levels available for muscles to use. Cortisol also antagonizes insulin effects. Adrenaline enhances release of glucose from glycogen as well as the release of fatty acids from adipose tissue. These hormones work against the action of insulin and, as a result, the body’s production of glucose increases, which results in high blood sugar levels. Persistent hyperglycemia associated with low insulin release or effects can induce development of ketoacidosis. Hyperglycemia weakened immune system and can lead to more serious conditions. There are contradictory reports on H pylori prevalence and its relationship to late complications of DM. Interestingly, diabetics with H. pylori infection had a higher incidence of neuropathy, although there was no association between the duration and regulation of DM, retinopathy, nephropathy and H. pylori status. Some data indicate a possible association of H. pylori infection with coronary insufficiency and/or cerebral occlusive vascular disease in adults with DM. Another consequence of this infection is the increase in insulin requirements in children with T1 DM. The efficiency of H. pylori eradication is lower in persons with DM, whereas the re-infection rates are seen to be higher. Periodontitis starts or disseminates insulin resistance, thus worsening glycemic control. Periodontal therapy and proper care produced a significant improvement in the clinical condition, but did not affect metabolic control (Liz et al., 2011). HCV infection is strongly associated with development of insulin resistance and T2 DM. HCV is able to induce insulin resistance (IR) directly and the role of specific viral genotypes responsible for such effect is disputed. IR has consistently been found to be closely linked to fibrosis in HCV infection, although also typically associated with T2 DM in pre-fibrotic stages (Lonardo et al., 2009). DM is a particular co-morbid illness that warrants attention as a threat to HIV-infected patients. Both HIV infection and use of antiretroviral medications to treat HIV may be risk factors for DM. 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 cachectic patients or by those with lypo-atrophy. The side effects of thiazolidinediones (e.g. higher cardiovascular morbidity, osteoporosis) may prevent their use in HIV patients with DM. Glinides and sulfonylureas may not be effective due to insulin resistance. Therefore, insulin is the drug of choice for HIV-associated DM (Satlin et al., 2011).

### 6 Diabetes and Vaccination

#### 6.1 Effect of Vaccines on Diabetes

The induction or exacerbation of autoimmune diseases is a potential adverse effect of immune-stimulating drugs. Some studies has raised the possibility that immunisation by vaccines can influence the pathogenesis of T1 DM. A link between childhood vaccinations and the development of T1 DM has been proposed for several reasons. First, there is a temporal association between the widespread introduction of general childhood immunizations and the increase in the incidence of T1 DM in developed countries. Second, it has been observed that specific vaccines prevent T1 DM in murine models and others induce it. And third, some findings suggest an association between infections and T1 DM (Hviid et al., 2004). Epidemiological studies, however, have so far failed to demonstrate any causal relationship between vaccination and autoimmune diseases, including T1 DM. Few studies claimed the role of some vaccines may share in pathogenesis of autoimmune DM. However, a study done by Wahlberg et al., showed that *hemophilus influenza B* (HIB) vaccination may have an unspecific stimulatory polyclonal effect increasing the production of GADA and IA-2A; an immune process that later may lead to T1 DM. This might be of importance under circumstances when the beta cell-related immune response is activated by other mechanisms (Wahlberg et al., 2003).

Some reports have suggested that natural mumps or mumps vaccinations can induce islet cell autoimmunity, but there is no evidence that mumps-measles-rubella mass vaccination programmes have changed the incidence of DM in any population. An independent protective role of measles virus has been suggested in one study. Recent studies have indicated that *enterovirus* infections may induce beta cell autoimmunity and clinical DM. The only currently available *enterovirus* vaccine is the poliovirus vaccine which, in theory, could modulate the protection against other *enteroviruses* by inducing cross-reactive T cell immune responses; however, this hypothesis has not been tested so far (Hiltunen et al., 1999). There are some sporadic reports of preserving β-cell function when BCG vaccination is administered soon after diabetes onset. A study done by Zhu et al showed that intranasal vaccination with HSP65 gene was derived from *Mybacterium tuberculosis var. bovis* NOD mice could prevent the development of DM. Their results demonstrated that intranasal vaccination with HSP65 reduced significantly the inflammatory process associated with auto-immune diabetes. They suggested that this approach may offer novel therapeutic avenues for the treatment for of T1 DM (Zhu et al., 2011). However, a previous study done by Allen et al. showed that vaccination with BCG at the time of onset of type T1 DM does not increase the remission rate or preserve beta-cell function (Allen et al., 1999). However, repeated BCG vaccination is safe and may be more effective than a single dose in preventing T1 DM in NOD mice (Shehadeh et al., 1997). Ravel et al showed that the incidence of autoimmune diabetes was slightly reduced by the DTaP-IVP vaccine with significant reduction of blood glucose level treated with the DTaP-IVP vaccine relative to the untreated control mice (Ravel et al., 2003). There were no solid causal relation between childhood vaccination and T1 DM. Larger epidemiological studies are still needed to obtain more reliable data in most suggested associations (Salemi & D'Amelio, 2010).
6.2 Effects of Diabetes on Vaccine

Enhancement of personal DM management and increased media messages about DM could improve DM knowledge or awareness and hence increase the patient awareness about the need for proper vaccination. Adhesiveness to vaccination is affected by several factors that may include race, gender, patient’s knowledge, socioeconomic status, vaccine availability, the access to and the quality of the medical service available. Dunlap & Rudenko reported that the diabetic patients who are younger than 65 years tend to be more likely to recognize that they are at high risk of complications from influenza and pneumococcal disease; however, their vaccination rates tend to be lower than those of patients who are over 65. Patients aged 65 and over have a higher rate of vaccination, but are vaccinated because of their age, not recognizing that having diabetes and being older puts them into a high-risk category. Many patients are not receiving the influenza vaccine because they fear becoming ill or experiencing adverse effects. They also found that a large proportion of patients are not receiving the pneumococcal vaccine because they were unaware that it is needed or their physician had not recommended it to them (Dunlap & Rudenko, 2012).

Younossi & Stepanova found that despite the vaccination rates in diabetic cohorts are increasing, they remain low and there is a need for a better implementation of the vaccination recommendations for these populations is warranted (Younossi ZM, Stepanova M, 2011).

The Immune response induced by the vaccines in diabetic patients may be not equal to that induced by healthy controls. Leonardi et al studied the efficacy of HBV vaccine in diabetic children. They observed a reduced seroprotection rate for HBV vaccination in diabetics. They found significantly-lower mean antibody titre against HBV in IDDM children than healthy controls. However, there was no correlation found between antibody titre, age, duration of disease and HbA1c. They did not find any difference of gender, age, years of onset of the disease and metabolic control, between diabetics with anti-HBs antibodies and those without (Leonardi et al., 2012). A similar finding was observed with inactivated influenza A (H1N1) 2009 monovalent vaccine. Kostinov & Tarasova found that intensity of immunity after HBV vaccination in children with T1 DM decreased with increasing number of diabetic complications. If number of T1 DM-associated complications exceeds 3, especially in children living in rural area, serologic monitoring is essential for deciding whether booster vaccination against HBV is needed (Kostinov MP, & Tarasova AA, 2008). The same was observed for pneumococcal vaccine. Tarasova et al, found lower intensity of immune response and antibody titres to polysaccharide pneumococcal vaccine in children with DM compared to children with respiratory diseases (Tarasova et al., 2007). Nam et al noted low cross-reactive antibody carrying rate and low seroconversion rate in adult patients with DM who were vaccinated with single-dose adjuvanted, inactivated, pandemic H1N1 influenza vaccination. This finding stimulated them to recommend two-dose vaccination or to have antibody titres measured after the first vaccination to ensure the protective efficacy of the vaccine.

6.3 Recommendations

It should be emphasized that vaccination in diabetic patients is free of any risk; provided that there are no other contraindications, e.g. allergy to vaccine components or severe acute febrile illness. In case of unstable glycaemia and significantly impaired immune system due to DM, vaccination with live attenuated vaccines should be carefully considered and measured against the risks of exposure to each and every specific infectious agent. There is no reason to be afraid of vaccination in diabetic patients provided that general contraindications are respected. On the contrary, this risk group can benefit from vaccination more remarkably since it may have some life-saving potential (Mad'ar et al., 2011). For example; adults
with T2 DM, like other individuals from recognized risk groups, can benefit considerably from influenza vaccination, and no difference in vaccine effectiveness was observed between first-time and repeat vaccination (Looijmans-Van den et al., 2006). Effective DM management, including self-care, healthcare provider-care, and getting vaccinated against influenza and pneumonia, is vital in reducing DM morbidity and mortality. Providing directed education to patients about the importance of vaccination and discussing with them the expected adverse effects may improve rate of vaccination.

The basic vaccinations recommended for diabetics include immunizations against influenza, pneumococcal infections, tetanus and viral hepatitis B. Other vaccines are administered only after individual assessment of benefits and risks for the diabetic patient. Most often, these are vaccinations against viral hepatitis A, tick-borne encephalitis, meningococcal infections and other infections that put risk in diabetic patients travelling abroad (Beran J, 2006). Because serum levels of tetanus antibody decreased in diabetic patients older than 50 years of age, whereas this period of time is prolonged to 65 years in healthy individuals; it is recommended that all individuals over 65 years should be vaccinated against tetanus. However, vaccination over 50 years of age might be considered for diabetic patients (Tamer et al., 2005). According to the Centers for Disease Control and Prevention (CDC) guidelines for vaccination of adults with diabetes; the following vaccines are recommended:

- **Pneumococcal Vaccine**: All adults ≥ 65 years of age and Adults < 65 years of age with diabetes; it is recommended to give 1 dose once in their life with 1 additional dose at ≥ 65 and ≥ 5 years from first dose.

- **Influenza Vaccine**: should be given for all adults 1 dose annually. The best time to get is between October and mid-November, before the flu season begins.

- **Hepatitis B vaccine**: It should be administered to unvaccinated adults with DM who are aged 19 through 59 years. Hepatitis B vaccination may be administered at the discretion of the treating clinician to unvaccinated adults with diabetes mellitus who are aged ≥60 years. Although the HBV vaccination series traditionally consists of doses at 0, 1, and 6 months, the CDC recommends incorporating the series into regular visit intervals, as effectiveness is comparable even when the intervals between doses are longer than those stated above (CDC, 2011). Early vaccination against HBV is indicated in patients likely to progress to end-stage kidney disease.

- **Tetanus/Diphtheria (Td) Toxoid Vaccine/Tdap**: Most people get Td toxoid as part of their routine childhood vaccinations, but all adults need a Td booster shot every 10 years with Tdap in place of one Td vaccine. Other vaccines may be given at the same time as Td toxoid.

- **Shingles**: All adults should have 1 dose at ≥ 60 years of age.

- **HPV**: it is given for all women up to age 26, unless immunized earlier and all men up to age 21 (may be vaccinated up to age 26), unless immunized earlier. Three doses are given at 0, 2, 6 months.

### References


