REVIEW ARTICLE

Evaluation of Immunoglobulin A in Diabetic Patients and its Relation with Oral Complications

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Abstract

Diabetes mellitus is a group of metabolic diseases caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cell. In 2007, 246 million people (roughly 6%) were affected by diabetes worldwide and it is estimated that this will increase to 380 million in 2025. Diabetes is associated with several long-term complications such as cardiovascular disease, nephropathy, retinopathy, neuropathy and some oral complications. In addition, Diabetes mellitus causes an increased risk of morbidity because of infection disease. It seems that, the increased frequency of infections associated with Immunoglobulin-A (IgA) deficiency in these patients. Therefore a low IgA secretion rate is suspected to be one of these mechanisms. Moreover, it shows a main antiviral activity by neutralizing toxins and viruses. It by inhibiting the attachment and replication of pathogenic microorganisms prevents colonization of these pathogens.Therefore, it acts as a first line of defense against pathogens and early detection of immunoglobulin A deficiency in diabetic patients can prevent the vicious cycle of recurrent infections and reduces risk for morbidity and metabolic decompensation. Moreover, the Salivary-IgA is the widespread immunoglobulin in mixed saliva and is assumed to be an important factor for adaptive immunity in the oral cavity. Therefore, according to these studies, Immunoglobulin A, its mechanism, IgA deficiency and diabetes and its relation with oral complications are explained in this paper.

Keywords: Immunoglobulin A, Diabetic patients, Immunodeficiency, Oral complications

Introduction

Diabetes mellitus is a group of metabolic diseases caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cell. Today, more than 200 million people in worldwide have type 2 diabetes. The total number of people with diabetes is expected to reach 380 million worldwide in 2025 (1-4).

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Diabetes is associated with several long-term complications such as cardiovascular disease, nephropathy, retinopathy, neuropathy (5), increased risk of morbidity from infectious diseases (6,7) and some oral complications like xerostomia, tooth loss, gingivitis, periodontitis, odontogenic abscesses and soft tissue lesions of the tongue and oral mucosa (8). Moreover, alterations in salivary flow rate and its compositions can affect the development, symptoms and severity of oral changes in diabetic patients. On the other hand, higher rate of dental problems in diabetic patients is associated with salivary dysfunction, existing acidogenic microorganisms, poor glycemic control, poor dental hygiene and higher dental plaques (8). In addition, Diabetes mellitus causes an increased risk of morbidity because of infection disease, like as pneumonia and urinary tract infections. Several studies reported that diabetes mellitus is associated with impaired chemotaxis of the immune cells, defective phagocytosis of macrophages, and increased production of free radicals (9). Several mechanisms can cause susceptibility of infections in patients with diabetes (9). Immunoglobulin A and G via affecting cavity microorganisms in the saliva, gingival and plasma prevent bacterial metabolism and adhesion of microorganisms to the oral tissue (10). It seems that the increased frequency of infections associated with IgA deficiency in these patients (11). Therefore a low s-IgA secretion rate is suspected to be one of these mechanisms. However, these patients are more susceptible to frequent infections, autoimmune disorders, gastrointestinal diseases and atopy (11). Branco-de-Almeida et al reported that DM patients were associated with lower mean levels of s-IgA than non-DM patients, while Ya vuzyilmaz et al, reported that DM patients had higher mean levels of s-IgA than healthy controls (9). The aim of this study was to evaluate serum and salivary IgA level in diabetic patients. In another section, immunoglobulin A (IgA) and its mechanism are explained. Immunoglobulin A deficiency (IgA deficiency) and autoimmune disorders are discussed in next section.In osection 2, 3, Immunoglobulin A deficiency (IgA deficiency) and Diabetes and salivary immunoglobulin A and oral complication are explained.

Immunoglobulin A (IgA) and its mechanism

Immunoglobulin- A (IgA) is the second most abundant immunoglobulin (12) in the body and two forms can be identified: IgA1 and IgA2. Immunoglobulin A1 found mainly in the serum in monomeric form (13) and cannot be transported to mucous secretions (9). IgA2 (dimeric) is found in exocrine secretions and mucous defense systems like saliva, tears, colostrum and nasal and gastrointestinal secretions (14,15), bronchoalveolar lavage fluid, urine (9) and plays a main role of antigen excretion (9). The regulation of secretion and synthesis of secretory IgA is dependent on antigenic stimulation and strong neuroendocrine function like stress, exercise, pregnancy and menstrual cycle (11). In addition, it can protect mucous membranes against infections via activating the alternative way of the complement and prevent binding of virus to epithelial cells of the respiratory, gastrointestinal and urogenital tracts. Therefore, it shows a main antiviral activity (14) by neutralizing toxins and viruses (9). It by inhibiting the attachment and replication of pathogenic microorganisms prevent colonization of these pathogens (9), and may be protective against periodontal disease (16). Therefore, it can act as a first line of defense against pathogens (16). Study of mucosal humoral immunodeficiency in humans showed that the absence of secretory IgA results to increase mucosal infections and respiratory tract infections. In addition suppression of s-IgA causes increased incidence of upper respiratory tract infection (9). Studies showed that IgA proteases can cleavage IgA in vivo, resulting in generation of intact Fab alpha and (Fc alpha) 2 fragment (17). When bacteria are exposed to Fab alpha fragments, it released

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from IgA after cleavage by IgA protease, their surface antigens are likely to be occupied by Fab alpha fragments. These Fab alpha fragments left on the bacterial surface may mediate adhesion. Together, these results indicate that IgA proteases, by promoting adherence, contribute the pathogenic potential of bacteria in the oral (17). Early detection of immunoglobulin A deficiency in diabetic patients can prevent the vicious cycle of recurrent infections and reduces risk for morbidity and metabolic decompensation (18).

- ***Immunoglobulin A deficiency (IgA deficiency) and autoimmune disorders***

IgA deficiency is the commonest type of immunodeficiency (19-24) and associated with autoimmune disorders (14). Prevalence of immunoglobulin A deficiency (IgA-D) as most common primary immunodeficiency disease (25,26) varies widely within different geographical regions from 1/143 to 1/185000 (11,18). Immunoglobulin A deficiency is associated with autoimmune disease such as systemic lupus erythematus, Graves' disease, celiac, recurrent parotiditis, inflammatory bowel syndrome, Crohn's disease, juvenile idiopathic arthritis and type 1 diabetes (11).

Immunoglobulin A deficiency (IgA deficiency) and Diabetes

The association between type 1 diabetes and IgA-D has long been recognized in many populations (18). High prevalence of IgA-D has been found in children and adults (18). Prevalence of autoimmune thyroid was significantly higher in IgA-D patients (18). Moreover, the prevalence of IgA deficiency in type 1 diabetes is estimated between 0.4 % and 5.4%. It is more than 10 times the prevalence of the general population (18). Moreover, prevalence of Immunoglobulin A deficiency in Iranian patients with diabetes mellitus reach to 0.7% (1:150), which is much higher than other prevalence in general populations (27). Greco et al, reported in diabetic patients, because of the availability of serological screening for celiac disease (CD), more cases of IgA-D are now being diagnosed (18). Mohiti-Ardekani et al. reported that secretory IgA levels in Iranian diabetic patients were higher than in non-diabetics patients (28). Another study performed in Western part of Sicily (Italy) and reported that IgA-D was seen in eight out of the 150 subjects (children and adult patients) with type 1 diabetes. They reported that Immunoglobulin- A deficiency was found in 5.3% of patients (18). In one study, no significant differences were found in salivary IgA levels between diabetic patients and control group (6). In another study, the mean level of IgA concentration is low in diabetic patients than control, it seems that infection and other autoimmune disorders are absent in these patients (11). Akefeh et al, reported that there was no significant association between serum and salivary IgA level among diabetic and nondiabetics and also, no association between serum and salivary IgA levels (11). Yavuzyilmaz et al, demonstrated a significant increase in salivary IgA levels in diabetic patients. Vaziri et al, reported that there was no difference in salivary IgA between type 1 and 2 diabetic patients and control group. Also, lower salivary flow rate was detected in diabetic patients than control group (6). Studies reported that these differences can be due to diversity in sample selection criteria, study design (6), or detection methods (10). Moreover, these differences may be due to differences in the type of saliva collected (stimulated or unstimulated), the salivary collection methods, the stage of the disease, and the metabolic control status of the disease (6). Sayarifard in another study reported increased prevalence of immunoglobulin (Ig) A deficiency in a number of autoimmune diseases and type 1 diabetes mellitus (DM1) (27). Smith Jr et al, reported that there is an increased IgA deficiency prevalence in juvenile-onset insulin-dependent diabetes mellitus, but not in adult with insulin-dependent diabetes. Also diabetes in juvenils is associated with other immune disease like thyroiditis, chronic active hepatitis, infections and thymus deficiency. They suspected that thymus deficiency and autoimmunity play a

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main role in the pathogenesis of some types of juvenile-onset diabetes mellitus. Moreover, they reported that excess morbidity of the IgA-deficient in juvenile diabetic patients can be due to IgA deficiency in older insulin-dependent diabetic patients (29). Segade et al, showed patients with type 1 and 2 diabetes have higher level of circulating IgA. Also this phenomenon is more among in male than female (30). Imagava et al, reported that high level of serum enterovirus IgA antibodies in type 1 diabetic patients is due to recurrent enterovirus infection in them (31). Figueredo et al, in one study reported that increased level of immunoglobulin A in diabetic patients suggested a possible role of IgA in the pathogenesis of the vascular complications of diabetes mellitus (32).

Salivary immunoglobulin A and oral complications

It has been shown that salivary component detection in patients with diabetes may help to diagnosis, prevention and management of the oral manifestations (28). Secretory immunoglobulin antibody (S-IgA) plays a main role in the oral homeostasis. The S-IgA is the widespread immunoglobulin in mixed saliva and is assumed to be an important factor for adaptive immunity in the oral cavity. Thus it works as an index of the adaptive local immunity of mouth. S-IgA works synergetically with other antibacterial factors, including lysosym, lactopherin, salivary peroxidase, mucine, etc. Thus they prevent the piercing of antigens via the oral mucous membrane (33).

Conclusion

Diabetes mellitus causes an increased risk of morbidity because of infection disease. It seems that low s-IgA levels may be a mechanism to explain susceptibility of infection in DM patients. Early detection of immunoglobulin A deficiency in diabetic patients can reduces risk for morbidity.

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