Why vitiligo in diabetes?

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Introduction

Diabetes Mellitus is a group of metabolic diseases that share the phenotype of hyperglycemia. The metabolic deregulations associated with diabetes causes secondary pathophysiological changes in multiple organ systems including the skin. Diabetes mellitus is associated with many skin diseases one of which is vitiligo.

Vitiligo is an acquired idiopathic disorder of melanogenesis characterized by depigmented macules in an otherwise normal skin. Why does vitiligo develop in diabetes? What is responsible for the depigmentation of vitiligo in diabetes? Sezary and Dupuy [1] were the first to mention the association between diabetes and vitiligo and they attributed the skin discoloration to some pancreatic influence. Since that time, many cases of diabetes with vitiligo has been documented [2, 3].

The incidence of diabetes mellitus in vitiligo patients ranges between 1-7% in literature and vitiligo may precede the onset of diabetes mellitus [4]. Dawber [5] suggested that diabetes mellitus should be excluded in all cases of late onset vitiligo. Among 457 diabetic subjects attending an outpatient clinic, 9% had vitiligo lesions [6]. In another series in Karachi, 10% of 100 patients with diabetes mellitus had vitiligo compared with incidence of 1% in general population [7]. Vitiligo is a consistent finding in literature concerning skin complications of diabetes. The possible etiopathogenesis of this relationship need consideration.
The Autoimmune Connection:

Both diabetes and vitiligo share a common theory of autoimmunity. The evidence to support that insulin dependent diabetes is a slow autoimmune disease include HLA-linked genetic predisposition, association with other autoimmune disorders, circulating islet cell and insulin autoantibodies, mononuclear cell infiltration of pancreatic cells and recurrence in pancreatic grafts \[8\]. Anti-islet cells have been documented in insulin dependent diabetes.

Whittingham et al \[9\] noted an increased level of autoantibodies in four hundred diabetics particularly those with insulin dependent diabetes. Pathologically, particularly in Type 1A Diabetes, the pancreas is infiltrated with lymphocytes causing inflammation followed by Islet cell atrophy. There are activated T cells, release of lymphokines, tumor necrosis factor, Interferon and Interleukin \[10\]. Vitiligo also has been found to be associated with diseases believed to be autoimmune such as Grave’s disease, Hashimoto thyroiditis, pernicious anemia, alopecia areata, Addison’s disease and diabetes mellitus \[11\].

Immunosuppressive therapy has been found to be effective in the treatment of vitiligo. Antimelanocyte antibody has been isolated in vitiligo \[1\]. A primary disturbance in immunological mechanisms is what results in melanocyte dysfunction. This results in inhibition of melanin production or melanin cytotoxicity. An alternative mechanism is that some injuries to melanocytes result in the release of antigenic substance so that antibody formation occurs and melanogenesis is inhibited \[1\].

The occurrence of vitiligo in diabetes may be as a result of a basic autoimmune disturbance in the same patient affecting two organ systems. Longstanding Diabetes Mellitus may cause an injury to melanocytes resulting in the release of an antigenic substance, antimelanocyte antibody formation, inhibition of melanogenesis and occurrence of vitiligo.

There is considerable evidence that depigmentation may be an important cutaneous marker for immunological based diseases. The depigmentation of vitiligo is seen in halo naevus, malignant melanoma and Vogt-Koyanagi-Harada syndrome \[1\]. In patients with halo naevus, vitiligo surrounds a melanocytic naevus, which is a localized developmental abnormality of the skin with increased number of melanocytes. Halo naevus is considered as an immune process and vitiligo can occur at remote sites.

Vitiligo occurs in malignant melanoma following stimulation
of the immune system arising from damaged and aberrant melanocytes. This vitiligo may occur at sites distant to the primary lesion and in regressing lesions melanomas. Clinical depigmentation occurs in Vogt-Koyanagi-Harada syndrome in which hypersensitivity to uveal pigments and disturbances of cell mediated immunity is found [1].

**Genetic Considerations**

Diabetes mellitus and vitiligo share a common risk factor of familial predisposition. Diabetes is often present in close relatives of patients with Vitiligo [12]. Both diabetes and vitiligo are associated with HLADR3 and HLADR4 [13]. No race is spared in vitiligo and diabetes. Vitiligo has been observed in monozygotic twins although the extent, age of onset, and course may be similar or dissimilar in to the other twin [14].

Inheritance pattern is thought to be autosomal dominant with variable penetrance. In 30% of vitiligo patients there is history of vitiligo in another family member [1]. The occurrence of Type1A Diabetes in identical twins ranges between 30-70% [10]. Maturity onset diabetes of the young (MODY) is of autosomal dominant inheritance [10].

Mutations in insulin receptor cause a group of rare disorders characterized by severe insulin resistance. The genetic contributions to diabetes mellitus involve multiple genes and development of the disease requires inheritance of sufficient complements of genes to confer susceptibility. The major susceptibility gene is located on HLA region on chromosome 6. This region contains genes that encode the classic 11 MHC molecules that present antigens to helper T cell that are involved in initiating an immune response [10]. The genetic predisposition can therefore be linked with autoimmunity. It is possible that the same patient may have a genetic predisposition to both vitiligo and diabetes as opposed to a causal relationship.

**Cell Destruction Theory**

Lerner proposed the self-destruction theory of vitiligo [15]. He said that melanocytes are destroyed by the very factors that are required for melanogenesis. He proposed that a melanin precursor might have a toxic lethal effect when the naturally occurring protective mechanisms are lost. There is usually a selective destruction of melanocytes in vitiligo. The two known mechanisms for the destruction of cells are necrosis and apoptosis. Some workers reviewed available data to find out which of the two mechanisms was operative in vitiligo. The histological data and some laboratory data suggested apoptosis rather than necrosis as the mechanism for the removal of melanocytes [16]. Apoptosis can
be induced by a variety of factors including immune cytokines.

Moretti et al [17] found that a significant amount of epidermal cytokines exists in vitiligo skin compared with perilesional, non-lesional and healthy skin suggesting that cytokine production of epidermal microenvironment may be involved. Confirmation of apoptosis as a mechanism in causation of vitiligo in diabetes can serve as a basis for devising medication to stop the disorder. The study of apoptosis, mechanism of its induction, and the ways to block apoptosis is one possible way to find the cause of depigmentation in diabetes mellitus.

**Diabetic Neuropathy and Neurologic Theory**

Nervous system affectation in diabetes called diabetic neuropathy affects 50% of individuals with longstanding diabetes. It manifests as polyneuropathy, mononeuropathy, autonomic neuropathy or a polyradiculopathy. Affectations of multiple isolated nerves result in mononeuritis multiplex [10]. Histopathological findings in diabetic neuropathy reveal axonal shrinkage, fragmentation, and degeneration of both myelinated and unmyelinated nerves. There are also abnormalities of intraneural capillaries, thickening of basement membrane and micro thrombi [10].

Can the neuronal damage in diabetic neuropathy account for development of vitiligo in diabetes? Dermatomal vitiligo has been associated with dysfunction of sympathetic nerves in affected skin areas [18]. Yokota [18] noted degenerative changes in the terminal portions of peripheral nerves in vitiliginous areas by using histochemical studies and Mori [19] in 1964 using the light microscope.

Numerous clinical observations have been reported in which vitiligo patients became white in cutaneous areas corresponding to areas of neurological damage [4]. Leukoderma occurring in a leprous macule would favor neurogenic hypothesis of leukoderma since the leprosy bacillus primarily affects the nerves. The fact remains however that vitiligo lesions have no sensory loss. Spontaneous repigmentation has been documented in vitiligo lesions of diabetic neuropathy and loss of Merkel cells have been seen in early vitiligo lesions [20].

**General Mechanisms of Diabetic Complications**

The primary disturbance in diabetes is chronic hyperglycemia. There are three major theories on how hyperglycemia leads to chronic complications in organ systems.
Glycosylation of cellular proteins

 Increased intracellular glucose leads to formation of advanced glycosylation end products via non-enzymatic glycosylation of cellular proteins. This causes atherosclerosis, glomerular dysfunction, reduced nitric oxide synthesis, endothelial dysfunction and alteration of cellular matrix.

The Sorbitol pathway

 Increased glucose metabolism through sorbitol pathway, which affects various aspects of cellular physiology causing, decreased myoinositol and altered redox potential and cellular dysfunction.

Increased Diacylglycerol

 Increased formation of diacylglycerol leads to activation of certain isoforms of protein kinase C (PKC) that alters gene transcription for fibronectin, collagen, contractile proteins and extra cellular matrix proteins.

Conclusion

 The occurrence of depigmentation of vitiligo is certain but the etiopathogenesis remains an enigma. Vitiligo and diabetes may have a causal relationship and both are associated with autoimmunity.

 Familial-hereditary tendencies occur in both diseases. There is neuropathic complications in diabetes and in vitiligo dermatodermal variety occur with evidence of degenerated nerve endings. Multiple pathogenetic mechanisms may be involved. Vascular and non-vascular pathogenetic mechanisms play a role in diabetic complications. The products of oxidative stress, free radical generation and release of various growth factors may be cytotoxic affecting melanogenesis.

References

Introduction


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