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Intraocular Inflammation in Diabetic Populations

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Abstract
Purpose of review The purpose of this review is to determine the prevalence of uveitis in the diabetic population, the clinical features of the uveitis and diabetes when coexisting and pathophysiology of a possible correlation. We also aim to review the cases of diabetes and uveitis in the literature.
Recent findings The basis of an association between uveitis and diabetes mellitus (DM) is the common pathophysiology of inflammation. There are several reports on a DM-related uveitis, defined as idiopathic anterior uveitis in the presence of poorly controlled DM, but causation has not been established.
Summary There are conflicting results in the literature regarding an association between uveitis and DM. More studies are needed to determine if an association truly exists.

Keywords Uveitis · Diabetes mellitus · Blood-retinal barrier · Blood-aqueous barrier · Panretinal photocoagulation · Intraocular inflammation

Introduction

Intraocular inflammation and its association with diabetes mellitus (DM), whether type 1 or 2, has been explored by several authors [1–6], starting with Noyes in 1868 [7]. Since then, several case reports have highlighted a possible link between uveitis and DM [8–12]. In fact, uveitis has been considered to be an ocular manifestation of DM [13]. In addition, several authors have defined a DM-related uveitis, which is uveitis in the presence of poorly controlled DM and in the absence of any other underlying cause [3, 6, 14–16]. Although an association between uveitis and DM has been suggested, causation has not been established [14, 15, 17]. Despite that, many articles discuss the postulated immunological link between diabetes and uveitis [1, 3, 18].

In our paper, we aim to explore the prevalence of uveitis in the diabetic population, the pathophysiology of the proposed correlation, clinical features of the uveitis, and diabetes when coexisting. We will also review the different cases of diabetes and uveitis published in the literature.

Methodology

A systematic search of the literature was conducted by accessing Pubmed, Medline, and Scopus databases on December 2016 and January 2017. The keywords *uveitis*, *iritis*, *iridocyclitis*, *vitritis*, *chorioretinitis*, *retinitis*, *vasculitis*, *sympathetic ophthalmia*, *Vogt–Koyanagi–Harada*, and the Medical Subject Headings (MeSh) term *uveitis* were used to collect all articles covering uveitis. The keywords *diabetes*, *glucose intolerance*, *hyperglycemia*, *diabetic*, *glucosuria*, *microglobinuria*, and the MeSh term diabetes mellitus were used to collect all articles covering diabetes. Non-English language articles were excluded from the review. The combination of the two search strategies led to the identification of 41 articles, of which 23 included case reports/series. Six articles were excluded because they were not relevant to the subject matter. A search of immunological mechanisms relating to diabetic retinopathy was also conducted using the key words

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immunology, *immunological mechanisms*, *cytokine**, *leukocyte**, *VEGF*, *inflammation*, *and diabetic retinopathy.*

The following information was collected from the case reports when available: patient characteristics, type of DM, type and location of uveitis, precedence of onset of diabetes versus onset of uveitis, probable precipitating event, and concurrent illnesses or infections.

Prevalence

There have been several studies that have surveyed uveitis patients for systemic diseases including DM [2, 3, 6, 14, 15, 19]. In their series of 71 patients presenting with their first episode of uveitis above the age of 60, Barton et al. found type 2 DM to be the most common systemic disease (5/71 patients, 7%) [19]. Similarly, type 2 DM was also found to be the most common systemic disease in the elderly with uveitis in a study by Nalcacioglu-Yuksekkaya et al. Out of 68 patients, 8 (11.7%) has type 2 DM alone and 1 case had both type 2 DM and hypertension [20]. Chatzistefou et al. found that 18 out of 138 (13%) uveitic patients had DM (15 type 2, 2 type 1, 1 steroid-induced). Whether or not these [21] findings can be extrapolated to elderly patients with uveitis is controversial. In a study by Gregoire et al. on 91 elderly patients presenting with their first episode of uveitis, none of these patients were found to have DM [22].

The prevalence of diabetes has also been studied in patients with Vogt-Koyanagi-Harada (VKH) [4]. Al-Halafi et al. found that in 256 patients diagnosed with VKH disease, 12 patients (4.7%) had type 1 DM. The authors had excluded any patients with type 2 DM from the study [4]. The coexistence of VKH and type 1 DM has also been published in several case reports [8, 23–25].

As mentioned, a few authors have defined a DM-related uveitis, which is fibrinous anterior uveitis in the presence of poorly controlled DM and in the absence of any other underlying cause [3, 6, 14, 16]. In a study on 865 patients with uveitis carried out in 1992, Rothova et al. found that 20 patients had DM-related uveitis (2.3%). Nine other patients had DM but it was deemed by the authors as unrelated to their uveitis since another cause of uveitis was identified [6]. In 2009, Oswal et al. found that among 48 eyes of 34 patients with uveitis, 2 patients and 4 eyes had uveitis whose cause was uncontrolled DM [3]. In 2013, 6 eyes of 4 patients were presumed to have DM-related uveitis by Oswal et al. [16••]. Most recently in 2014, Liberman et al. identified DM-related uveitis in 17 (2.8%) out of 611 patients enrolled in the study [14]. This DM-related uveitis is described as an association rather than well-defined causation.

Patients with existing DM have been reported to develop uveitis as well [9–12, 21, 26–28]. Two cases of anterior uveitis are thought to have occurred as a direct result of panretinal photocoagulation (PRP) in patients with DM [10, 12]. Anterior uveitis, more specifically iritis, has also been noted in patients with DM and autonomic neuropathy [28]. Guy et al. found that out of 47 patients with diabetic autonomic neuropathy, 14 (29.8%) had a history of developing iritis [28].

These reports of patients with uveitis and DM, however, do not establish an association between the two conditions. To this day, there is no consensus on an association due to conflicting results published in the literature. In a study by Rothova et al. in 1988, 20 patients (5.9%) out of the 340 with anterior uveitis had DM, a figure found to be significantly higher than the prevalence of DM in the normal Dutch population (1.4%, P value < 0.001) [15]. Herranz et al. found similar results in the Spanish population in 1997. In a study on 111 patients referred for a diagnosis of uveitis, 54 patients had idiopathic uveitis, of which 35 had anterior idiopathic uveitis. Among these, 5 out of 35 (14.3%) had DM, while no patients in the anterior uveitis with an established diagnosis group had DM. Moreover, the prevalence of DM in the idiopathic anterior uveitis group was higher than that in the normal Spanish population [2]. Since topical or regional rather than systemic corticosteroids is the typical treatment for anterior uveitis, it is unlikely that treatment of uveitis with corticosteroids caused the DM in these patients.

In a study on elderly patients by Chatzistefou et al. [17] in 1998, the percentage of DM (13%) was higher than in the same age group in the general population (7–8%) in the USA suggesting an association between uveitis and diabetes. The frequency of DM was lower in idiopathic uveitis than in uveitis with a specific diagnosis, however, which does not support such an association [17]. Waite and Beetham [5]also reported evidence against an association in 1935; the frequency of iritis and cyclitis was found to be the same in people with and without DM and unlike other authors [3, 6, 14, 16], they could not recognize "a distinctive 'diabetic' iritis or cyclitis [5]." The suggested association of diabetes in uveitis patients may be confounded by uveitis treatment with systemic corticosteroids which potentially exacerbates DM. However, since uveitis described with DM is most commonly anterior, systemic corticosteroids would not have been indicated for the treatment and thus would not be a confounding concern [2, 15, 17].

Etiology

Inflammation is an important part of the pathophysiology of both diabetic retinopathy and uveitis [3, 29–34]. Proinflammatory factors such as interleukin-1 beta (IL-1 beta), IL-6, IL-8, interferon-induced protein 10 (IP-10), and tumor necrosis factor alpha (TNF-alpha) are up-regulated in eyes with diabetic retinopathy [29, 35–42]. Over 16 different vascular endothelial growth factor (VEGF) independent inflammatory cytokines have been implicated in proliferative diabetic retinopathy [43, 44]. Increased levels of inflammatory cytokines in the serum of diabetic patients [45], as well as in the aqueous and vitreous of eyes with diabetic retinopathy [46] are related to

progression of proliferative diabetic disease. Alternate complement pathway activation has also been investigated in the eyes with diabetic retinopathy [47].

In fact, patients with DM and uveitis have been reported to have severe inflammation and reduced vision [3]. This could be attributed to the breakdown of the blood-retinal barrier and the blood-aqueous barrier in both uveitis and DM [3, 48–51].

In 1975, Cunha et al. [48] measured fluorometric values, or the fluorescein concentration in the vitreous, in the eyes of diabetic patients with variable retinal involvement, and in normal controls. The fluorometric values were significantly higher in all diabetic patients compared to normal subjects, even if they did not have any evidence of diabetic retinopathy on fundus exam. Eyes with diabetic retinopathy had the highest fluorometric values of all patients [48].

Another method of assessing blood-retinal barrier dysfunction is through the measurement of aqueous flare by the laser flare cell meter (LFCM) [49, 52], which is essentially quantifying blood-aqueous barrier dysfunction [51]. Nguyen et al. [52] examined 112 eyes of 112 type 2 DM patients and found a correlation between retinal capillary changes and aqueous flare. Patients with retinal capillary dilatation and exudation had higher flare values [52]. Other studies by Jandratis et al. [49], Inoue et al. [50], and Moriarty et al. [51] support the idea that laser flare intensity provides a qualitative method of assessment of diabetic dysfunction of the blood-ocular barrier. Moreover, blood-ocular barrier dysfunction has been found to be directly correlated with the extent of diabetic retinopathy [50, 51]. Jandratis et al. also showed that aqueous flare intensity decreases in eyes after successful treatment of diabetic macular edema with modified grid pattern photocoagulation [49].

As mentioned, there have also been reports of uveitis acutely after PRP in patients with DM [10, 12]. Moriarty et al. [53] studied this phenomenon by measuring aqueous flare using LFCM after laser photocoagulation treatment was performed on the eyes of patients with DM. They found that the breakdown of the blood-aqueous barrier might occur after PRP, especially in heavily pigmented irides, and attributed these changes to laser affects in the anterior segment [53], thus postulating causation for uveitis after PRP in patients with DM. The authors suggested clinicians consider the use of topical steroids, non-steroidals, mydriatics, or apraclonidine in the first few days after heavy PRP, especially in heavily pigmented irides [53].

It has been postulated that the coexistence of iritis and symptomatic autonomic neuropathy suggests an underlying immunological basis for autonomic neuropathy in DM [28]. Guy et al. propose that this may result from a cross-reaction of insulin antibodies and nerve growth factor [28]. In a study by Martyn et al., and contrary to evidence by Guy et al., the authors found that the prevalence of iritis in patients with DM and autonomic neuropathy was not significantly higher than those with normal autonomic function [21].

Autonomic neuropathy is not the only manifestation of DM that has been suggested to have an immunological basis. The link between diabetes and uveitis has been supported by the notion that DM in general is to some degree immune driven [35, 54]. Castagna et al. [1] only found a significant association between anterior uveitis and type 1 DM. They also found a significant increase in CD8+ lymphocytes, normal values of CD4+ lymphocytes and a decrease in the CD4+/CD8+ ratio in all patients concurrently affected by anterior uveitis and type 1 DM [1]. The authors postulate that this immune cell imbalance may contribute to the maintenance of the uveitis [1]. In an immunohistological study by Baudouin et al. [54], authors found the expressio of major histocompatibility complex type II (MHC-II) on the endothelial cells of neovessels in the eyes with proliferative diabetic retinopathy. Retinal pigment epithelial cells and normal retinal vessel endothelial cells do not express MHC-II or form immune complexes [54]. This study further supports the proposed immunological link between DM and uveitis.

Alternatively, authors have investigated the possibility of patients with uveitis developing hyperglycemia or glucose intolerance. In a study on 20 patients with VKH disease, Yamato et al. [18] assessed glucose intolerance in patients before the administration of systemic corticosteroids. They found a high incidence of glucose intolerance in the acute stage of VKH; 11 patients (55%) exhibited glucose intolerance on the 75 g oral glucose tolerance test. None of the patients, however, had insulin secretion deficiency. The authors suggested that the autoimmune inflammatory process in VKH might be related to the glucose intolerance finding in these patients. The postulated immune mechanism is the role of cytotoxic T-cells against melanocytes in VKH and against pancreatic beta-cells in insulin-dependent DM [18].

This suggested link between the autoimmune inflammatory process in uveitis patients to glucose intolerance or hyperglycemia is debatable. Udoetek et al. [55] explored the risk of hyperglycemia requiring treatment in patients with inflammatory eye diseases.

The risk of hyperglycemia requiring treatment was found to be low (relative risk equals 1 within 1 year) in patients with uveitis.

Cases

A summary of information collected from case reports and series on patients found to have both diabetes and uveitis is outlined in Table 1 [3, 6, 7, 10, 12, 14, 16, 21, 23–28, 56–60]. The total number of patients reported is 82, with 26/37 patients having bilateral involvement and 11/37 having unilateral involvement. The percentage of female patients is 59.4% (19/32 patients). Of the 18 patients whose

Table 1 Case reports and series of patients with diabetes and uveitis

Year	Author	No of cases	Age	Sex	Type of DM	Cause of uveitis	Location of uveitis	Diabetes preceding	Precipitating event	Concurrent illness or infection
1868	Noyes [7]	1 pt., 2 eyes	60	F	Glycosuria	Pure glycosuria	Iritis and Retinitis	–	–	None
1969	Savin [56]	1 pt., 1 eye	61	M	–	Sarcoidosis	Iridocyclitis	Yes	–	Sarcoidosis, Necrobiosis Lipoidica
1984	Guy et al. [28]	14 pts. , 25 eye	31.2 mean	4 M, 10 F	Insulin requiring diabetes	No known cause	Iritis	Yes	–	Autonomic neuropathy
		1 pt	–	–	Insulin requiring diabetes	Associated with Reiter's disease	Iritis	Yes	–	Reiter's disease
1986	Martyn et al. [21]	2 pts	–	–	–	–	Iritis	Yes	–	Abnormal autonomic function
		1 pt	–	–	–	s/p cataract extraction	Iritis	Yes	Cataract extraction	Abnormal autonomic function
		1 pt	–	–	–	s/p ultraviolet light exposure	Iritis	Yes	Welding	Abnormal autonomic function
		1 pt	–	–	–	-	Iritis	Yes	-	Normal autonomic function
1989	Jaggaroa et al. [24]	1 pt., 2 eyes	45	M	Insulin-dependent DM	Vogt-Koyanagi-Harada (VKH)	Anterior uveitis and inflammatory changes in posterior pole	Yes	–	VKH and Hypothyroidism
1992	Rothova et al. [6]	20 pts	–	–	–	diabetes-related uveitis	Anterior	–	–	–
1999	Murray et al. [26]	1 pt., 1 eye	56	M	Type II DM	Fuch's heterochromic cyclitis	Anterior	Yes	–	–
2000	Gordon [57]	1 pt., 2 eyes	17	F	Type I DM	–	Anterior	No	–	None
2000	Maruyama et al. [25]	1 pt., 2 eyes	29	M	Insulin-dependent DM	VKH	Panuveitis	No	–	VKH
2003	Yamamato et al. [58]	1 pt., 2 eyes	47	F	Type II DM	Toxoplasma gondii	necrotizing retinitis	Yes	–	Systemic Lupus Erythematosis
2006	Hemidan et al. [23]	1 pt., 2 eyes	3	F	Type I DM	VKH	Panuveitis	Diagnosed simultaneously	–	VKH and Celiac disease
2006	Knol et al. [59]	1 pt., 1 eye	27	F	Type I DM	Toxoplasma	Chorioretinitis	Yes	–	None
		1 pt., 1 eye	58	M	Type II DM	Herpez Zoster	Acute retinal necrosis	Yes	–	Clinical polyneuropathy
2008	Suzuki et al. [60]	1 pt., 2 eyes	30	F	Type I DM	VKH Exudative Uveitis	Posterior	No	–	VKH, Grave's disease

Table 1 (continued)

Year	Author	No of cases	Age	Sex	Type of DM	Cause of uveitis	Location of uveitis	Diabetes preceding	Precipitating event	Concurrent illness or infection
2009	Al Shehri [27]	1 pt., 2 eyes	42	F	Type II DM	Sarcoidosis	Anterior	Diagnosed simultaneously	–	Sarcoidosis
2009	Oswal et al. [3]	2 pts., 4 eyes	–	–	–	diabetes-related uveitis	Anterior	Yes	–	–
		1 pt., 2 eyes	–	–	–	diabetes-related uveitis	Panuveitis	Yes	–	–
2009	Rottgers et al. [9]	1 pt., 2 eyes	54	M	Type II DM	West Nile Virus (WNV)	Chorioretinitis	Yes	-	Metastatic melanoma, Pneumonia, volume depletion, WNV infection
2010	Krifa et al. [61]	1 pt., 1 eye	9	F	Type I DM	Celiac Disease	Panuveitis	Yes	–	Celiac disease
2011	Takahashi et al. [11]	1 pt., 1 eye	38	F	–	Idiopathic dacryoadenitis	Anterior	Yes	–	Dacryoadenitis
2012	Ojaimi et al. [8]	1 pt., 2 eyes	11	M	Insulin-dependent DM	VKH	Panuveitis	No	–	VKH and Psoriasis
	Oswal et al. [16••]	4 pts., 6 eyes	–	–	–	diabetes-related uveitis	–	Yes	–	–
2014	Sinha et al. [10]	1 pt., 1 eye	42	M	Type II DM	Hypopyon uveitis s/p PRP	Anterior	Yes	PRP	–
2014	Liberman et al. [14]	17 pts	–	–	–	diabetes-related uveitis	Anterior	Authors unsure	–	–
2016	Tyagi et al. [12•]	1 pt., 1 eye	58	M	Type II DM	Acute anterior uveitis s/p PRP	Anterior	Yes	PRP	Primary hypertension

age is identified, 22.2% (4/18) are in the pediatric population (age 17 and below) and 11.1% (2/18) are elderly (60 and above). The type of DM is mentioned in 30 patients, with type 1 comprising 76.7% (23/30) and type 2 comprising 23.3% (7/30). The most common location for uveitis is anterior in 84.6% (66/78 patients), followed by panuveitis in 9% (7/78), and posterior in 6.4% (5/78). DM preceded uveitis in 62.3% (38/61 patients) and uveitis preceded DM in only 6.6% (4/61). Authors were unsure about precedence in 27.9% (17/61), and both conditions were diagnosed simultaneously in 3.3% (2/61). A description of the clinical features of these case series/reports is elaborated on below.

Clinical Features

There are few studies that examine the clinical features of uveitis in patients with DM (**Table** 1). In a study consisting of mostly patients with type 2 DM (35/36) by Oswal et al. [16••], the most common location for uveitis was anterior (32/58, 55.2%). Rothova et al. [6] found that all 20 patients with uveitis and DM had anterior uveitis. This is consistent with reports of DM-related uveitis by Liberman et al. [14]. Reported infectious causes of uveitis in patients with DM are tuberculosis, syphilis, toxoplasmosis, West Nile virus, and Herpes Zoster virus [9, 16, 58, 59]. Aside from diabetes-related uveitis, non-infectious causes include VKH, Sarcoidosis, Fuch's heterochromic cyclitis (FHC), HLA-B27 related, Celiac disease, and idiopathic [16••, 21, 23, 24, 26–28, 56, 60, 61]. Other linked precipitating factors for uveitis were cataract extraction, ultraviolet light exposure from welding, and PRP for proliferative diabetic retinopathy (PDR) [10, 12, 21].

Regarding the type of DM in patients with uveitis, there is no clear dominance of one type over the other. Rothova et al. found that 10/16 (63%) of patients with anterior uveitis and DM had type 1 DM [15]. Interestingly, Oswal et al. only had 1 patient with type 1 DM in their series [16••]. No distinction between type 1 and 2 DM was made by authors in the cases of DM-related uveitis [3, 6, 14, 16]. In the cases summarized in Table 1, 23 patients had type 1 DM or insulin-dependent DM, and 7 had type 2 DM and 51 patients had DM of unknown type.

Diabetic complications that occur in patients with uveitis include maculopathy/macular edema and progression to proliferative disease [16••, 59]. In fact, Knol et al. reported on the rapid progression of retinopathy to PDR in 2 uveitic eyes of 2 patients as compared to the non-uveitic eyes of the same patients [59]. Systemic complications include angiopathy, retinopathy, and autonomic neuropathy [15, 28]. Several authors also comment on the difficulty in controlling blood sugar in the context of uveitis treatment with systemic steroids [8, 57, 62]. This becomes apparent when looking into the onset of DM and uveitis (Table 1). Most authors reported that the diagnosis of diabetes preceded the diagnosis of uveitis, and a couple reported that both conditions were diagnosed simultaneously. In three cases, DM was diagnosed after steroids were used to treat VKH [8, 24, 60]. Gordon et al. [57] diagnosed DM in a 17-year-old girl with history of anterior uveitis attacks after she presented with diabetic ketoacidosis. The authors suggest that testing for DM upon initial presentation of uveitis may have prevented that morbidity [57].

Conclusion

Intraocular inflammation has been associated with DM and this has been the focus of several studies reviewed in this paper. Diabetes has been found to be a prevalent systemic disease in elderly individuals presenting with their first episode of uveitis, with prevalence ranging from 7 to 13%. Whether that represents a real association or a consequence of increasing prevalence of DM with age remains to be determined. Several reports have reported a higher prevalence of DM in the elderly uveitis patients compared to the elderly population in their countries (Spain and Netherlands). Furthermore, there are several reports on a DM-related uveitis, defined as idiopathic uveitis in the presence of poorly controlled DM. However, this is not a commonly described entity as these cases would be labeled as idiopathic uveitis in the vast majority of the uveitis literature. An association between uveitis and DM is controversial with conflicting results in the literature. The basis of the association is the common pathophysiology of inflammation in diabetes and uveitis. Uveitis in people with DM has been attributed to the dysfunction of the blood-ocular barriers in these patients, an example of which is uveitis in patients with DM occurring after PRP. Uveitis in people with DM is most commonly anterior and has been reported in people with both type 1 or type 2 DM. It has been suggested that uveitis eyes of patients with DM are more likely to have progression of diabetic retinopathy and to develop macular edema.

More studies are needed to systematically delineate the characteristics of uveitis in people with DM as well as to determine if an association truly exists between these two potentially morbid conditions. For meaningful results, a large cohort of patients with coexisting DM and uveitis needs to be identified. Features to be studied include prevalence of type of DM, location of uveitis, inflammatory markers in these eyes compared to DM and uveitis alone, progression of DR in these eyes compared to DM alone, inflammation grade and control compared to uveitis alone, and the effect of the treatment of either condition on the manifestation or control of the other.

Compliance with Ethical Standards

Conflict of Interest Wajiha J. Kheir, Huda A. Sheheitli, and Rola N. Hamam declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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