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Obesity and Retinopathy in Diabetes

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Abstract

Diabetes mellitus a chronic metabolic disorder is a fast-growing global problem with significant social, health and economic consequences. It is estimated to have affected 366 million people worldwide and is expected to nearly double by 2030 with this rising trend observed for both type 1 and type 2 diabetes. An ageing population and rising prevalence of obesity reaching almost epidemic proportions are the main reasons for this increase. Diabetic retinopathy (DR) a common and progressive microvascular complication of diabetes represents one of the leading causes of vision impairment and blindness in working-age adults in developed countries. Epidemiological and clinical studies have confirmed that the main risk factors for DR are diabetes duration, prolonged poor glycaemic control, hypertension and hyperlipidemia. In addition to the well-known risk factors increasing attention is assigned to obesity specifically due to its frequency and inter-relationship with diabetes. To date this relationship has been examined in a number of epidemiologic studies giving conflicting results with most studies confirming the positive association. Although the underlying pathophysiological mechanisms supporting the relationship between obesity and DR are yet to be defined several biological theories have been suggested comprising the potential involvement of platelet function, blood viscosity, aldose reductase activity, vaso proliferative parameters, oxidative stress and inflammation. Given that weight is changeable and can be modified by lifestyle intervention opens up implications for further research and intervention in order to elucidate the role of obesity and body weight variations on the pathogenesis of DR.

Key words:

Obesity; Diabetic retinopathy; Risk factor, Pathogenesis

Diabetes Mellitus and Obesity

Overweight (body mass index, BMI ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) have become a growing global public health problem with increasing prevalence in many affluent societies as well as in developing countries [1-3]. Currently 300 million people are considered to be obese and due to this rising trend it is anticipated that this figure could double by the year 2025. Addressing the problem of obesity becomes important since being a disease itself it represents a risk for many metabolic and cardiovascular diseases including diabetes [4]. Diabetes mellitus another widespread and serious public health issue represents the most frequent endocrine disease in developed countries. It is estimated to have affected 366 million people worldwide and is expected to nearly double by 2030 with this growing trend observed for both type 1 and type 2 diabetes [5-8]. The number of patients with type 2 diabetes is rapidly increasing and it is projected that by 2025 there will be 380 million people affected and 418 million people with impaired glucose tolerance owing to an increase in obesity, inactivity, life span extension and better detection of the disease [9]. Type 1 is less widespread, accounting for 5–10% of the total cases of diabetes and its increased incidence is also seen across the world in various population studies with the range being between 2% and 5% [5-8]. Contemporary studies suggest that possible causes of this epidemic include the role of infections, early childhood diet, environmental pollutants, insulin resistance and recently more significance has been given to obesity [8]. As already stated obesity is a chronic disease with a rising prevalence across all age groups over the last 20 years [10] and like diabetes it is also a dysmetabolic disorder whose long term complications include severe impairment of the vascular system [10-12]. The relationship between obesity and type 2 diabetes is well known with growing evidence also confirming its connection with type 1 diabetes. Libman et al. reported that 50% of young Americans with type 1 diabetes are overweight or obese and some studies have suggested that weight gain may also be an accelerating factor for the onset of this type of diabetes and may contribute to its rising incidence as confirmed in type 2 [10].

Diabetic Retinopathy: Epidemiology and Risk Factors

Diabetes mellitus represents one of the most detrimental diseases and significant public health problems due its growing incidence and prevalence as well as high risk of macro- and microvascular complications among which diabetic retinopathy (DR) takes an important place [9,13]. Despite the availability of effective treatment DR remains a leading cause of acquired blindness in working-age adults and has been estimated to represent 12% of blindness in developed countries [14,15]. Although type 1 diabetes is much less common its relevance should not be disregarded since the incidence of any stage of retinopathy in patients with type 1 diabetes is higher than in those with type 2 and the advanced forms of DR usually develop throughout the patients most productive age [5-9]. According to a study conducted to estimate the global prevalence of DR 35% of people with diabetes had some form of DR, 7% had proliferative DR (PDR), 7% had DME (diabetic macular oedema) whilst 10% had vision

threatening DR, defined as the presence of PDR and/or DME [16]. Prevalence of DR in individuals with long-standing diabetes (20 years or more) exceeded 50% [17]. Furthermore age standardized prevalence of any form of DR in type 1 diabetic subjects aged 20-79 years after 10 to 20 years of diabetes duration was 55.55% and 86.22% after more than 20 years whilst prevalence of PDR after 10 to 20 years was 19.46% and 40.36% after more than 20 years [16]. The diagnosis of type 2 diabetes is often preceded by years of undiagnosed hyperglycaemia. Thus in a number of patients DR is in fact present at the time of diagnosis: 37% of them already having microaneurisms or more severe retinopathy in one and 18% having retinopathy in both eyes [18,19].

The prevalence of retinopathy increases with the duration of diabetes and is related to hyperglycemia, hypertension, hyperlipidemia, pregnancy, genetic predisposition, nephropathy and anemia as confirmed by many previous epidemiological and clinical studies [20-24]. Tight glycaemic control, strict hypertension and hyperlipidemia treatment cannot entirely eliminate the risk of microvascular diabetic complication and therefore there is a continuing need for the development of new management strategies [14,15,25-27]. In addition to the well-known risk factors recently increasing attention is assigned to obesity specifically due to its frequency and inter-relationship with diabetes. Obesity intensifies the risk of diabetes, its macrovascular complications and reduces life expectancy in all age groups [4,28]. An increase in obesity also correlates significantly with the deterioration of HbA1c, a decrease in HDL-cholesterol, an increase in triglycerides as well as a higher prevalence of hypertension, all known risk factors for DR development [29,30]. Diabetic vascular complications including DR are often asymptomatic during their early stages and thus when visible symptoms develop unfortunately only a few options for effective treatment are available. Therefore screening needs to be started at the very onset of the disease. Identification of the risk factors and subclinical signs of complications is essential for early implementation of preventive and therapeutic strategies which could change the course of vascular complications and improve the prognosis of patients with diabetes. Since DR has become a main cause of vision loss and blindness worldwide intense focus has also been directed to the early prevention of DR and a better comprehension of the benefit of controlling modifiable risk factors. Given that it is manageable by lifestyle intervention namely nutrition, exercise and education there is a growing need to shift focus on obesity itself.

The relationship of obesity and DR has been examined in a number of epidemiologic studies yielding inconsistent results (Table 1). Nevertheless the majority of studies have reported a significant association between obesity and high BMI with DR [30-38]. Conversely others have reported an association between low BMI and DR [39-41]. This lack of consensus may be partly explained by methodological differences, differences in study participants, lack of comprehensive anthropometric measurements, inadequate clinical sample size and particularly racial or ethnic differences [39,40].

Year/ Authors	Study	Country/ Population	Number of patients	DM type	Relationship between DR and obesity
1984 Klein et al. [38]	The Winsconsin epidemiologic study of DR	Southern Winconsin	1370	Type 2 according to age of 30 years or more at time of diagnosis	Negative
1997 Klein et al.	The Winsconsin epidemiologic study of DR	Southern Winconsin	1370	Type 2 according to age of 30 years or more at time of diagnosis	Negative
1998 Dowse et al. [40]		Multiethnic population of Mauritius	911 of 6553 participants	Type 2 and impaired glucose tolerance	Negative
2001 Zhang et al. [29]	Diabetes Control and Complications Trial (DCCT)	Belgium	1441	Type 1	Positive
2005 Chaturvedi et al. [52]	The EURODIAB Prospective Complications study	Europe	764	Type 1	Positive
2003 Van Leiden et al. [32]	The Hoorn Study	Netherlands	626 of 3553 participants	Type 2	Positive
2003 Henricsson et al. [30]	Diabetes Incidence Study in Sweden (DISS)	Sweden	806	Type 1 and type 2	Positive
2005 De Block et al. [36]		Belgium	592	Type 1	Positive
2010 Raman et al. [39]	SankaraNetheralaya DR Epidemiology and Molecular Genetic Study (SN-DREAMS-I)	Urban Indian population	1414	Type 2	Negative

2010 Lim et al. [34]	Singapore Malay Eye Study (SiMES)	Urban Malay adults	718 of 3280 participants	Type 2	Negative
2011 Dirani et al.	Diabetes Management Project (DMP)	Victoria/ Australia	492	Type 1 and type 2	Positive
2013 Li et al.		Beijing/China	2194	Type 2	Positive
2013 Kaštelan et al.		Croatia	545	Type 2	Positive

Table 1: Studies investigating the relationship between diabetic retinopathy and obesity.

DM: Diabetes Mellitus; DR: Diabetic Retinopathy

Diabetic Retinopathy and Obesity - Proposed Pathophysiological Mechanisms

Although the underlying pathophysiological mechanisms supporting the relationship between obesity and DR are yet to be defined several biological theories have been suggested comprising the potential involvement of platelet function, blood viscosity, aldose reductase activity and vasoproliferative parameters such as Vascular Endothelial Growth Factor (VEGF). Further both metabolic syndrome and increased oxidative stress due to their association with obesity and DR have also been suggested as possible pathophysiological mechanisms [15,35,42-44].

Many investigations have been directed to the role of angiogenic factors particularly the VEGF in the pathogenesis of DR whereby the concentration of VEGF a potent growth factor which promotes angiogenesis has been found to be higher in the vitreous of eyes with PDR [45]. Patients with proliferative retinopathy also demonstrate elevated peripheral markers of angiogenesis and endothelial dysfunction, suggesting a participating role for these processes in the pathogenesis of PDR [46]. Adipose tissue produces several vascular growth factors which stimulate angiogenesis and are known to be associated with the expansion of the capillary bed in regional adipose areas [43]. In the serum of obese individuals' elevated angiogenic factors including VEGF have been observed partially owing to the presence of oxidative stress [11] providing additional confirmation of the possible link between obesity and PDR [11,43-46]. Further a positive correlation between BMI and serum concentration of VEGF, angiopoietin-2 and angiogenin was also found [43].

Recent evidence suggests that the biochemical link between diabetes and development of its complications in both types of diabetes includes the two interactive mechanisms namely increased inflammation and oxidative stress. In diabetes a chronic state of low-intense body inflammation episodically aggravated by hyperglycemic fluctuations which appear to be related to elevated indicators of inflammation, immune activation and oxidative stress is present [47]. Likewise obesity is also associated with the state of elevated inflammation, oxidative stress and insulin resistance with growing evidence connecting their mutual interrelationship [48]. Obesity increases the prevalence of several risk factors which have previously demonstrated to be involved in DR onset and development particularly including inflammatory markers. New data suggests that obesity is associated with both increased local adipose and more generalized systemic inflammation [47-49].

Adipose tissue is regarded to be an active endocrine and paracrine pro-inflammatory organ which releases a large number of cytokines and bioactive mediators such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) leptin, adiponectin, that influence not only body weight homeostasis but also lipid levels, coagulation, atherosclerosis and diabetes occurrence, inflammation, oxidative stress, insulin resistance and DR development. Moreover endothelial dysfunction (ED) as an early indicator of DR is also present in obesity and is characterized by increased levels of intracellular adhesion molecule-1 (ICAM-1) [49-52]. ED caused by oxidative stress and inflammation processes both connected to diabetes and obesity plays a key role in the pathogenesis of diabetic angiopathy and arterial wall damage. It is well established that endothelial dysfunction is involved in diabetic retinopathy as well as nephropathy and microalbuminuria is considered to be a marker of ED [51]. Oxidative stress has been proposed to be a potential pathogenetic mechanism linking obesity and insulin resistance with ED [48]. It is considered to be the common factor underlying insulin resistance and may explain the presence of inflammation since the release of IL-6, mainly from abdominal tissue may have a key role in the relationship between oxidative stress and ED. IL-6 contributes to C-reactive protein (CRP) elevation and low-grade inflammatory state and also has an obvious relationship with coagulation, insulin resistance, dyslipidemia and ED [48]. Hyperglycemia via glucose auto oxidation and/or non-enzymatic glycation with concurrent impairment of the antioxidant defence system leads to an increased production of reactive oxygen species (ROS). Previous reports have demonstrated that ROS, the signalling molecules of endothelial cell damage contribute to the modulation of endothelial function as well as the over expression of inflammatory cytokines [50]. Schram et al. investigated the association of inflammatory markers with vascular complications in type 1 diabetes and has shown a strong and independent association of CRP, IL-6 and TNF-α with DR [53]. The profile of intraocular TNF-α and IL-6 in diabetic subjects with different degrees of DR show that intraocular inflammation seems to be involved in PDR however is not prominent in the early stages of retinopathy development. Diabetic subjects exhibit overall increased inflammatory activity compared to non-diabetics, as demonstrated by increased serum levels of TNF-α [54]. A study conducted to determine a possible association between serum levels of inflammatory markers and PDR show the association between

TNF- α and PDR in type 1 diabetic patients indicating that inflammation may play a significant role in the pathogenesis of PDR [55].

Some results suggest that nitric oxide (NO), soluble IL-2 receptor (sIL-2R), IL-8 and TNF-α may play important roles in the pathophysiology and progression of DR and via activity on the endothelial cells may jointly effect the course and progression of DR [56]. A study conducted to investigate the involvement of the inflammatory processes in the pathogenesis of PDR demonstrate an increase in soluble ICAM-1 (sICAM-1) and soluble vascular adhesion molecule-1 (sVCAM-1) levels, as well as their correlation with high vitreous IL-6 and TNF-α concentrations in patients with PDR which in turn confirm their inflammatory nature [57].

Pathways of inflammation and ED are considered to be important in the pathogenesis of DR [58]. In a clinical study with type 2 diabetic patients' the level of adhesion molecules were higher in subjects with as opposed to those without retinopathy [59]. Likewise in another study inflammatory and endothelial function markers were strongly associated with the presence of DR [60]. Similarly E-selectin values were found to be increased in patients with type 1 diabetes mellitus and retinopathy [61] however not observed in subjects with type 2 and retinopathy [62]. Tomić et al. demonstrated that the association between obesity, inflammation and other risk factors plays an important role in the endothelial impairment involved in the pathogenesis of DR [41,63]. However, only a few studies have examined the role of systemic inflammation in DR development [53]. In two case-control studies diabetic subjects with macular oedema (ME) or PDR had higher levels of vascular endothelial growth factors and cytokines in their vitreous then those without ME or PDR [64,65].

Oxidative stress has been proposed to be a potential pathogenetic mechanism linking obesity and insulin resistance with ED. It may explain the presence of inflammation since the release of IL-6, mainly from abdominal tissue may have an essential role in the relationship between oxidative stress and ED. IL-6 contributes to CRP elevation and a low-grade inflammatory state and is also closely linked to coagulation, insulin resistance, dyslipidemia and ED [48]. Ultimately obesity and DR may also be connected owing to increased oxidative stress as a result of its association with hyperleptinemia [48,52]. Plasma leptin levels are seen to be elevated in obesity and correlate positively with both visceral and subcutaneous fat areas [52]. High plasma leptin levels have been found to be related to both hypertensive and diabetic retinopathy [52]. Pertinent to DR recent findings show that leptin promotes vascular endothelial cell proliferation and angiogenesis *in vitro* and neovascularization *in vivo* [52,66]. Known data demonstrate leptin involvement in retinal diseases with elevated leptin levels in the human vitreous in PDR and retinal detachment as well as its presence in fibrovascular epiretinal tissue [67,68]. Uckaya et al. show a positive correlation of advanced forms the DR with the increase of the plasma leptin levels. Previously observed leptin-induced promotion of angiogenesis and neovascularization supports the possibility that it may have a role in the advancement of DR to its proliferative phase [51]. Leptin levels in vitreous humour may be a possible factor in the course of vascular and proliferative retinal diseases [69]. It is considered that the intraocular production of leptin is not critically involved in the etiopathogenesis of PDR, however recent results indicate that serum diffusion is a relevant source of leptin in vitreous fluid [70].

Alternatively, adiponectin levels correlate negatively with visceral and subcutaneous fat areas whilst its low levels are associated with obesity and insulin resistance [42,50,71]. An increased level of adiponectin was found in diabetic and nondiabetic subjects with impaired kidney function as well as in type 1 diabetic patients without complications and particularly in those with diabetic nephropathy [63,66,72,73]. Adiponectin inhibits monocyte attachment to the vascular bed by decreasing the expression of adhesion molecules (VCAM-1, ICAM-1, E-selectin) in endothelial cells and also suppresses the production of proinflammatory cytokine TNF-α by macrophages [74,75]. Further adiponectin protects against the development of inflammation and provides an additional link between obesity and vascular inflammatory processes [75]. Clinically lean patients with type 2 diabetes having DR (proliferative as well as non-proliferative) are reported to have lower levels of adiponectin than patients without retinopathy [76]. Adiponectin is likely to be on of the main contributors to the pathogenesis of both type 2 diabetes and DR. Conversely, type 1 diabetic patients with microvascular complications have higher serum adiponectin levels than those without complications [77]. The elevated adiponectin concentrations observed in subjects with microvascular disease may indicate altered regulation of this adipocytokine in patients with complications associated with type 1 diabetes [78]. The clinical significance of adipocytokines in terms of a causative role in metabolic disorder and microangiopathy in diabetes should certainly be investigated in the future.

Epidemiological data from various studies have identified hyperlipidemia and hypertension which are connected with obesity as risk factors for DR [30,43,66]. In fact, metabolic syndrome encompassing these conditions has also been shown to be associated with retinopathy [79]. Moreover, many overweight type 1 diabetic patients are difficult to treat and require a relatively high dose of insulin to achieve adequate glycemic control [35,63]. Thus it is possible that metabolic syndrome and its associated insulin resistance although usually associated with type 2 diabetes may also be a clinical feature for some patients with type 1 [10,79]. It is generally established that in obese and diabetic individuals inflammatory and oxidative processes are found to be consistently elevated with complex underlying activating mechanisms. Further, the level of inflammatory activation seems to be proportional to severity of obesity in overweight individuals and the quality of glycemic control in type 1 diabetic patients respectively. A better and more detailed understanding of all the facets linking obesity and diabetes with the components of the underlying inflammatory and oxidative dysregulation represents the basis for future ability of successful prevention and management of DR [11,80].

Concisely obesity may increase the risk of DR development via several established mechanisms such as hypertension, dyslipidemia and glucose dysmetabolism as well as some new mechanisms which still need to be elucidated such as IL-6, TNF-α, leptin, adiponectin, and adhesion molecules. Mutually they may lead to an increase in oxidative stress, insulin resistance, endothelial dysfunction and consequently DR development [50,80] (Table 2). Furthermore, physical activity and weight loss as lifestyle factors provide some additional evidence to support the relationship between obesity and DR whereby weight loss has been seen to delay the onset of diabetic complications including DR [81]. Taking this into account the application of interventions that promote weight reduction may therefore also reduce the risk of DR. Lifestyle changes with personal responsibility specifically towards weight loss has been advocated as a key factor in the prevention of diabetes and delaying diabetic complications including retinopathy in susceptible patients [42,81].

Established factors	Novel factors
Hyperglycaemia	Vasoproliferative factors
Hypertension	Oxidative stress
Dyslipidaemia	Low grade inflammation

Table 2: Obesity in the pathogenesis of diabetic retinopathy.

Conclusion

In conclusion, DR is a complex disease with many proven and some insufficiently verified risk factors including obesity. It has been shown that obesity in correlation with poor glycaemic control, hypertension and dyslipidemia appears to be associated with the progression of DR and may be a relevant factor involved in DR occurrence and development. Several findings demonstrate the value of obesity assessment as a possible modifiable risk factor with potential clinical implications in the management of DR. Since weight gain is changeable and may be managed by lifestyle intervention additional studies are required to investigate and fully clarify the pathogenic role of obesity and weight loss in retinal diabetic complications. Thus study findings which confirm the association of obesity with the presence and severity of DR undeniably open up the necessity for further research and intervention.

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