Insulin resistance and diabetic macular oedema in type 2 diabetes mellitus

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ABSTRACT

Objective To evaluate the association between insulin resistance and diabetic macular oedema in type 2 diabetes.

Methods Patients with type 2 diabetes who agreed to undergo blood sampling were enrolled into this cross-sectional study. Patients who had received treatment for macular oedema within the past 3 months and those with other retinal diseases were excluded. The following data were recorded: age, sex, time of diabetes evolution, HbA1c, ophthalmologic and systemic treatment, and lens status. Optical coherence tomography (OCT) was performed to determine the morphological patterns of macular oedema. Insulin resistance was established by a McAuley index of <6.3 and fasting insulin levels of >16 mU/l.

Results A total of 177 eyes from 90 patients were included; 27.1% of eyes were from insulin-resistant patients. There were no differences in age, time of evolution, sex, HbA1c level or lens status between insulin-resistant and non-resistant patients. Insulin-resistant patients were more likely to have exogenous insulin therapy ($p<0.05$; OR=3.8). An association was found between diabetic cystoid macular oedema and insulin resistance (Fisher exact test $p=0.007$; OR=2.53, 95% CI 1.52 to 4.2). There were no associations between insulin resistance and the other morphological patterns of oedema. Patients undergoing insulin therapy were found to have an association with a diffuse retinal thickening pattern on OCT ($p=0.036$; OR=1.4). However, no association was found between insulin therapy and the presence of cystoid macular oedema.

Conclusions The findings of this study indicate a relationship between insulin resistance and cystoid macular oedema that unrelated to the use of insulin. Insulin treatment was associated with diffuse macular oedema.

INTRODUCTION

Type 2 diabetes mellitus is the most common metabolic disease worldwide. Whereas low plasma insulin levels are seen in type 1 diabetes mellitus, insulin resistance is a characteristic feature in type 2 patients. Macular oedema is a major complication of diabetes and is the leading cause of blindness in patients aged 25 to 74 years in developed countries.

The origin of diabetic macular oedema resides in a series of local and systemic injuries to the retina, including vascular dysfunction, neural degeneration and retinal inflammation. It remains unclear whether diabetic retinopathy is initiated by vascular dysfunction leading to neural degeneration and subsequent inflammation, or by dysregulation of the neural retina metabolism with subsequent inflammation and vascular damage.[1]

The relationship between diabetes mellitus and inflammation was first recognised more than 60 years ago,[2 3] and recently an association between insulin resistance and systemic inflammation was reported.[4 5] Abnormalities in glucose and lipid metabolism, obesity and high blood pressure occur together commonly enough in the same individuals to suggest that they are interrelated. This cluster of metabolic abnormalities is attributable to insulin resistance; that is, a reduced sensitivity to the action of insulin in tissues. In the early stages of this condition there is a compensatory state of hyperinsulinaemia, and later on, hyperglycaemia. Insulin resistance is an inherently proinflammatory state that begins before the onset of overt hyperglycaemia and is related in part to excess nutrients in adipose tissue, skeletal muscle and liver. Inflammation induces a catabolic state that counteracts normal anabolic processes, probably as an adaptive mechanism to prevent excessive cellular nutrient uptake. Systemic inflammation increases with the onset of clinical diabetes and contributes to the development of complications, including nephropathy and retinopathy. In addition, high insulin levels have a vasoreactive effect that results in increased permeability of the retinal vessels.[6 7]

Insulin resistance has been investigated and correlated with clinical risk factors, mainly in non-diabetic patients. Direct methods (the reference standard) can be used to measure insulin resistance, but they are complex to perform and expensive. Indirect measures of insulin resistance, such as fasting insulinaemia[8] and mathematical models, have shown a good correlation with the reference standard in non-diabetic patients.[9]

OBJECTIVE

This study evaluated the association between an indirect measure of insulin resistance and diabetic macular oedema in patients with type 2 diabetes mellitus, specifically the cystic type, and assessed the effect of exogenous insulin treatment on macular oedema.

METHODS

This is a cross-sectional study performed in a clinic- and hospital-based population, enrolled over a 3-week period in our hospital's general ophthalmology department and dedicated retinal outpatient clinic. The study included all patients with type 2 diabetes who agreed to undergo blood sampling. Patients who had received treatment for

macular oedema within the past 3 months and those with other retinal diseases were excluded.

The following data were recorded in all cases: age, sex, time of diabetes evolution, HbA1c levels, ophthalmological and systemic treatment, and lens status. The Early Treatment Diabetic Retinopathy Study (ETDRS) criteria were used to determine whether clinically significant macular oedema was present or not. In patients with clinically significant macular oedema, optical coherence tomography (OCT) (Stratus OCT Humphrey Zeiss Inc., San Leandro, California, USA; software version 4.0) was performed to determine the morphological patterns of macular oedema according to the classification of Kim *et al*[10] OCT scans were graded by one trained reader according to the predominating morphological patterns present: type I, diffuse retinal thickening; type II, cystoid macular oedema; type III, serous retinal detachment without posterior hyaloidal traction; type IV, posterior hyaloidal traction without traction retinal detachment; and type V, traction retinal detachment.

Blood samples were collected from all patients. Insulin resistance was established on a McAuley index of <6.3 and fasting insulin levels of >16 mU/l.[8 11]

Determination of sample size was based on the normal asymptotic CI for the estimated occurrence of an event in an infinite population, considering the percentage of insulin resistance in the general population [9] to be 32% (95% CI) to achieve an accuracy of ±10.0%. The calculation was performed with ENE 2.0 software (Biometry Department of GlaxoSmithKline and Statistics Service of the Autonomous University of Barcelona). At least 84 patients were required to fulfil these conditions, and 90 were ultimately included in the study.

Results were analysed with SPSS, version 15.0. The Student t test for independent samples was used to compare patients with and without insulin resistance. Associations were studied in 2×2 tables with the χ^2 and Fisher's exact test. ORs were calculated at a 95% CI.

RESULTS

A total of 177 eyes from 90 patients with type 2 diabetes were included in the study; 27.1% of eyes were from insulin-resistant patients. There were no differences in age, HbA1c, time of evolution of diabetes, sex or lens status between the insulin-resistant and non-resistant patients. However, these groups showed some differences related to the treatment received: insulin-resistant patients were more likely to have exogenous insulin therapy (p<0.05; OR=3.8).

The morphological patterns of diabetic macular oedema differed according to whether or not the patients were insulin resistant (p=0.031) (tables 1 and 2, figure 1). When each morphological pattern was compared with insulin resistance, an association was found between diabetic cystoid macular oedema (type II) and resistance (Fisher exact test p=0.007; OR=2.53, 95% CI 1.52 to 4.2) (tables 3 and 4). There were no associations between insulin resistance and the other morphological patterns of diabetic macular oedema.

In addition, patients undergoing insulin therapy were found to have a direct association with a diffuse retinal thickening pattern on OCT (type I) (p=0.036; OR=1.4). However, no association was found between insulin therapy and the presence of cystoid macular oedema (p=0.78).

Table 1 Differences between morphologic pattern of oedema and insulin-resistance

Macular oedema	No oedema	Insulin resistance: Yes 30	Insulin resistance: No 99	Total 129
	Type I	5	17	22
	Type II	8	5	13
	Type III	5	7	12
	Type IV	0	1	1
Total		48	129	177

Type V is not included in the table because there were no patients with this pattern.

Table 2 Differences between morphologic pattern of oedema and insulin-resistance

	Value	df	p Value
Pearson χ^2	10.638*	4	0.031
Likelihood ratio	9.758	4	0.045
Linear-by-linear association	4.803	1	0.028
N of valid cases	177		

*Four cells (40.0%) have an expected count of less than 5. The minimum expected count is 0.27.

DISCUSSION

Direct methods, the reference standard for determining insulin resistance, are difficult to perform and expensive; thus, they are not recommended for epidemiological or clinical studies.[9] Insulin resistance was established as fasting insulin level >16 mU/l in the Paris Prospective Study,[8] which, in our view, is one of the most important prospective studies on this subject. The McAuley index has been described as the most sensitive and specific indirect method to evaluate resistance to insulin.[9] McAuley *et al* define insulin resistance as a score of <6.3.[11] Although these methods have been validated in non-diabetic patients, we have used them in our diabetic population as a simple way to evaluate insulin resistance for the purpose of our study. To provide a stricter definition of resistance, we used both methods—fasting insulin levels and the McAuley index—in the patients studied.

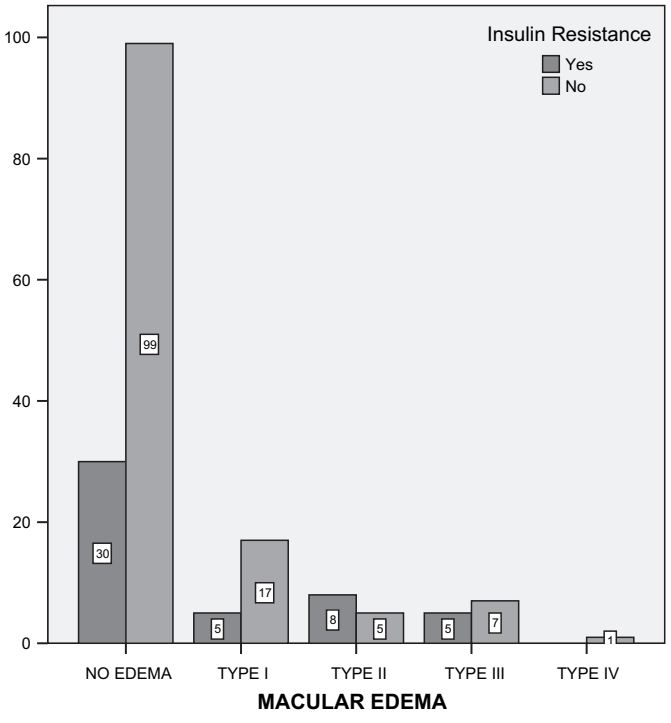

Figure 1 Association between macular oedema pattern and insulin resistance.

Table 3 Type II oedema and insulin-resistance

	Insulin resistance		
	Yes	No	Total
Type II oedema			
Yes	8	5	13
No	40	124	164
Total	48	129	177

The fact that some of our patients were treated with exogenous insulin may have led to an increase in fasting insulin levels, but we consider this an indirect parameter of is less efficiently, and this results in higher fasting insulin levels. The concept of resistance includes exogenous and endogenous insulin. For this reason, we did not differentiate between exogenous/endogenous insulin levels at the time of blood analysis.

Our results showed an association between insulin resistance and exogenous treatment with insulin. It is reasonable that resistant patients would need higher doses of insulin for metabolic control, and this would require exogenous intake of the hormone.

Each patient's eyes were analysed separately because the presence and type of macular oedema was different between eyes in some cases.

The main finding of our study is the differing morphological pattern of macular oedema related to insulin resistance and, of course, the association between cystoid macular oedema and insulin resistance. As mentioned earlier, insulin resistance is a proinflammatory state, and the pattern of oedema found in these patients is very similar to the pattern seen in inflammatory diseases such as Irvine–Gass syndrome and uveitis.[12] In fact, the pathogenesis of cystoid oedema includes both vasoreactivity and chronic inflammation,[13] which we believe may be a result of the patient's insulin-resistant status. In other diseases such as vein occlusion, which are primarily considered vascular events, it has been reported that an inflammatory factor and clinical cystoid macular oedema are often present.[14]

To define whether the association we found was only related to resistance or was also due to insulin treatment, we investigated the relationship between insulin and macular oedema. The fact that a patient is receiving insulin therapy seems to have no relationship with cystoid macular oedema. However, there was an association with a pattern of diffuse retinal thickening, perhaps a result of the vasoreactive effect of insulin.[6 7]

The potential limitations of our study arise from the design and inclusion criteria. This is a cross-sectional clinic- and hospital-based population study with a broad range of inclusion criteria, a simple 'photograph' of our patients that involves no treatment interventions. Therefore, there is the possibility of some bias, such as ongoing treatment for macular oedema in the 3 months before inclusion, or OCT reading by only one observer. Nonetheless, we believe that our cohort provides a close representation of daily practice, with patients consulting at our specialised retinal outpatient clinic and our general ophthalmology department, which implies that patients with and without diagnosed diabetic retinopathy were included. This is also the reason why there are many more patients in the group without oedema than in the group with diabetic macular oedema.

Table 4 Type II oedema and insulin-resistance

	Value	df	p Value
Pearson χ^2	8.410†	1	0.004
Continuity correction*	6.636	1	0.010
Likelihood ratio	7.351	1	0.007
Fisher's exact test			0.007
Linear-by-linear association	8.363	1	0.004
N of valid cases	177		

*Only calculated for 2×2 table.
†One cell (25.0%) has an expected count of less than 5. The minimum expected count is 3.53.

The sample size was difficult to determine. We knew the prevalence of cystoid macular oedema in the diabetic population, but we did not know the prevalence of insulin-resistant patients with macular oedema or with diabetes. Our sample size reflects the percentage of resistance in the population, but the number of participants was not determined according to the purpose of the study because there was not enough data in the literature to provide a basis for the calculation.

Despite these potential limitations, our results indicate that insulin resistance plays a central role in the pathogenesis of macular oedema, particularly in the cystoid pattern. Future longitudinal studies, with more accurate inclusion criteria and other methods to evaluate resistance are needed to confirm our findings. It could be of great interest to investigate the association between insulin resistance and local factors of inflammation.

In summary, the findings of this study indicate a relationship between insulin resistance and cystoid macular oedema that is not related to the use of insulin. Insulin treatment was associated with diffuse macular oedema. Prospective, longitudinal studies are needed to evaluate the role of insulin and insulin resistance in diabetic macular oedema.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

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