Possible Correlation between Diabetic Retinopathy and Atherosclerosis in Type 2 Diabetes Mellitus

Tomina Popescu(1), Christina Pritulescu(1), Maria Mota(2)

(1) University Hospital CF Craiova; (2) Diabetes, Nutrition and Metabolic Diseases Department University of Medicine and Pharmacy, Craiova;

ABSTRACT Diabetes and especially type 2 diabetes is currently a global problem for public health, through the epidemic evolution that this disease gained, but especially through the macro and micro-vascular complications, diabetic retinopathy being one of the first signs of micro-vascular damage. The fact that retinal changes may be a signal for cardiovascular events is not yet clearly demonstrated and is a theme which can offer us big surprises in the future.

KEY WORDS diabetes mellitus, diabetic retinopathy, atherosclerosis, intima-media thickness, cardiovascular risk

Introduction

It is known that diabetes currently affects 246 million people worldwide and the prevalence is estimated to increase around 380 million until 2025. In 2007 top 5 countries with the largest number of people suffering from diabetes were: India (40,9 million), China (39,8 million), USA (19,2 million), Russia (9,6 million), Germany (7,4 million). Every year, about 7 million people will develop diabetes. Besides, every year, 3,8 million deaths are also attributed to diabetes, but the number is even higher if we consider deaths due to cardio-vascular disease aggravated by the diabetes. Diabetes is therefore, the 4th cause of death worldwide. It is estimated that over 50% of people with diabetes are not diagnosed, in some countries this percentage can reach up to 80% (17). Regarding the complications of diabetes, this is the most important cause of renal failure in developed countries, being responsible of the high cost of dialysis. In the industrialized countries, diabetic retinopathy is also the main cause of blindness among persons of working age (20-65 years). Global estimated, over 2,5 million people are affected by retinopathy. Macro-vascular complications make people suffering from diabetes to have a life expectancy of approximately 5-10 years smaller than those without diabetes.

Taking into account this data, results that prevention of specific complications of diabetes is the key issue because of the morbidity associated.

Diabetic retinopathy

Diabetic retinopathy can be defined as the alteration of micro-vascular system of retina, due to prolonged hyperglycaemia (11). We can say that this is the most important long-term complication of diabetes, one of the first signs of vascular damage being the retinal microangiopatia. It affects both patients with type 1 and type 2 diabetes and it can lead to blindness untreated on time (16). There are also some studies that showed that regarding patients with diabetic retinopathy, chances of survival are lower, because of the cardio-vascular complications (10).

Diabetic retinopathy may involve peripheral retina, macula or both of them. The degree of severity may evolve from nonproliferative retinopathy (slight or moderate) until proliferative retinopathy or up to advanced eye disease.

The prevalence of diabetic retinopathy varies greatly, depending on the population studied (9). The background retinopathy is almost universal, after a 20 years period of diabetes, while the proliferative retinopathy affects 70% of patients with DZ type 1, after a 30 years period of diabetes (5).

The factors influencing the development of diabetic retinopathy are:

- The age of the patient at the beginning of diabetes - diabetic retinopathy rarely occurs before the age of 13. The installation of puberty greatly increases the risk of microvascular complications, probably due to the changing of the hormonal status. Besides, patients diagnosed after the age of 70, have a lower risk of retinopathy (16).
− Time and duration of diabetes - In type 1 diabetes, any form of retinopathy occurs in greater proportion than in type 2 diabetes, as we can see in the tables 1.2. (14):

| Table 1 Risk of any form of retinopathy according to the time and duration of diabetes: |
|---------------------------------|---|---|---|
| The duration of diabetes       | < 2 years | > 15 years |
| DZ type 1                      | 2%    | 95%    |
| DZ type 2                      | 10%   | 58%    |

| Table 2 The risk of proliferative according to the time and type of diabetes: |
|---------------------------------|---|---|---|
| The duration of diabetes        | < 4 years | > 15 years |
| DZ type 1                      | 0%    | 26%    |
| DZ type 2                      | 3%    | 4%     |

− HbA1c level - A good metabolic control lates the appearance of retinopathy or improves its progression in both type 1 and type 2 DM, fact demonstrated by the United Kingdom Prospectives Diabetes Study (3).
− Blood pressure - There are studies which have proved that high diastolic blood pressure among young people and the high systolic blood pressure among elderly worsen the retinopathy (7).
− The pregnancy may be associated with the worsening of women’s retinopathy.
− Dislipidemia - an increased level of cholesterol and/or of triglycerides is an important risk factor for diabetic retinopathy. Is not already demonstrated that hipolipemiant therapy would have any positive effect on the evolution of retinopathy, future research will demonstrate or disprove this.
− Proteinuria and the high level of creatinina - the coexistence of kidney diseases increases the risk of neovascular glaucoma and worsens the retinopathy’s evolution, so the aggressive management is indicated in such situations.
− The ethnicity - Although there are so many studies regarding this matter, the diversified design of these leads problems of interpretations. Althought, it seems that afroamericans have a higher risk of retinopathy than Caucasian people.
− Smoking seems to be related to the development of the diabetic retinopathy, but the evidence is not so clear as in diabetic nepropathy. While EURODIAB IDDM Complications Study (1) demonstrated that smoking is a risk factor for the development and progression of diabetic retinopathy, other studies showed that smoke is not a significant risk factor in this case. Perhaps the connection between smoking and diabetic retinopathy can be established by the fact that smoking is an important factor for cardio-vascular risk, influencing both macrocirculation and microcirculation.

Although diabetic retinopathy is a specific sign of microvascular damage in diabetes, it is not yet clearly demonstrated in what measure it can become a predictor of macrovascular damage in diabetes, because there are few studies in the field and contradictory data.

### Aterosclerosis in diabetes

It is well known that type 2 diabetes is an independent risk factor for developing atherosclerosis. Accelerated atherosclerosis is responsible for most deaths of people with diabetes. In fact these are 4 times more prone to atherosclerosis comparing to those with normal blood glucose. Another well-known fact that raises problems is that the life expectancy of people suffering for diabetes is similar to a person without diabetes, but who had suffered a myocardial infarction. Diabetes is in fact equivalent for cardiovascular disease (6).

In spite of numerous studies related to this topic and in spite of the 30 years of debate, there have not been determined the molecular mechanisms involved, nor the molecular mechanisms which could explain the close connection between diabetes and atherosclerosis or between atherosclerosis and microvascular complications of diabetes. Thus, we can understand the contradictory results regarding this matter.

Diabetes and atherosclerosis are actually two sides of the same picture, namely, a complex disorder of the entire metabolism, a disorder which can reach implication at molecular level. Based on actually knowledge, we cannot say if the lesions are purely atherosclerotic or diabetical. Perhaps both changes develop at the same time and the appearance of hyperglycaemia is in fact a really late stage of this process. In practice it is important to find out the earliest time in the application which may have a therapeutic benefit for patient, without being too expensive. Atherosclerosis remains a multifactorial disease with poorly understood mechanisms, determined by both genetic factors and environmental factors, with implications for public health.

The most used method at present, in order to detect the early atherosclerosis, is the ultrasound measurement of the intima-media thickness.

The B mode ultrasound allows visualisation in vivo, with enough accuracy of the arterial intima-
media complex. Intima-media thickness is associated with most cardio-vascular risks factors (age, HTA, diabetes, smoking, dyslipidemia) and represents a surrogate marker for asymptomatic atherosclerosis.

In 2002 a group of American researchers studied retinopathy associated with atherosclerosis and cardio-vascular risks factors in patients with diabetes. They concluded that intima-media thickness is associated with the presence of the retinopathy and that lipid profile is correlated with the presence of hard exudates, without finding other associations between the other cardio-vascular risk factors and retinopathy or other clinical manifestations of the atherosclerosis (8).

The debate continues to exist at an international level. It seems that patients with dyslipidemia are more prone to macular edema, the hipolipemiant treatment solving this problem somehow. Yet, knowing that high levels of lipids is involved in atherosclerosis and in vascular stenosis on one side, on the other side it is demonstrated that a moderate carotid stenosis protects against the diabetic retinopathy while severe stenosis resulting in ischemic retinopathy we might have some correlation. The ARIC study (The Atherosclerosis Risk in Communities) (8), showed a weak correlation between the intima-media thickness and diabetic retinopathy. Based on these studies Paul Dodson summarized the studies on the effects of the statines in retinopathy’s treatment (4). The CARDS study for instance, observed the effect of the atorvastatin on the retinopathy’s progression. Although the data were relatively difficult to interpret, it seems that there is still a protective effect on retina’s treatment (2).

Can the eye be considered a cardio-vascular risk factor?

The retina had been considered like a “window” of the systemic circulation for a long time, even from 1898, when Gunn demonstrated its transformations among patients suffering of hypertension. Gabrielle Tikellis, (Center of Eye Research Australia, Melbourne) (12) summarized the results of six studies which demonstrates that retina can be considered as a cardio-vascular risk factor: ARIC, Cardiovascular Health Study (CHS), Beaver Dam Eye Study, Blue Mountain Eye Study, Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESD) and Rotterdam Study.

There had been analized two types of lesions:

1) Diffuse lesions (microaneurysms, bleeding point haemorrhages, cotton-wool spots)
2) Focal lesions (arterial shrinkings, arteriovenous changes, venous dilatations)

There were observed the following things:

− The progressive arterial shrinking was associated with a higher risk of developing metabolic syndrom and therefore, diabetes;
− Isolated venous dilatations were associated with a risk for developing proteinuria;
− The cotton-wool spots indicated a 6,4 times higher risk for AVC, and the same risk for microaneurysms, but only 4 times higher. Both lesions were correlated with the risk of cardiac insufficiency.

Based on new methods of statistical analysis, it seems that retina can provide independent information on morbidity and cardiovascular mortality.

Manon van Hecke, from Amsterdam University (13), did not agree with this, and he showed that the studies mentioned have not fully demonstrated a highly significant association between retinal changes and cardio-vascular events and that the problem is more complex that it seemed at first sight. Depending on the type of the study and the parameters taken into account, the retina does not always reflect what happens at the macrovascular level. The exact mechanism, by which retinal changes may or may not be correlated with macrovascular changes is not yet elucidated.

So, I consider this report in the context of still existing international debates, on a topic that may offer us big surprises in the future.

References


16. Yamagishi S; Nakamura K; Matsui T; Sato T; Takeuchi M Department of Internal Medicine, Kurume University School of Medicine, Japan.- Med Hypotheses.2006; 66(5):1019-21.


Correspondence Adress: Tomina Popescu MD, University Hospital CF Craiova University of Medicine and Pharmacy Craiova, Str Petru Rares nr. 4, 200456,