MODULE 8.3
Diabetic Retinopathy Phenotypes

The duration of diabetes and the level of metabolic control are known to affect the progression of diabetic retinopathy (DR).[1] However, these factors do not account for the wide variability in the evolution and progression of DR that is experienced by different individuals with diabetes.

Lobo and colleagues[2] conducted a prospective 3-year follow-up study involving the macular region of 14 patients with type 2 diabetes mellitus and mild nonproliferative DR (NPDR). From this study,[3] patterns or phenotypes of DR progression were identified[1]:

1. Pattern A included eyes with a small amount of abnormal fluorescein leakage, a slow rate of microaneurysm (MA) formation, and a normal foveal avascular zone. This group represented eyes with slowly progressing retinal disease.
2. Pattern B included eyes with persistently high leakage values, indicating a substantial alteration in the blood-retinal barrier (BRB), relatively higher rates of MA accumulation, and abnormal foveal avascular zone. This group represented a wet or leaky form of DR.
3. Pattern C included eyes with variable and reversible leakage, increased MA formation and an abnormal foveal avascular (ischemic) zone.

A more recent study by Nunes et al[3] followed 410 patients with mild NPDR for 2 years. Evaluations were performed using only noninvasive procedures, such as digital color fundus photography and ocular coherence tomography (OCT). The eyes were classified according to predetermined threshold values[1]:

1. Phenotype A: MA turnover <6 with normal retinal thickness (central subfield <220 µm, eg normal mean + 1 standard deviation [SD])
2. Phenotype B: MA turnover <6 with increased retinal thickness (central subfield >220 µm)
3. Phenotype C: MA turnover >6

Using this classification paradigm, to estimate the risk for the development of clinically significant macular edema (CSME), phenotype A demonstrated a negative predictive value for developing CSME of 99.2%. Phenotype B had a sensitivity and a specificity of 88.9% and 60.5%, respectively, when compared to phenotype A. Phenotype C had a sensitivity and specificity of 94.4% and 55.9%, respectively, when compared to phenotype A. This study revealed that using the mathematical model of hierarchical cluster analysis and only noninvasive procedures,[3] different phenotypes of DR, which show different risks of progression to CSME, could be identified. Interestingly, these 3 phenotypes were consistent with the number of patterns of DR progression proposed previously by Lobo and colleagues.[2]

Using an integrated approach, it is apparent that chronic hyperglycemia causes cellular damage to the entire neovascular unit of the retina, with varying degrees of damage depending on the cell type and the individual phenotype.[1,4] Patients with phenotype A tend to develop generalized low-grade vascular, neuronal, and glial damage that manifests as a slowly progressing neuropathy with slowly progressing vascular damage.

Other patients (phenotype B) experience breakdown of the BRB, resulting in retinal edema, possibly associated with neuroglial damage and an active inflammatory repair process.[5] Patients with phenotype C, potentially because of genetic factors or an abnormal accumulation of vascular endothelial growth factor (VEGF) and other angiogenic factors associated with rapidly developing hypoxia, are affected by an abnormal interaction between endothelial and blood cells. These patients show signs of active microvascular disease and experience a more rapid progression to vision-threatening complications than their phenotype A and B counterparts.

References

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