REVIEW ARTICLE

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Importance of Metabolic Memory in the Development of Vascular Complications in Diabetic Patients

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DIABETES MELLITUS (DM) is the most commonly found metabolic and endocrine disorder during anesthesia. This situation is increasing because the diabetic population requires surgery more frequently than the nondiabetic population.[1-4] DM represents an independent risk factor for morbidity and mortality in major surgeries. Diabetic patients have more perioperative complications than do nondiabetic patients, and the extent and duration of DM are directly proportional to the severity of the complications.[2-5] Many large-scale and prospective type-1 and type-2 diabetes clinical trials have demonstrated that early intensive glycemic control can reduce the incidence and progression of microvascular (retinopathy, nephropathy, neuropathy) and macrovascular complications (atherosclerosis, stroke, myocardial infarction, limb amputation).[6-13] On the other hand, periods of chronic hyperglycemia due to poor glycemic control during the initial stages of DM create a cellular imprint that gives rise to the development and progression of vascular complications even when euglycemic control is reached. Several studies have shown worse surgical outcomes in patients with poor control of DM.[3-6] Metabolic memory (MetM) is defined as the long-term effect of an initial glycemic status on the development of diabetic vascular complications. The MetM concept suggests the need for an early aggressive treatment and opens up new possibilities for research on the pharmacologic control of complications. Currently, drugs exist (such as metformin, pioglitazone, angiotensin II receptor-1 blockers, angiotensin-converting enzyme inhibitors, and others) that are able to stop or reverse the persistence of inflammation and oxidative stress (OxS) even after prolonged poor management of DM.[14-19] A new group of drugs that affect the gene expression acting on enzymes that change the structure of histones, which are proteins that modulate the deoxyribonucleic acid (DNA) expression, recently has been proposed.[20-23] All these drugs are potential tools for the treatment of MetM. However, it still is necessary to better understand the physiopathologic mechanisms of the phenomenon to design an optimal therapeutic approach. The aim of this review is to offer anesthesiologists an understanding of MetM, to discuss the proposed mechanisms that explain this condition, and to review its therapeutic implications.

ORIGIN OF THE CONCEPT

The concept of MetM was born as a result of several studies that showed that changes in microcirculation were relatively reversible if an early and adequate control of blood glucose was achieved after a hyperglycemic period. Randomized studies conducted on a large scale[7-11] have shown that early intensive glycemic control decreased the risk of diabetic microvascular complications. It was observed that the body behaved as if the initial glycemic environment could be remembered by the target organs (eg, eyes, kidneys, heart, limbs), and therefore this phenomenon has been called "MetM," "hyperglycemic memory," or "legacy effect."[12,13] The first experimental evidence about MetM was demonstrated in the 1987 report from Engerman et al,[24] who assessed the extent of the arrest in the development of diabetic retinopathy derived from improved glycemic control. In that study, normal dogs were assigned randomly into the following 4 groups: 1 nondiabetic group and 3 groups with DM induced by intravenous injection of alloxan monohydrate. The diabetic groups were classified according to their degree of glycemic control during the study (Fig 1). One group underwent good control of glycemia (GCG) for 5 years. In this group, insulin was given twice a day with a measured diet so that hyperglycemia and glucosuria were mild and infrequent and glycated hemoglobin (HbA1c) was comparable with that in the control subjects. A second group was maintained with poor control of blood glucose for 5 years (food ad libitum and a single injection of insulin daily just to prevent chronic hyperglycemia and glucosuria). The third group was maintained with poor control of blood glucose (PCG) for 2.5 years and then was changed to GCG for the remaining 2.5 years. The retinopathy was evaluated by the presence of capillary aneurysms and several other signs of intraretinal microvascular alterations (eg, excessive numbers of nonperfused capillaries, widespread loss of intramural pericytes, varicose vessels, blot, hemorrhages). After the 5-year study, the retinopathy clearly was inhibited by GCG. The intraretinal alterations in the group with GCG were not

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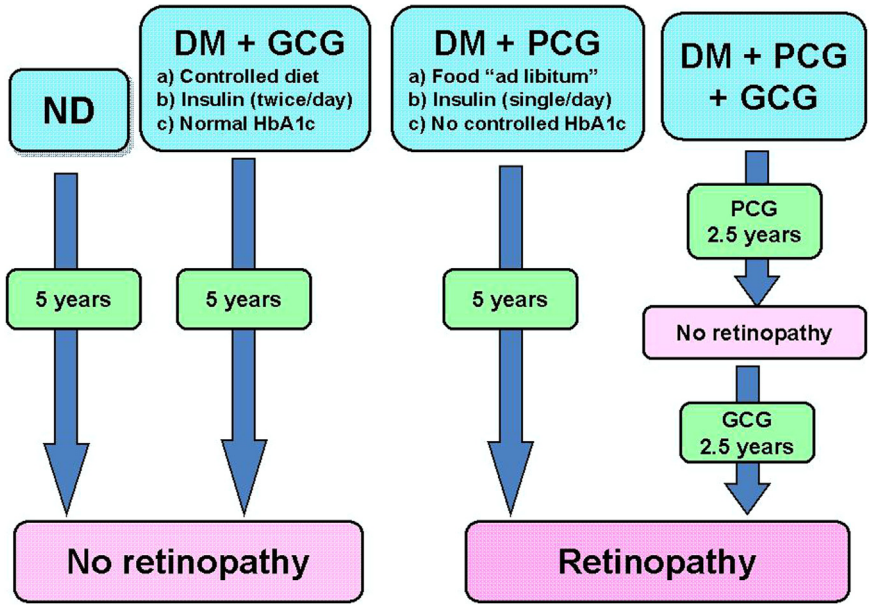

Fig 1. Experimental design and results of the study by Engerman et al[24] on metabolic memory. DM, diabetes mellitus; GCG, good control of glycemia; ND, normal dogs; PCG, poor control of glucose.

significantly different from those of normal dogs. By contrast, animals with DM initially receiving a PCG and then GCG had an incidence of retinopathy similar to that of the group with glycemic mismanagement throughout the study (see Fig 1). In this last group, the retinopathy was absent during the first 2.5 years with PCG, appearing after the treatment had been changed to GCG. This suggested that some events present in the initial period of hyperglycemia remained and could have triggered the microvascular damage.

Other Experimental Evidences

In 1990, Roy et al[25] demonstrated the development of a "hyperglycemic memory" that activated the overproduction of fibronectin and collagen IV in both isolated endothelial cells and streptozotocin-induced diabetic rats (renal cortex and heart). In that study, glucose was maintained at high levels during 2 weeks, and the response in overproduction of fibronectin and collagen IV persisted even 1 week after normalizing the glucose blood level. In addition, Hammes et al[26] reported in 1993, in a diabetic rat model induced with sucrose, that transplantation of islets of Langerhans 6 weeks after the DM onset, but not after 12 weeks, reversed the characteristics of diabetic retinopathy.

MetM in Humans

Clinically, the concept of MetM arose from the results of a landmark study with DM type 1 (DM1) patients published in 1993, the Diabetes Control and Complications Trial (DCCT).[27] In this study, patients underwent 2 types of treatment to normalize their blood glucose levels: standard and intensive. The study was suspended prematurely (at 6.5 years) because of the evident decrease in the progression of vascular complications in patients with intensive treatment. From this point onward, all patients were subjected to strict treatment to obtain the most benefits. In a subsequent study in 2003, Epidemiology of Diabetes Interventions and Complications, in which the same patient population was studied,[7] it was found that patients who had undergone standard treatment during the first study (DCCT) continued to have a higher incidence of diabetic microvascular complications, such as nephropathy and retinopathy, compared with those who had received strict glycemic control throughout the study, even several years after they were changed to intensive treatment. The average HbA1c levels in the groups remained almost equivalent.[7,8] The monitoring of these patients for almost 10 years demonstrated a persistent beneficial effect of early glycemic control on the progression of macrovascular alterations such as the thickness of the intima-media of the carotid artery. The patients demonstrated a significant reduction in the risk of fatal myocardial infarction, stroke, or death by cardiovascular disease.[9-11] These findings suggested that strict, early metabolic control could have beneficial effects on both the microvasculature and the macrovasculature, and the idea of MetM was extended to humans. MetM apparently also occurs in DM type 2 (DM2), as shown by the United Kingdom Prospective Diabetes Study, a study that included 5,102 patients with newly diagnosed DM2 and with a median follow-up of 10 years.[28] That study showed that long-term complications in DM2 could be prevented by intensive blood glucose and blood pressure management. Patients with DM2 who underwent standard treatment during the study had a higher incidence of microvascular and cardiovascular complications compared with their counterparts who received intensive treatment throughout the study and during the follow-up period, in a similar way as had occurred with patients with DM1 in the DCCT/Epidemiology of Diabetes Interventions and Complications study.[11] These results showed that good early metabolic control (from newly diagnosed until 5 years after diagnosis) also had beneficial effects in DM2. All of these evidences are the basis for the