Editorial

Macrovascular disease in type 2 diabetes: We do need animal models for in vivo studies

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See article by Bouvet et al. [6] (pages 504–511) in this issue.

Type 2 diabetes and its complications has become a major public health problem in Western countries. The number of diabetic patients in the world is estimated to be about 200 million, and prevalence of type 2 diabetes will increase not only in the West due to overweight and obesity epidemics, but also in emergent countries because of changes in eating habits.

In diabetic patients, atherosclerosis develops earlier than in other subjects and accounts for excessive morbidity and mortality [1]. Epidemiological studies have shown that cardiovascular diseases are the first cause of morbidity and mortality in patients with type 2 diabetes: coronary artery disease is increased by 3- to 4-fold, stroke is increased by 1.4- to 2.2-fold, peripheral artery diseases is increased by more than 10-fold, and 75 to 85% of hospitalisations and deaths are due to vascular complications of diabetes. Thus, in the coming years, type 2 diabetes will become the most important cause of morbidity and mortality linked to cardiovascular diseases.

Structural and functional changes in vessels of type 2 diabetic patients have been shown to be predictive of cardiovascular events. Thus, in diabetic patients, medial calcifications of lower limbs are predictive of vascular complications and death [2], and in type 2 diabetic patients with angiographically normal coronary arteries, endothelial dysfunction evidenced by coronary artery constriction induced by a cold pressor test is predictive of long-term cardiovascular and cardiac events [3]. Moreover, cardiovascular events were more frequent, more severe, and occurred earlier in type 2 diabetes than in arterial hypertension [3], suggesting that vascular alterations are more important in diabetes, unless the longer silent phase of diabetes allows the insidious development of vascular alterations. For a better understanding of type 2 vascular complications and for the understanding of the similarities and differences between vascular complications of diabetes and what we call vascular risk factors, we need research tools that reproduce the human disease in an accelerated time frame that allows valid experimental observations.

Although a considerable number of in vitro and in vivo studies have been dedicated to the knowledge of the mechanisms underlying the accelerated development of atherosclerosis and arteriosclerosis of calcium deposition in the elastic network in large vessels in diabetes [4], there are still a lot of unanswered questions. As with other cardiovascular risk factors, diabetes accelerates vascular “aging” [5], but the cascade of events that links hyperglycemia and vascular diseases remains an incomplete puzzle. The challenge is of major importance, and to complete the puzzle, we need new tools, particularly for in vivo studies, that allow observation of a pathophysiological process normally taking decades in humans that can be generated in a relatively short time in animal models of disease that can be compared to the human disease.

In this issue, Bouvet et al. report very interesting results concerning the development of medial calcifications in large arteries in a model of diabetic rats [6]. To mimic the natural process of vascular complications and development of medial calcifications stemming from type 2 diabetes, animals were...
fed with a high fat diet for 8 weeks in order to induce an insulin resistance phase, and diabetes was induced by a single dose of streptozotocin. Medial elastocalcinosis was induced by administration of warfarin, which inhibits the recycling of vitamin K, because it has been shown i) that the activity of matrix G1A protein, a protein that prevents deposition of calcium in the vascular wall, is a vitamin K-dependent process [7], and ii) that matrix G1A protein is reduced in arteries of diabetic patients [8]. In their results, Bouvet et al. show that femoral elastocalcinosis localized in the media was not elevated by warfarin alone but that it was significantly increased in diabetic rats where warfarin was administered for 3 weeks starting 4 weeks after streptozotocin injection. In addition, in their rats they found an increase in levels of osteopontin, alkaline phosphatase, transforming growth factor-β, and tumor necrosis factor-α in adventitia that have been reported to be upregulated in diabetes [8].

Although this model presents similarities with human type 2 diabetes with respect to two phases – the first one characterized by insulin resistance and hyperinsulinemia and the second one characterized by hypoinsulinemia – the authors point out differences with the human disease that could serve as a basis for improvement of the model: i) this model does not explore the combined effect of hyperglycemia and hyperinsulinemia; ii) the transition to hypoinsulinemia is very rapid and the animals became strongly hypoinsulinemic; iii) cholesterol and triglyceride levels remained normal or low; iv) treated animals were underweight when compared to controls; v) femoral circulation is different in rats compared to humans because of the upright position; vi) the duration of observation was short, which may explain why pulse wave velocity was not increased. All of these points should be taken into account in future studies.

Moreover, this animal model and other models that mimic human type 2 diabetes should be used to better explore the crosstalk between adventitia, media, and endothelium in diabetes, this latter cell layer remaining the first target of diabetes that dysfunctions very early in the disease before any morphological changes within the vessels occurs [9]. All the vessel layers are involved in the vascular complications of diabetes, and it seems that, because hyperglycemia, hypertriglyceridemia, and hyperinsulinemia are generators of reactive oxygen species throughout the vessel wall, oxidative stress is largely involved in the atherosclerotic process [10]. Indeed, reactive oxygen species are at the origin of a cascade of pathophysiological events that result from activation by oxygen free radicals of nuclear factor-κB [11], an ubiquitous transcription factor that controls the expression of many genes and that is involved in immunity, inflammation, regulation of cell proliferation and growth, and apoptosis [12,13]. Thus, the consequences of the activation of the nuclear factor-κB and gene control by this factor in endothelial and smooth muscle cells should be studied extensively in order to determine whether oxidative stress and nuclear factor-κB might be involved in the activation of proteins that lead to medial calcifications and whether they might be the cause and not the consequence of the inflammatory process [14,15] (Fig. 1).

In summary, because we do need animal models of human diseases for in vivo studies, the rat model of elastocalcinosis of Bouvet et al. should be a useful tool to study the mechanisms of vascular diseases in type 2 diabetes as well as to evaluate the therapeutic interventions used to prevent or treat these disorders.

References


