Workshop Reports

Diabetic Complications

Report of The Tenth Canadian Workshop on Diabetes, 26–27 October 1981, Toronto, Canada

O. V. Sirek

Department of Physiology, University of Toronto, Toronto, Ontario, Canada

The Workshop was held at the Guild Inn, in the vicinity of Toronto, on the 26th and 27th October 1981. Under the joint sponsorship of Connaught Laboratories Limited of Toronto and Clinical and Scientific Section of the Canadian Diabetes Association, 30 members of the profession from across Canada gathered to discuss the impact of diabetes mellitus on the cardiovascular and nervous systems. The purpose of this report is to record some of the highlights of the meeting.

Lipid Metabolism and Atherosclerosis

Dr. N. Kalant, Lady Davis Institute, Jewish General Hospital, Montreal, spoke on 'Effects of serum lipoproteins on glycosaminoglycan synthesis by cultured human cells.' Human skin fibroblasts and smooth muscle cells were cultured in media supplemented with lipoprotein-free serum; the effect of added low- and high-density lipoproteins (LDL and HDL) on cell number, cholesterol and glycosaminoglycan (mucopolysaccharide) production was determined. In the absence of serum lipoproteins, the secretion of glycosaminoglycans varied inversely with cell density and the rate of cell proliferation. LDL had little effect in non-proliferating cultures, but the addition of LDL to proliferating fibroblasts caused an increase in total glycosaminoglycan production, an increase in cell cholesterol content and a decrease in cell number. HDL, on the other hand, had little effect on proliferating cells but inhibited glycosaminoglycan production of stationary cultures; it did not affect cell number. The results suggest that LDL is atherogenic only after cell proliferation has been initiated, while HDL exerts its protective action before the onset of smooth muscle cell proliferation.

Dr. G. Steiner, Department of Medicine, University of Toronto, spoke on 'Insulin and hypertriglyceridaemia, a vicious and potentially atherogenic cycle.' Alterations in glucose and insulin homeostasis are interrelated in a vicious cycle to the triglyceride-rich lipoproteins, namely to very-low-density lipoproteins (VLDL) and VLDL-remnants. A glucose challenge given to triglyceridaemic subjects resulted in hyperinsulinaemia, which was interpreted as an overcompensation by the B cells for the insulin resistance associated with the hypertriglyceridaemic state. Insulin resistance was present in both obese and non-obese hypertriglyceridaemic subjects. It was suggested that in the latter group, the elevated VLDL may be the cause of impaired insulin binding to cells, leading to hyperinsulinaemia, and chronic hyperinsulinaemia in man can lead to an increased VLDL production and thus to hypertriglyceridaemia. Hence, not only is the relationship between insulin and hypertriglyceridaemia seen as a vicious cycle, it is also potentially atherogenic.

Dr. M. H. Tan, Department of Medicine, Dalhousie University, Halifax, spoke on 'The lipoprotein lipase system in diabetic hypertriglyceridaemia in rats.' The roles of various extrahepatic tissue lipoprotein lipase (LPL) activities in the pathogenesis of hypertriglyceridaemia were studied in three rat models of diabetes. (1) Insulin-deficient diabetic rats (streptozotocin 75 mg/kg, IV) had marked hyperglycaemia and hypertriglyceridaemia and lower soleus and heart muscle LPL activity when compared with pair-fed controls; their adipose tissue LPL activity and triglyceride secretion rate were not altered. Compared with normally fed controls, these rats had lower fat and heart LPL activity. (2) Hyperinsulinaemic diabetic rats (triamcinolone 0.5 mg/kg, IM for 5 days) showed marked hyperglycaemia, but only mild hypertriglyceridaemia. In contrast to the insulin-deficient model, hypertriglyceridaemia in this case was due to an enhanced rate of hepatic triglyceride secretion. There was no difference in LPL activity in soleus, gastrocnemius, heart muscle and adipose tissue between the diabetic and control rats. (3) Mildly diabetic rats (streptozotocin 45 mg/kg, IV) did not show hypertriglyceridaemia and their tissue LPL was similar to that of control rats. Thus, it appears that depending on the model, changes in LPL activities may or may not play a role in the pathogenesis of diabetic hypertriglyceridaemia.

The special guest speaker was Dr. Edwin L. Bierman, Department of Medicine, University of Washington, Seattle, who spoke on 'Diabetes mellitus and atherosclerosis: the lipid connection.' He reviewed the present status of the interrelationships between hyperlipidaemia, diabetes and atherosclerosis.

Dr. G. Moncton, Department of Medicine, University of Alberta, Edmonton, spoke on the Treatment of autonomic neuropathy in the streptozotocin diabetic rat. The pathological changes in autonomic neuropathy, followed for 6 weeks, consisted of axonal destruction followed by regeneration after 4 weeks. When streptozotocin-diabetic rats were then treated with insulin for 2 weeks, the regenerative response became predominant and many of the neurons almost had a normal appearance.

Neuropathy

Dr. D. Robertson, Department of Pathology, Queen's University and Kingston General Hospital, Kingston, reported on 'Diabetic neuropathy in the *db/db* mouse – effect of therapy.' In this animal model, motor nerve conduction velocity fell below that of the control animals at about 6 weeks of age, shortly before the onset of hyperglycaemia, and persisted throughout the 36 week duration of the experiment. During the early stages, only minor morphological alterations could be detected by light and electron microscopy and by morphometric methods. By 26 weeks, there was a conspicuous axonopathy involving both myelinated and unmyelinated fibres. The study of the effects of therapy with insulin or diet or both was disappointing with respect to nerve conduction velocity and morphometric observations. Following treatment, nerve conduction velocity was intermediate between that of control and untreated animals and morphometric studies showed

that fibre diameter resembled that of untreated diabetic, rather than that of control animals.

Dr. A. A. Sima, Division of Neuropathology, Department of Pathology, University of Toronto, spoke on 'Structural and functional characterization of the neuropathy in the spontaneously diabetic BB-Wistar rat.' The qualitative and quantitative pathology of peripheral nerves was studied longitudinally and these studies were temporally correlated with electro-physiological features. Motor nerve conduction velocity was significantly reduced only 3 weeks after the onset of diabetes. Both amplitudes of evoked muscle potentials and distal latencies were altered in diabetic rats. No increase in the permeability of the protective barriers could be demonstrated before, during or after the onset of the nerve conduction defects. Ultrastructural changes in peripheral nerves could be detected 4 months after the onset of diabetes and coincided with a further decrease in the maximal conduction velocity. Early changes consisted of mitochondrial accumulation of glycogen in the axons and the development of honeycombed Schwann cell axon networks. Later stages showed axonal dwindling and distal Wallerian degeneration. Teased fibre studies and quantitative analyses of axon-myelin ratios confirmed a primary axonal pathology. Decreased sodium ion currents with intra-axonal sodium ion accumulation occurred at early stages and resulted in decreased excitability of the nerve. It was suggested that a reduced availability of energy in the axons of diabetic nerves may be a plausible explanation of this type of neuropathy.

Retinopathy

Dr. M. E. Paetkau, Retinal Angiography Unit, Department of Medicine, University of Alberta, Edmonton, spoke on 'Prognostic factors for maintaining normal vision in patients with diabetes mellitus.' Juvenile onset diabetic patients with histories of smoking and angiographic data were being reviewed, with special attention given to the vascular occlusive aspects of retinopathy, such as capillary closure and proliferation. Similarly, adult-onset diabetic patients were examined to determine whether there is a relationship between cigarette smoking and lipid maculopathy. Whereas a direct relationship was found between the severity of lipid maculopathy and the use of oral hypoglycaemic agents, no relationship was found between smoking and vascular lesions or severity of maculopathy and duration of diabetes.

Dr. A. K. Hanna, Department of Medicine, University of Toronto, spoke on 'A search for factors associated with diabetic retinopathy.' A study was carried out on insulin-dependent diabetic patients of long duration (< 25 years), comparing those without retinopathy with those with proliferative retinopathy (but without severe complications). Significant associations were identified between proliferative diabetic retinopathy and poorer diabetic control, increased diastolic blood pressure, impairment of renal function, higher triglyceride levels and impaired motor and sensory nerve conduction. The following variables did not show statistically significant differences: smoking, diet, insulin dosage, serum magnesium and cholesterol.

Dr. C. B. Mortimer, Department of Ophthalmology, University of Toronto, spoke about 'Diabetic retinopathy - changing concepts in management.' He reviewed the history of both laser and vitrectomy treatment and summarized the indications for and results of laser treatment.

Dr. J. D. Walton, Carbohydrate Research Institute, Queen's University, Kingston, spoke on 'Carbohydrate-protein interactions in the lens of the eye.' A procedure involving citraconylation in 6 M guanidine hydrochloride was used to obtain the following fractions from decapsulated bovine eye lenses: water-soluble proteins (crystallins), cell membrane and water-insoluble proteins. It was suggested that the water-insoluble proteins formed in human cataracts result from aggregation of both membrane and non-membrane glycoproteins or crystallins and of intrinsic proteins released by disruption of the plasma membrane.

Nephropathy

Dr. D. G. Oreopoulos, Peritoneal Dialysis Unit, Division of Nephrology, Toronto Western Hospital, University of Toronto, spoke on 'Treatment of diabetic patients with end-stage renal disease with continuous ambulatory peritoneal dialysis.' Approximately one-half of insulin-dependent diabetic patients are known to develop end-stage renal disease within 20 years from the onset of diabetes. It is widely accepted that diabetic patients should be started on dialysis, or be considered for a kidney transplant, at an earlier stage of their renal disease (i.e. serum creatinine: 400-500 $\mu\text{mol/l}$) than their non-diabetic counterparts. Diabetic patients with end-stage renal disease comprise 10% of all dialysis patients in North America and continuous ambulatory peritoneal dialysis appears to be the treatment of choice for these individuals. The advantages of this treatment are: (1) continuous control of the nitrogenous waste products; (2) superior control of hypertension; and (3) superior control of blood glucose by administration of insulin intraperitoneally, i.e. by a more physiological route than subcutaneous injections.

During the last 3 years, Dr. Oreopoulos has treated 14 diabetic patients with continuous ambulatory peritoneal dialysis for periods of 6-36 months. The infection rate was one episode every 20 patient months, which was similar to that encountered in the non-diabetic population on peritoneal dialysis. Patient survival rate was 89% and 76% for the first and second years, respectively.

Dr. J. T. Brosnan, Department of Biochemistry, Memorial University of Newfoundland, spoke on 'Metabolism in the ketoacidotic kidney.' The excretion of β -hydroxybutyric and acetoacetic acids require augmented rates of renal ammoniogenesis. The muscles of diabetic animals release appreciable quantities of glutamine into the blood and ammonia is generated from this substrate in the proximal tubules of the kidney by the sequential action of glutaminase and glutamate dehydrogenase. The carbon skeleton of glutamine is largely converted to glucose by the process of renal gluconeogenesis, thus contributing to hyperglycaemia. Control of ammoniogenesis involves an acute phase, probably directly controlled by hydrogen ion concentration, in which increased ammonia production can be achieved by modulation of the existing enzymatic machinery, and a chronic phase, requiring the synthesis of new enzyme proteins and possibly new mitochondrial transporters.

Overview

Dr. G. D. Molnar, Department of Medicine, University of Alberta, Edmonton, spoke on 'The relevance of control to diabetic complications.' He summarized the definitions of diabetic control and the various categories of chronic complications and critically reviewed the evidence linking the metabolic regulation of both diabetes and other pathogenic mechanisms to diabetic complications.

Conclusion

The Workshop was informative in that it provided a great deal of new and descriptive knowledge concerning the nature and progression of diabetic complications. On the whole, one was left with the impression that as far as prevention of cardiovascular and particularly neurological complications is concerned, present day conventional therapy with insulin and diet has probably reached the limits of efficiency. It is becoming increasingly evident that if diabetic complications are to be alleviated or eliminated, normalization of both plasma glucose and hormone concentrations should be attempted.

O. V. Sirek, M.D., Ph.D.
Department of Physiology
Medical Sciences Building
University of Toronto
Toronto, Ontario M5S, 1A8, Canada