

Chronic complications in diabetes mellitus

Ryuichi Kikkawa*

Third Department of Medicine, Shiga University of Medical Science, Otsu, Shiga, 520-2129, Japan

Diabetes mellitus is one of the most prevalent diseases among adult population in Japan. The persistent hyperglycemia is responsible for the appearance of various organ and tissue damage in diabetic subjects. Eyes, kidneys and peripheral nerves are frequently damaged due to diabetes-specific alteration in microvessels. Furthermore, large vessels are also damaged causing severe diseases such as myocardial infarction, cerebral infarction and gangrene. The pathogenesis of these alterations in small and large vessels has been extensively studied and various metabolic abnormalities induced by hyperglycemia are proposed to play a major role in the development of these diabetic vascular complications. Among those metabolic abnormalities, the activation of the diacyl glycerol-protein kinase C pathway has been proposed to play a pivotal role in the pathogenesis of not only microvascular complications but also macrovascular complications. The beneficial effect of a protein kinase C inhibitor on renal, retinal and atherosclerotic lesions in diabetic animal models may support this notion. The results of several large-scale clinical trials have confirmed the efficacy of glycemic control as well as blood pressure control in the management of diabetic complications. It is a prerequisite, therefore, to obtain near-normal glycemic and blood pressure control in order to prevent the appearance of diabetic complications and also suppress their progression. In this aspect nutritional consideration may be an important way to improve the quality of these managements.

Diabetic complications: Protein kinase C: Glycation: Oxidative stress: Glycemic control: Blood pressure control

Persistent hyperglycemia is known to be responsible for serious damage to various organs and tissues in diabetic subjects. The chronic complications of diabetes include retinopathy, nephropathy, neuropathy, and atherosclerosis. Diabetic retinopathy, a retinal disease in diabetes, is the leading cause of severe visual impairment in adults, disabling nearly 5000 patients per year in this country. Diabetic nephropathy, a kidney disease in diabetes, was the leading cause of end-stage renal failure at the end of 1998 in Japan after introduction of dialysis therapy and appears to still be so. According to the report from the Japanese Society for Dialysis Therapy, the number of diabetic patients introduced to dialysis therapy in 1998 was 10 729, approximately 35 % of total number of patients introduced to dialysis therapy during this year (Japanese Society for Dialysis Therapy, 2000). This trend may continue further because of the large number of candidate diabetics being present in Japan (Table 1).

Diabetic neuropathy, a peripheral nerve disease in diabetes, is the most prevalent type of neuropathy in Japan and contributes to various disabled states in

diabetics. Furthermore, atherosclerotic diseases such as cerebral infarction, myocardial infarction, and gangrene, though they are not specific to diabetes, are more prevalent and severe in diabetics compared with the non-diabetic population.

Pathogenesis of diabetic complications

The main lesion in diabetic complications resides in small and large vessels. The mechanism by which hyperglycemia causes vascular lesions appears to be multifactorial. The exaggerated glucose flux into vascular cells may cause a variety of metabolic derangements inside vascular cells such as activation of protein kinase C, sorbitol accumulation, and myo-inositol depletion (Kikkawa & Haneda, 1997). Among these factors, recent evidence suggests that protein kinase C activation plays a major role in the development of diabetic complications since an inhibitor of protein kinase C is reported to be able to correct renal and retinal dysfunction in diabetic animals (Ishii *et al.* 1996). We have recently found that the inhibition of protein kinase

Abbreviations: UKPDS, UK Prospective Diabetes Study Group.

* **Corresponding author:** Ryuichi Kikkawa, tel 81 77 548 2221, fax 81 77 543 3858, email kikkawa@belle.shiga-med.ac.jp

Table 1. Estimated number of patients suffering from diabetic nephropathy in Japan (1999)

Diabetes mellitus	6.9 million
Overt nephropathy (proteinuric)	0.8–1.0 million
Renal failure (Scr > 2 mg/dl)	30 000–50 000
Dialysis therapy (JSDT)	39 000

Scr: Serum creatinine.

JSDT: Japanese Society for Dialysis Therapy.

C is able to prevent the accumulation of extracellular matrix proteins in renal glomeruli in spontaneously diabetic db/db mice. This effect of protein kinase C inhibition appears to be transforming growth factor-beta mediated, that is, increased transforming growth factor-beta, which is a potent pro-sclerotic cytokine, may be protein kinase C-dependent (Koya *et al.* 2000). Furthermore, hyperglycemia increases the nonenzymatic glycation reaction between glucose and free amino groups in proteins, and therefore disturbs the biological function of various proteins. The products of nonenzymatic glycation such as AGE (advanced glycation end product) are known to induce various cytokines in vascular cells. These factors are likely to play some role in the development of diabetic complications (Brownlee *et al.* 1988).

Oxidative stress is increased in diabetes via either scavenger dysfunction or elevated production of reactive oxygen species. Heme oxygenase 1, which is a sensitive indicator protein for detecting oxidative stress, is increased in various tissues of experimental diabetic animals a few weeks after the induction of diabetes. Although the precise source of reactive oxygen species has not been clarified as yet, auto-oxidation of glucose per se, AGE-producing processes, mitochondrial dysfunction, and others have been reported as possible sources. The mechanism by which oxidative stress causes diabetic complications has been extensively studied and there have been several reports suggesting that oxidative stress may injure endothelial cell function that may be related to the development of diabetic complications (Nishio *et al.* 1998).

Management of diabetic complications

How these complications could be prevented or reduced in the diabetic population is the most imminent issue in the field of clinical diabetology in many countries. Glycemic control is the most effective means to prevent the appearance of diabetic complications. The importance of glycemic control has been confirmed by several large-scale controlled clinical trials such as the DCCT (The Diabetes Control and Complications Trial Research Group, 1993), UKPDS (UK Prospective Diabetes Study Group, 1998) and KUMAMOTO (Ohkubo *et al.* 1995) study. In UKPDS, the preventive effect of various therapeutic agents on diabetic complications has been compared, and similar results have been obtained, which indicates that glycemic control by any means is able to prevent diabetic complications. Furthermore, a recent large-scale clinical study has indicated that blood pressure control is also effective in the prevention and treatment of diabetic complications. In UKPDS, type 2 diabetic patients under tight blood pressure

Table 2. Effect of glycemic and blood pressure control on diabetes-related morbidity and mortality in type 2 diabetic subjects.

(UK Prospective Diabetes Study Group, 1998)

	Risk reduction	
	Blood pressure control	Glycemic control
Any diabetes-related events	24 %	12 %
Diabetes-related death	32 %	10 %
Microvascular disease	37 %	25 %
Cost difference (pounds sterling per patient)	949	261

control (144/82 mmHg) have shown a significantly lower incidence of diabetes-related death, stroke and microvascular complications compared to those under less tight blood pressure control (154/87 mmHg). It appears that blood pressure control may be more effective than glycemic control in the management of various complications in type 2 diabetes (Table 2). There is general agreement that diabetic patients should be more strictly controlled in respect of their blood pressure levels compared with their non-diabetic counterparts. As stated above, the pathogenic mechanisms of diabetic complications have been extensively studied, and various new therapies resulting from this basic research are under investigation. In the early part of this century more effective and practical therapeutic means might be applied to the management of diabetic complications. However, the results from a survey recently conducted by the Ministry of Health and Welfare suggests that the majority of diabetic population have not been cared for in medical institutions in Japan. Therefore, the most important therapeutic means may be to encourage those diabetic patients to go to the doctor by convincing them of the importance of the regular management of diabetes mellitus.

References

- Brownlee M, Cerami A & Vlassara H (1988) Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. *New England Journal of Medicine* **318**, 1315–1321.
- Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SJE, Kern TS, Ballas LM, Heath WF, Stramm LE, Feener EP & King GL (1996) Amelioration of vascular dysfunctions in diabetic rats by an oral PKC inhibitor. *Science* **272**, 728–731.
- Japanese Society for Dialysis Therapy (2000) An overview of dialysis treatment in Japan (as of 31 December 1998). *Journal of Japanese Society for Dialysis Therapy* **33**, 1–27.
- Kikkawa R & Haneda M (1997) Pathogenesis of diabetic nephropathy. *Clinical and Experimental Nephrology* **1**, 3–11.
- Koya D, Haneda M, Nakagawa H, Isshiki K, Sato H, Maeda S, Sugimoto T, Yasuda H, Kashiwagi A, Wada K, King GL & Kikkawa R (2000) Amelioration of accelerated diabetic mesangial expansion by treatment with a PKC beta inhibitor in diabetic db/db mice, a rodent model for type 2 diabetes. *FASEB Journal* **13**, 2329–2337.
- Nishio Y, Kashiwagi A, Taki H, Shinozaki K, Maeno Y, Kojima H, Maegawa H, Haneda M, Hidaka H, Yasuda H, Horiike K & Kikkawa R (1998) Altered activities of

- transcription factors and their related gene expression in cardiac tissues of diabetic rats. *Diabetes* **47**, 1318–1325.
- Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N & Shichiri M (1995) Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Research and Clinical Practice* **28**, 103–117.
- Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* **329**, 977–986.
- UK Prospective Diabetes Study Group (1998) Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *British Medical Journal* **317**, 705–713.