INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

Review Article

A SHORT REVIEW ON CHRONIC COMPLICATIONS IN DIABETES MELLITUS

SK. Sarje[1*] NB. Ghiware[1], RM. Kawade[1], VN. Gunjkar[1] and SM. Vadvalkar[2]

[1]Department of Pharmacology, Nanded Pharmacy College,
Shyam Nagar, Opp Kasturba Matruseva Kendra, Nanded-05, Maharashtra, India.
[2]Nanded Pharmacy College,
Shyam Nagar, Opp Kasturba Matruseva Kendra, Nanded-05, Maharashtra, India.

ABSTRACT

Diabetes Mellitus is one of the common metabolic disorders with micro and macro vascular complications that results in significant morbidity and mortality. 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 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 and herbal preparations may be an important way to improve the quality of these managements.

Keywords: Diabetic complications, Oxidative stress, Glycemic control, Herbal preparations.

INTRODUCTION

Diabetes Mellitus considered as one of the five leading cause of death in the world. A worldwide prevalence estimated to between 1% and 5%. Diabetes Mellitus leads to abnormalities in carbohydrate, protein and lipid metabolism and increases the risk of developing atherosclerotic arterial disease by two- to six-fold. Serum total cholesterol, triglycerides and LDL levels are seen tobe increased in diabetes. Diabetes mellitus also disturbs the liver function, due to which the levels of SGOT and SGPT are increased in the blood; beside this nephropathy is a major problem in Diabetes Mellitus. Prior to invention of Insulin this disorder was managed principally by the traditional practices by using medicinal plants. Even after insulin in clinical use, it is not possible to complete cur of Diabetes Mellitus or prevent Diabetes related complications.

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 thousands of patients per year. Diabetic nephropathy, a kidney disease in diabetes, was the leading cause of end-stage renal failure.

Diabetic neuropathy, a peripheral nerve disease in diabetes, is the most prevalent type of neuropathy 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.

Examples of chronic complications

The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following

- Diabetic cardiomyopathy, damage to the heart, leading to diastolic dysfunction and eventually heart failure.
- Diabetic nephropathy, damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world.
- Diabetic neuropathy, abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands. When combined with damaged blood vessels this can lead to diabetic foot. Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy. Diabetic amyotrophy is muscle weakness due to neuropathy.
- Diabetic retinopathy, growth of friable and poor-quality new blood vessels in the retina as well as macular edema, which can lead to severe vision loss or blindness. Retinal damage (from microangiopathy) makes it the most common cause of blindness among non-elderly adults in the US.

Macro vascular disease leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor:

- Coronary artery disease, leading to angina or myocardial infarction ("heart attack")
- Diabetic myonecrosis ('muscle wasting')
- Peripheral vascular disease, which contributes to intermittent claudication (exertion-related leg and foot pain) as well as diabetic foot.
- Stroke (mainly the ischemic type)

Diabetic foot, often due to a combination of sensory neuropathy (numbness or insensitivity) and vascular damage, increases rates of skin ulcers (diabetic foot ulcers) and infection and, in serious cases, necrosis and gangrene. It is why diabetics are prone to leg and foot infections and why it takes longer for them to heal from leg and foot wounds. It is the most common cause of non-traumatic adult amputation, usually of toes and or feet, in the developed world.

Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality and operative risks with these conditions.

Diabetic encephalopathy is the increased cognitive decline and risk of dementia-including (but not limited to) the Alzheimer's type- observed in diabetes. Various mechanisms are proposed, including alterations to the vascular supply of the brain and the interaction of insulin with the brain itself.

In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly and the leading cause of non-traumatic amputation in adults, and diabetic nephropathy is the main illness requiring renal dialysis in the United States.

A review of type 1 diabetes came to the result that, despite modern treatment, women with diabetes are at increased risk of female infertility, such as reflected by delayed puberty and menarche, menstrual irregularities (especially oligomenorrhoea), mildhyperandrogenism, polycystic ovarian syndrome, fewer live born children and possibly earlier menopause. Animal models indicate that abnodmalities on the molecular level caused by diabetes include defective leptin, insulin and kisspeptin signaling.

Restrictive lung defect is known to be associated with diabetes. Lung restriction in diabetes could result from chronic low-grade tissue inflammation, microangiopathy, and/or accumulation of advanced glycation end products. In fact the presence restrictive lung defect in association with diabetes has been shown even in presence of obstructive lung diseases like asthma and copd in diabetic patients.

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, some 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 C is able to revent 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 prosclerotic cytokine, may be protein kinase Cdependent (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 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. 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 majority of diabetic populations have not been cared as per severity. 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

1. Essentials of Pharmacotherapeutics by FSK Barar S. Chand publications 342-349.
2. Brownlee M, Cerami A and Vlassara H. Advanced glycosylation end products in tissue and the biochemical basis of diabetic complications. New England Journal of Medicine. 1988;318:1315-1321.
3. Ishii H, Jirousek MR, Koya D, Takagi C, Xia P, Clermont A, Bursell SJE, Kern TS, Ballas LM, Heath WF, Stramm LE, Feener EP and King GL. Amelioration of vascular dysfunctions in diabetic rats by an oral PKC an inhibitor. Science. 1996;272:728-731.

4. Japanese Society for Dialysis Therapy. An overview of dialysis treatment in Japan (as of 31 December 1998). Journal of Japanese Society for Dialysis Therapy. 2000;33: 1-27.
5. Kikkawa R and Haneda M. Pathogenesis of diabetic nephropathy. Clinical and xperimental Nephrology. 1997;1:3-11.
6. Koya D, Haneda M, Nakagawa H, Isshiki K, Sato H, Maeda S, Sugimoto T, Yasuda H, Kashiwagi A, Ways K, King GL and Kikkawa R. 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. 2000;13:2329-2337.
7. Nishio Y, Kashiwagi A, Taki H, Shinozaki K, Maeno Y, Kojima H, Maegawa H, Haneda M, Hidaka H, Yasuda H, Horiike K and Kikkawa R Altered activities otranscription factors and their related gene expression in cardiac tissues of diabetic rats. Diabetes. 1998;47:1318-1325.
8. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N and Shichiri M. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with noninsulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Research and Clinical Practice. 1995;28:103-117.
9. Diabetes Control and Complications Thal Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulindependent diabetes mellitus. New England Journal Medicine. 1993;329:977-986.
10. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. British Medical Journal. 1998;317:705-713.