PJN
ISSN 1680-5194

Pakistan Journal of Nutrition

ANSInet
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan
Mob: +92 300 3008585, Fax: +92 41 8815544
E-mail: editorpjn@gmail.com

Pakistan Journal of Nutrition 2 (1): 1-12, 2003

Role of Diet, Nutrients, Spices and Natural Products in Diabetes Mellitus

Alam Khan and Mahpara Safdar
Department of Human Nutrition, NWFP Agricultural University, Peshawar, Pakistan
E-mail: alamkhandr@yahoo.com

Abstract: Diabetes mellitus is a global disease, prevails all over the world, though the prevalence rate differs from country to country. Diabetes, a disorder of carbohydrate metabolism, is characterized by high blood glucose level and glycosuria resulting from dysfunction of pancreatic beta cells and insulin resistance. In advance stages of diabetes, metabolism of protein and lipid is also altered. Many factors like heredity, age, obesity, diet, sex, sedentary life style, socio economic status, hypertension and various stresses are involved in the etiology of diabetes mellitus. Drug, diet and recently spices therapies are the major approaches used for treatment and control of diabetes mellitus. In drug therapy, hypoglycemic medicines and insulin are used. In diet therapy, diet composition, amount, distribution and time of food intake are important factors. The diet must be acceptable, must supply adequate amount of nutrients, and be formulated in a way to normalize body weight. The diet for diabetic children should have sufficient calories for adequate nutrition, normal weight gain and growth. The diet should be high in complex carbohydrate, low in simple carbohydrate, low in fat and high in mono-unsaturated fatty acid. High fiber diets are beneficial for treatment of diabetes. Soluble fibers are more effective than insoluble fibers. Chromium is important for diabetes and functions in carbohydrate and lipid metabolism primarily via its role in potentiating insulin action in carbohydrate metabolism. In the spices therapy, cinnamon, cloves, bay leaves and turmeric have an insulin potentiating activity and are beneficial for diabetic individuals. Cinnamon is effective in reducing glucose level in type 2 diabetic individuals. The effective ingredient in cinnamon for hypoglycemic function has been identified as methyl hydroxy chalcone polymers. Other plant products have also hypoglycemic activities and may have beneficial role in treatment of diabetes mellitus. Cinnamon should be a part of diabetic diets for its hypoglycemic effect in diabetic individuals.

Key words: Diabetes mellitus, diet, spices, natural products, cinnamon

Introduction

Diabetes mellitus is a global disease, found in all nations of the world. The worldwide prevalence of diabetes mellitus is expected to double between 1994 and 2010 to more than 240 million people (McCarty and Zimmet, 1997). The prevalence rate of the disease varies from country to country. Khan *et al.* (1993a) have reported 1.49% prevalence of diabetes in NWFP, Pakistan. Their calculation was based on the information of respondents and not on actual serum glucose determination in the laboratory. Prevalence of diabetes, if reported on actual blood glucose level, may be high.

There are two main types of diabetes mellitus depending upon its etiology and treatment. Type 1 or insulin dependent diabetes mellitus (IDDM) or juvenile on-set diabetes involves autoimmune or idiopathic etiology. Type 2 or non-insulin dependent diabetes mellitus (NIDDM) or maturity on-set diabetes is basically due to predominant insulin resistant or predominant insulin secretary defects. Type 1 diabetes mellitus can only be controlled by insulin therapy (Khan *et al.*, 1993b). Type 2 diabetes is the most common one and usually starts at later life (over the age of 40) and mainly in obese individuals. In this type, the insulin producing cells in the pancreas produce insulin, but the output is inadequate for the body's need or there is a defect in liberation or/and action of insulin. This type of diabetes is mostly common in elderly population and can be controlled with diet and spices, hypoglycemic drugs and insulin (Khan *et al.*, 1993b; Khan and Ahmad, 1994).

Diabetes mellitus is a chronic disorder of glucose intolerance. It is characterized by high blood glucose level and glycosuria resulting from dysfunction of pancreatic β-cells and insulin resistance. The defective β-cells result in lack of total or partial synthesis of insulin. The insulin resistance is caused by cell membrane where glucose is not transported to the cells for oxidation. As glucose is not metabolized, high amount of glucose is circulating in the blood (hyperglycemia). To keep the normal level of glucose in the blood, the kidney removes the extra sugar from the blood and excretes it in the urine. Because glucose is not utilized by the body cells, the body is under constant impression of hunger and that is why diabetics feel increased appetite (polyphagia) and eat more frequently (Robinson *et al.*, 1986).

Symptoms of insulin resistance include a decreased stimulation of muscle glycogen synthesis, defects in glycogen synthesis activity, hexokinase activity and glucose uptake (Cline *et al*., 1999). In addition, altered enzymatic activities, such as an increased phosphatase activity and/or seryl phosphorylation of the insulin receptor substrate by glycogen synthesis kinase 3 (GSK-3), have also been shown to be involved in some cases of Type 2 diabetes mellitus (Begum *et al*., 1991; Nadiv *et al*., 1994; Eldar-Finkelman *et al*., 1997).

Insulin resistance plays an important role in the etiology of many disorders including obesity, NIDDM, glucose intolerance, hypertension and other related disorders. Severe obesity and NIDDM are both characterized by the diminished ability of insulin dependent tissues to respond to insulin (Sasson *et al*., 1993). This insulin resistance could be the result of a number of defects in the insulin-signaling pathway (Olefsky., 1993; Moller and Flier, 1991; Almind *et al*., 1993; Imamura *et al*., 1994; Maddux *et al*., 1995). Much focus has been placed on evidence that insulin receptor kinase autophosphorylation and subsequent phosphorylation of its principal substrate, IRS-1, are markedly decreased in insulin-responsive tissues of subject with severe obesity or NIDDM (Nadiv *et al*., 1992). Dephosphorylation of the receptor β-subunit is associated with the deactivation of its kinase activity and therefore is associated with insulin signal down-regulation (King *et al*., 1991).

Jarvill-Taylor *et al*. (2001) performed the comparative experiments with the cinnamon methylehydroxy chalcone polymers (MHCP) and insulin with regard to glucose uptake, glycogen synthesis, phosphatidylinositol-3-kinase dependency, glycogen synthesis activation and glycogen synthesis kinase-3β activity. They also investigated the phosphorylation state of insulin receptor. They concluded that the MHCP is an effective mimetic of insulin. MHCP may be useful in the treatment of insulin resistance and in the study of the pathways leading to glucose utilization in cells.

In woman, gestational diabetes (glucose intolerance) is developed during pregnancy due to complex hormonal and metabolic changes. Glucose intolerance usually becomes normal when pregnancy is over. In other words, diabetes mellitus in pregnancy is a normal physiological state.

In diabetes mellitus, insulin is produced in insufficient amount or it is not working properly, hence formation of glycogen decreases and utilization of glucose is reduced. This increases the amount of glucose in circulation and causes hyperglycemia. The amount of glucose is also increased by gluconeogenesis. When blood glucose level exceeds the renal threshold (160 - 180 mg/L) glucosuria occurs with wastage of energy and increased excretion of water and sodium. Decrease amount of insulin in circulation decreases lipogenesis and increases lipolysis. Increased lipolysis release fatty acids from adipose tissues. Fatty acids are also absorbed from the intestinal tract. These fatty acids are oxidized in liver to form ketone bodies including aceto - acetic acid, beta-hydroxy butyric acid and acetone. The liver utilizes only limited amount of ketone bodies and releases the remaining ketones to circulation. In diabetes mellitus, ketones are produced at a rate that far exceeds the ability of the tissues to utilize them and the concentration in the blood is greatly increased. This condition is called ketonemia. Acetone is excreted by lungs and gives the characteristic fruity odor in the breath of diabetic individuals. Aceto-acetic acid and beta-hydroxy-butyric acid are excreted in urine (ketonuria). Ketones are strong organic acids, they combine with bases, so the alkaline reserve of the body is depleted and acidosis results. The accompanying dehydration leads to circulatory failure, renal failure and coma.

The rapid release of fatty acids in the blood leads to hyperlipidemia. The blood level of cholesterol increases, so the development of atherosclerosis occurs at an earlier age than in non-diabetics and is more pronounced (Khan and Ahmad, 1993).

Muscle glycogen almost disappears and muscle protein is broken down to support gluconeogenesis by the liver in diabetics. Cardiac and skeletal muscles meet their energy requirements from ketone and fatty acids. The protein catabolism also increases and the amount of nitrogen that is excreted as a result of deamination, is also increased. The catabolism of protein tissues is accompanied by the release of cellular potassium and its excretion in urine.

Many factors are involved in the etiology of diabetes mellitus. Heredity, age, obesity (over weight), diet and sex are the major contributors. Other factors which help in development of the disease are sedentary life style, socio economic status, hypertension and various stresses (Khan and Ahmad, 1994).

Different approaches have been used to reduce the incidence rate of the disease and to cure the diabetes. The most popular approaches are the drug therapy, dietary therapy and recently the spices and natural products therapy. Drug therapy is the most common approach but is costly and has side effects. The dietary therapy is the most natural, economical and more feasible. Proper dietary intake can stop the incidence of the disease and even can reduce the severity of existing cases. The food quality and diabetes mellitus has close association with each other. The broad aims of dietary prescription for people with diabetes remain, first, to abolish the primary symptoms, secondly to minimize the risks of hypoglycemia and thirdly to minimize the long-term macro-vascular and micro-vascular complications which together result in morbidity and shortened lifespan with all types of diabetes. Diet therapy in diabetic consists of basically of precaution concerning diet composition, the amount, distribution and timing of food intake (Camerini-Davalos and Cole, 1987). Precaution in eating needs a very strong will and many people may not restrict themselves to a particular way of eating.

Natural products like spices have been used for taste and flavor development in food preparations. So in a way, spices become a part of diet not as a nutrient but as taste and flavoring agents. Recently some of the spices like cinnamon, cloves, bay leaves, turmeric and jamon have been reported to have insulin-potentiating effect *in vitro*. It has been reported that cinnamon potentiates the insulin activity more than three folds in carbohydrate metabolism (Khan *et al.*, 1990).

The purpose of this review is to update the scientists of the field and concerned individuals about the effects of diet, nutrients and natural products on diabetes mellitus.

Effect of Diet on Diabetes Mellitus: Diet plays an important role in the development and control of type 2 diabetes mellitus. Development of type 2 diabetes mellitus is directly related to diet. Diet high in simple carbohydrate and fat usually results in type 2 diabetes mellitus in the latter stages of life. Also many patients with type 2 diabetes can be controlled by diet alone with out the use of hypoglycemic agents or insulin. Therefore, dietary restriction is an essential factor in management of type 2 diabetic individuals. Dietary restriction includes diet composition, amount, distribution and timing of food intake.

For proper management of diabetic individuals, the diet must be designed to supply adequate amount of nutrients namely carbohydrate, fat, protein, vitamins and minerals. The diet should be acceptable and should be formulated in a way to normalize body weight. The diet for diabetic children should have sufficient calories for adequate nutrition and normal weight gain and growth (Khan and Ahmad, 1994).

The diabetic diet should contain 60% carbohydrate, 20 - 25% fat and 15-20% protein. High carbohydrate diet increases the sensitivity of peripheral tissues to both endogenous and exogenous insulin. Such diet improves glucose tolerance and lowers the level of serum insulin. In addition, the liberalization of carbohydrate might facilitate the reduction of saturated fatty acids and cholesterol in the diabetic diet (Jenkins and Josse, 1985; Collier *et al.*, 1985).

Simple dietary restriction and increased exercise may help in preventing diabetes mellitus from becoming a major health problem, particularly in identified areas of high prevalence (Martin *et al.*, 1981). Also dietary management is a good approach in diabetics care. Diets that enhance glycemic control are high in dietary fiber, low to moderate in dietary fat and moderate in high biological value proteins. The quantity of food intake should be adjusted to maintain optimum body weight (Moser, 1988). Decreasing caloric intake for NIDDM patients results in weight reduction which is beneficial for diabetics (Wilson *et al.*, 1988). Very low energy diets produce greater improvement in glycemic control than more moderate diets in obese type 2 diabetes, even if weight losses are the same (Wing, 1995). Diet therapy especially weight loss is a corner stone in the management of obese NIDDM patients. Reduction in total and saturated fat and limited protein intake with replacement by complex carbohydrate and/or mono-unsaturated fatty acids are the recommended diets for NIDDM. Such diets improve the metabolic control in diabetic individuals and reduce the risk of chronic complications (Griver and Henry, 1994). Decrease in energy and saturated fat intake help in NIDDM control. Diet that contains 60% carbohydrate and is rich in fiber improves blood sugar and lipid (Fernandez *et al.*, 1990).

Dietary manipulation is the first line of therapy for diabetic patients. Dietary strategies should aim to normalize blood glucose and lipoprotein levels in order to reduce morbidity and mortality related to derangement of carbohydrate and lipoprotein metabolism in diabetes mellitus. To achieve these goals, quantity and quality of diets must be considered according to each individuals and his clinical condition. Total energy intake should attain and maintain desirable body weight. Total dietary energy should consists of < 30% of total fat with equal distribution of saturated, mono-unsaturated and polyunsaturated fatty acids, 10-20% of protein, 50-60% of carbohydrate with restriction of simple carbohydrate. Cholesterol intake should be reduced to less than 300 mg/day. In a study of 16 females with NIDDM adhered to diets containing 15% protein (soybean: chicken: rice = 2.5 : 1.0 : 1.5), 30% fat (soybean oil : structural fat = 2 : 1) and 55% carbohydrate - calories (complex: simple carbohydrate = 4.5 : 1.0), their serum total cholesterol, LDL-cholesterol and blood glucose level decreased (Tanphaichitr *et al.*, 1993).

Silvis *et al.* (1989) estimated nutrient intake of 40 black South African diabetic patients (18 male and 22 female) with a validated food frequency questionnaire and correlated it with metabolic variables. Their dietary intake was characterized by low fat intake and dietary fiber intake reached only 50% of recommended diet value. High incidence of hypertension (61% of men, 68% of women), obesity (mean body mass index of men was 26.6 ± 4 and women 32.7 ± 4.3) and hypercholesterolemia in women (mean total cholesterol of 6.8 ± 2.1 mmol/litre) was observed. A mean protective value of cholesterol carried by high-density lipoprotein (>20%) was found in the man and insulin treated patients. Glycated hemoglobin values indicated that only 33% of patients were in good glycemic control. They postulated that the observed normal coagulation profile of these patients, possibly a result of their prudent diet, might protect them against the long term complication of diabetes. Kerin *et al.* (1989) studied the effect of varying among of carbohydrate, fat and fiber on metabolic control in type 2 diabetes. High fiber and low fat diet improved metabolic control in type 2 diabetes. They recommended unrefined and high in fiber and carbohydrate diet for diabetics.

Bonanome *et al*. (1991) carried out study on 19 patients 55 ± 6 years old with NIDDM in good glycemic control. The patients were given 3 iso-energic dietary phases. In phase I and 3, the diet was rich in complex carbohydrate, while in phase 2 it was rich in mono-unsaturated fatty acid. The results indicated that both diets were well tolerated and did not alter glucose homeostasis or worsen plasma lipid concentration. They reported that a wider choice in diet selection was available to NIDDM patients with out producing unwanted side effects.

Brand *et al*. (1991) compared the effects of low glycemic index foods (porridge, pasta) with high glycemic index foods (processed cereals, potatoes) on long term glycemic control in NIDDM. The study was carried out on 16 subjects. They reported that glycemic control was improved by low glycemic index foods as compared with high glycemic index foods.

Effect of Carbohydrate on Diabetes Mellitus: Carbohydrate plays a very important role in the development and control of diabetes. Simple sugar is directly responsible for the onset of type 2 diabetes, while complex carbohydrate help in the control of type 2 diabetes. In the management of diabetes, higher carbohydrate diet allows reduction in the proportion of energy from fat when total energy is controlled and glucose tolerance is improved in diabetics. Mixture of carbohydrates assists glycemic control (Burgers, 1982). The recent approach is that the diet of diabetics should have 60% complex carbohydrate (Jenkins and Josse, 1985).

Viswanathan (1978) and Anderson and Sieling (1985) found that rates of glycogen synthesis and glycogen accumulation in liver, skeletal muscles and jejunal mucosa were greater with high rather than low carbohydrate diets. Glycolysis and activities of key glycolytic enzymes were also higher in several tissues with high carbohydrate diets. They argued on the basis of their data that many metabolic changes are accompanied with high carbohydrate and low fat diets.

Pun *et al*. (1988) studied the effects of diet with high carbohydrate contents on diabetics having hyperlipidemia and micro albuminuria. Dietary intakes of 28 patients with IDDM were assessed by dietary history of 3 days using dietary recall method. The results indicated that a high carbohydrate diet in treatment of diabetes mellitus was not associated with significant alteration in the amount of micro albuminuria or in hyper triglyceridaemia.

Birchwood and Jenkins (1988) studied fructose and sorbitol in the management of diabetes mellitus with replacement of sucrose. They noted that these sugars did not require additional secretion of insulin and had minimal effect on increasing blood glucose. They suggested that diabetes control might be favorably influenced by fructose usage.

Anderson *et al*. (1991) studied the metabolic effects of high carbohydrate (70%), high fiber (70 g) (HCHF) and low fiber (10 g), low carbohydrate (LCLF), (37%) diet in 10 IDDM subjects of 35-36 years old. After a control period of 1 week, subjects in a metabolic ward were randomly assigned to HCHF or LCLF diets for 4 weeks. After a 6-week wash period, subjects were re-entered to the metabolic ward for 4 weeks on the alternate diet. Artificial pancreas studies were made on each diet for estimation of insulin requirements. Compared with the LCLF diet, the HCHF diet reduced basal insulin requirement ($P<0.025$), increased carbohydrate disposed off per unit insulin ($P<0.0008$) and lowered total ($P<0.0004$) and high density lipoprotein cholesterol ($P<0.0013$). Glycemic control and other lipid fractions did not differ significantly. The results indicated that in IDDM high-carbohydrate - high - fiber diets enhance peripheral glucose disposal, decrease basal insulin requirements and lower total cholesterol with out altering glycemic control and triacylglyceroles.

Sun *et al*. (1977) found that if rats were fed on high carbohydrate diet will have more insulin receptors per liver cells than rats fed on high fat diet. They suggested that high carbohydrate had better controlling effect on diabetes as compared to high fat. Increased carbohydrate intake does not worsen glycemic control and decreases serum cholesterol concentration (Weinsier *et al.,* 1978).

Effect of Protein on Diabetes Mellitus: Diabetes mellitus is basically a disorder of carbohydrate metabolism, but with progression of the disease, protein metabolism is also affected. Gluconeogenesis, a major biochemical process that produces glucose from protein, is accelerated in diabetes mellitus. So kind and amount of protein may affect diabetic conditions. Jenkins and Josse (1985) have recommended 15-20% protein in the diet of diabetic individuals.

Raal *et al*. (1994) studied the effect of moderate dietary protein restriction on the progression of diabetic nephropathy on 22 subjects (20 to 41 years old) with IDDM. The subjects were randomly assigned to an unrestricted protein diet (> 1.6 g/kg body weight daily) or a moderately protein restricted diet (0.8 g/kg body weight daily) and followed for 6 months. Direct isotope method was used to asses renal functions. Protein intake was assessed by measurement of urinary urea nitrogen. The 2 groups were well matched for age, sex, duration of diabetes, glycemic control, blood pressure and degree of renal insufficiency. Patients consuming the unrestricted protein diet (n = 11) showed a progressive decline in glomerular filtration rate of 1.3 ml min^{-1} $month^{-1}$ with no change in proteinurea. The result indicated that patients consuming the moderately protein-restricted diet showed a marked decrease in the degree of proteinurea (2.15 to 1.13 g/day, P = 0.03) and stabilization of glomerular filtration rate. This occurred independently of changes in blood pressure or glycemic control. They suggested that moderate protein restriction could ameliorate progression of overt diabetic nephropathy.

Turnbull and Ward (1995) studied the effect of mycoprotein on acute glycemia and insulinaemia in normal healthy individuals. Mycoprotein reduced glycemia and insulinemia. They reported that the role of mycoprotein was significant in the dietary treatment of diabetics.

Effect of Fat on Diabetes Mellitus: Fat is an important constituent of diet. In diabetes, lipogenesis (synthesis of fat) is decreased and lipolysis (decomposition of fat) is increased. Type and amount of fat and fatty acids may have an affect on diabetes complications.

Garg *et al.* (1989) compared high carbohydrate diet with a high monounsaturated fat diet for effect on glycemic control and plasma lipoprotein in 10 patients with NIDDM receiving insulin. Patients were randomly assigned to receive first one diet and then the other, each for 28 days, in a metabolic ward. In the high carbohydrate diet, 25% of the energy was in the form of fat and 60% in the form of carbohydrate (47% of total energy in the form of complex carbohydrate). The high-mono-unsaturated fat diet was 50% fat (33% of total energy in the form of monounsaturated fatty acid) and 35% carbohydrate. The two diets had the same amount of simple carbohydrate and fiber. The monounsaturated fat diet resulted in lower mean plasma glucose concentration and reduced insulin requirement when compared with high carbohydrate diet. The same diet also lowered 25% plasma triglyceride concentrations, 35% very-low-density lipoprotein cholesterol and increased 13% of high-density lipoprotein (HDL) cholesterol. Total cholesterol and low-density lipoprotein (LDL) cholesterol concentration did not differ significantly between diets. They suggested that partial replacement of complex carbohydrate by mono-unsaturated fatty acid in diet did not increase plasma LDL cholesterol and might improve glycemic control and concentration of plasma triglyceride and HDL cholesterol.

Axelrod (1989) observed some apparently beneficial effects of omega - 3 fatty acids on platelet function, eicosanoid formation and plasma triglyceride values in diabetes mellitus. High doses (4 to 10 g daily) of these fatty acids affected the patients adversely, though these effects were very small (10 - 36%).

Sabina *et al.* (1992) examined the effects of glyburide for 4 weeks on glucose, insulin, lipid lipo-protein metabolism in 10 men with NIDDM receiving dietary fish oil concentrate containing omega-3-fatty acids. Glyburide with omega-3-fatty acid decreased fasting glucose concentration, basal insulin concentration were unaltered, VLDL cholesterol concentration decreased and apo-lipoprotein B concentration tended higher.

Effect of Fiber on Diabetes Mellitus: High fiber diets are effective in diminishing insulin secretion and lowering blood glucose and are thus beneficial for treating diabetics, particularly those with type 2 diabetes. A combined high carbohydrate, high fiber diet may blunt the post prandial elevation of blood glucose and reduce the insulin requirement.

Fibers of soybean and fenugreek seed are beneficial in reduction of plasma glucose in patients with NIDDM and in pregnant diabetic women (Madar and Thorne, 1987). It has been reported that 15 g daily of soluble dietary fiber in the average type 2 diabetic patient, has produced 10% improvement in fasting plasma glucose, glycosylated hemoglobin and in total and LDL cholesterol (Fuessle, 1987).

Different fibers have different effect on diabetic patients. Toma *et al.* (1988) studied the effect of soluble and insoluble dietary fibers in diabetic diet. Three different meals were formulated with similar quantities of available carbohydrate, protein and fat. These meals were having low fiber, high soluble fiber and high insoluble fiber. Ten patients with NIDDM in good metabolic control received each test meal in randomized order every two weeks. The high soluble fiber meal produced significantly lower glucose and insulin responses than diet containing low fiber or high insoluble fiber. Dietary fiber promotes satiety and assists in weight loss in diabetic patients and hence helps in controlling diabetes (Garrow and Owens, 1990).

Madar (1990) studied the effects of dietary fibers from legume seeds in control of blood lipids and glucose in diabetic rats and humans. The results indicated that dietary fiber could contribute to control lipid metabolism disorders in NIDDM. They suggested that combination of fibers from different sources might be more effective than a single fiber type. Soluble fiber of leguminous origin improved blood lipids, reduced LDL or VLDL cholesterol and maintained HDL cholesterol (Venik and Jenkins, 1988).

Vorster *et al.* (1988) studied the benefits from supplementation of the current recommended diabetic diet with gel fiber in 17 insulin treated and 10 on oral medication in a doubled blind placebo-controlled study. They found that gel fiber had significant beneficial effect on glycemic control, insulin requirement and HDL cholesterol values in insulin treated subjects. They further noted that increased intake of dietary fiber was associated with significant decrease in total serum protein and increase in serum albumen in all subjects.

Effect of Minerals on Diabetes Mellitus: Minerals are essential component of life and hence of diets. They perform important functions in the various biochemical processes of the body. Some minerals, particularly the trace minerals are active participants of metabolism. Some of the minerals are the essential part of some of the enzymes for their biological activities. As diabetes mellitus is a disease of metabolic abnormality so minerals as such or as a component of enzymes may be playing a significant role in development and control of diabetes mellitus. Amongst minerals, chromium is involved in the development and control of diabetes mellitus. Extensive research on the role of chromium in the development and control has been reported.

Chromium is an essential micronutrient that functions in carbohydrate and lipid metabolism primarily via its role in the potentiation of insulin action. In the presence of chromium in a usable form, much lower levels of insulin are required (Anderson, 1993). Dietary intake of chromium in most developed countries is suboptimal and symptoms of marginal chromium deficiencies appear widespread (Anderson *et al.*, 1992).

Chromium functions in maintaining normal glucose tolerance primarily by regulating insulin action. In the presence of sufficient amount of chromium, in a biologically active form, much lower amounts of insulin are required. Chromium functions by increasing the activity of insulin and therefore reducing the amount of insulin required to control blood sugar and related processes. It is important to keep insulin at low levels to prevent secondary signs of diabetes. For example, arterial plaque formation is an insulin sensitive process and increased levels of circulating insulin often stimulates increased plaque formation leading to atherosclerosis.

The role of chromium in diabetes should be considered primarily as a means of preventing maturity on set diabetes rather than as a cure or treatment. There is a very strong evidence that insufficient dietary chromium leads to impaired glucose tolerance that can be alleviated by supplemental chromium. Since essentially all those who go onto develop maturity onset diabetes will have initially impaired glucose tolerance and prevention of impaired glucose tolerance lead to prevention of maturity onset diabetes. Impaired glucose tolerance is the leading indicator of maturity on-set diabetes (Anderson, 1992).

Chromium is involved in both carbohydrate and lipid metabolism. Insufficient dietary chromium is associated with increased risk factors linked with non-insulin dependent diabetes and cardiovascular diseases. Chronic chromium deficiency is implicated in several cardiovascular and metabolic pathologies, including NIDDM. Low to marginal intakes of chromium over decades, coupled with decreased absorptive ability, are believed to be contributing factors in NIDDM. Glucose intolerant, type 2 diabetics and elderly subjects have all been shown to respond to supplementary chromium. Responses include improved glucose, insulin and lipid values (Podell, 1983; Offenbacher and Pi-Sunyer, 1980; Jeejeebhoy and Chu, 1977). Variables in human that have been shown to improve following chromium supplementation include fasting blood glucose concentration and glucose tolerance, serum insulin and insulin binding, total cholesterol and HDL cholesterol. Insufficient dietary chromium leads to elevated circulating insulin, elevating fasting glucose, impaired glucose tolerance decreased HDL cholesterol and elevated cholesterol and triglyceride (Anderson, 1986). Chromium is required for maintenance of normal glucose tolerance in several animal species including man. In its biologically active trivalent state, it forms complex with organic compounds that are important for stability, intestinal absorption and biological activity. One such complex, glucose tolerance factor (GTF), has been reported in brewers yeast. This compound has insulin potentiating activity *in vitro* (Mertz, 1982).

The suggested safe and adequate intake of chromium for adults was established at 50-200 ug/day in 1980. However, chromium intake in the US and other developed countries is usually 50-60% of the minimum suggested safe and adequate intake (National Academy of Science, 1989). Chromium supplementation leads to decreased total cholesterol and triglyceride, increased HDL cholesterol and improved total cholesterol/HDL ratio. Chromium supplementation of elderly subjects, mean age 78, resulted in improvements in total cholesterol and lipids with the greatest increase in subjects with highest initial cholesterol values (Offenbacher and Pi. Sunyer, 1980). The beneficial effects usually involve more than 200 ug daily of supplemental chromium on subjects with less advanced stages of diabetes. The suggested daily intake for chromium for normal adult subjects is 50-200 ug. Sixty days of supplementation with 500 ug/day of chromium led to decreased glucose and insulin of 12 diabetics (Nath *et al.*, 1979). Fasting blood glucose of 13 diabetics on either exogenous insulin or oral hypoglycemic agents decreased from a mean of 259 mg/dl to 119 following daily supplementation with 500 ug of chromium (Mossop, 1983). Anderson *et al.* (1996) studied the effects of chromium on 180 type II diabetics in Beijing, China. The diabetic individuals were divided into three groups. One group was given placebo and the other two groups were given 200 or 1000 ug/day for four months. Subjects were on their routine diet and usual medication during the study. Glycated hemoglobin improved significantly after two months in the group receiving 1000 ug of chromium per day and was lower in both chromium groups after four months (Placebo, 8.4 $\pm$ 0.2: 200 ug Cr. 7.5 $\pm$ 0.2 and 1000 ug, 6.6 $\pm$ 0.1%). Two hour meal tolerance glucose values were also significantly lower for the subjects consuming 1000 ug of supplemental chromium after both two and four months. Fasting and two hours meal tolerance insulin values decreased significantly in both groups receiving supplemental chromium after two and four months. Plasma cholesterol also decreased after four months in the group receiving 1000 ug of chromium. Supplemental chromium had significant beneficial effect of Glycated hemoglobin, glucose, insulin and cholesterol variables of subjects with type II diabetes. Chromium is a very safe nutrient, intakes 300 times of the upper level of the suggested safe and adequate intake result in no observed adverse effects (Dourson, 1994). Chromium absorption is also very low, 0.4 to 2.0% (Anderson and Kozlousky, 1985), and indigestion resulting in vomiting is likely to occur before any toxicity damage from absorbed chromium.

Chromium is an essential part of a dietary factor that improves glucose tolerance in chromium deficient rats (Mertz, 1969). The beneficial effects of chromium is related to a usable form of chromium and not to total chromium. This usable form of chromium may be present in foods, as such, or can be biosynthesized with in the body by most people (Mertz *et al.*,1989). Chromium deficiencies interfere with carbohydrate and lipid metabolism and severe cases may lead to diabetes mellitus and cardiovascular abnormalities. Many foods are low in endogenous chromium, but may be contaminated with chromium from external sources. Some of this contaminating chromium appears to be absorbed and utilized (Anderson and Brydon, 1983).

Khan *et al.* (1990) investigated an unidentified factor that had potentiated the action of insulin in glucose metabolism in selected foods and spices. Chromium content of these foods and spices was also determined. Among the selected foods, tuna fish, peanut butter, and vanilla ice cream had some insulin potentiating activity. Among the spices, cinnamon, cloves, bay leaves, and turmeric potentiated insulin activity more than three-fold. Insulin potentiating activity of foods and spices did not correlate with total chromium.

Janjua (1988) studied the role of micro minerals especially chromium on human health. He reported that chromium was present in spices, bark of kekar, and in the fruits of lasori, banana and amlah. He further reported that chromium in herbs improved glucose tolerance in malnourished children and elderly diabetics.

Other trace minerals may be playing a role in development or control of diabetes. However, organized work in the area of trace minerals other than chromium and incidence of diabetes has not been done. It will be a very beneficial work if the effect of individual minerals on diabetes is studied.

Lin *et al.* (1993) studied the levels of blood metals in healthy individuals and non-insulin dependent diabetics. They investigated the relationship between divalent metal ions and the development of diabetes mellitus. They studied 25 outdoor patients of newly diagnosed NIDDM and 54 healthy controls. Plasma and erythrocyte zinc, copper, calcium and magnesium concentrations in fasting were determined by flame atomic absorption spectrometry. The results showed that NIDDM patients had lower copper and magnesium levels, and higher calcium levels in plasma than healthy controls. Significantly lower zinc and higher calcium concentrations in erythrocytes were found in NIDDM patients. The erythrocyte levels of copper and magnesium in NIDDM were slightly lower than those of healthy controls. Variations of blood levels of these metals might be related to the metabolic alterations in NIDDM.

Copper is involved in normal carbohydrate and lipid metabolism. Signs and symptoms of insufficient dietary copper include anemia, pancreatic atrophy, heat hypertrophy, glucose in-tolerance and elevated blood lipids (Davis *et al.*, 1987). More data are required to evaluate the role of copper in diabetes.

Zinc is a multi functional nutrient involved in glucose and lipid metabolism, hormone function and wound healing (Hambidge *et al.*, 1987).

Effect of Spices and Natural Product on Diabetes Mellitus: Recently, spices and other natural products have been used in the treatment and control of diabetes mellitus. Spices and other plant products are considered more natural, economical and safe in the treatment of diabetes mellitus. It is really a kind of home treatment and can be a part of usual diet. Control of diabetes by natural products is becoming popular more and more and is more appropriate for use in developing countries. These products especially the spices may have a direct role in the prevention and control of diabetes. It will be appropriate if research work on the effect of natural product on diabetes is collected.

Glazer and Halpern who observed that a yeast extract had insulin-potentiating property reported the first evidence that natural products have insulin-potentiating activity in 1929. In 1979, Bever and Zahnd published a list of plants which had oral hypoglycemic action (Bever and Zahnd, 1979). Almost a decade later, Rahman and Zaman (1989) and Ivora *et al.* (1989) published lists of several hundred species, which had anti-diabetic properties. Hypoglycemic property of bitter gourd has been reported by many researchers (Khana, 1985; Satyavati *et al.*, 1987).

In 1955, Mertz and Schwarz (1959) reported that extract of brewer's yeast could reverse the impaired tolerance to glucose load in torula yeast fed rats. They termed the active substance in brewer's yeast extract as glucose tolerance factor (GTF). Toepfer *et al.* (1977) reported that the biologically active extract from brewer's yeast contained chromium, nicotinic acid, glycine, cysteine and glutamic acid. They provided further evidence for their claim by synthesizing biologically active complexes comprised of trivalent chromium, nicotinic acid, glycine, cysteine and glutamic acid. Biologically active chromium is that chromium, which potentiates insulin activity, measured *in vitro*.

In 1988, working on purification of biologically active chromium, Khan *et al*. (1990) discovered that certain spices like cinnamon, cloves, bay leaves and turmeric displayed insulin potentiating activity. They termed this activity as insulin potentiating factor (IPF) present in these spices. This activity of spices did not correlate with chromium content of spices. Khan *et al*. (2003c) elaborating on the list of natural products that potentiate insulin activity, reported that jaman seed, bitter gourd, fenugreek and tea had insulin potentiating activity. The tea activity was inhibited by addition of milk to the tea.

Anderson *et al*. (2001) characterized this unidentified factor present in cinnamon as methyl hydroxy chalcone polymers (MHCP). They reported that MHCP found in cinnamon increased insulin dependent glucose metabolism roughly 20 fold *in vitro*. They explained that MHCP makes fat cells more responsive to insulin by activating the enzyme that causes insulin to bind to cells (insulin-receptor-kinase) and inhibiting the enzyme that blocks this process (insulin-receptor-phosphatase) leading to maximal phosphorylation of the insulin receptor, which is associated with increased insulin sensitivity.

Khan *et al*. (2003a; 2003b) studied the effect of cinnamon doses on blood glucose, triglyceride (TGL), cholesterol, high-density lipoproteins (HDL) and low-density lipoproteins (LDL) for 60 days in Type 2 diabetic individuals. Sixty, Type 2 diabetic individuals of both sexes and of age 48 ± 6.5 years were divided into 6 groups; each group was having 10 individuals. Groups 1, 2 and 3 were assigned for 1g, 3g and 6g cinnamon doses/day respectively. Groups 4, 5 and 6 were assigned for 1g, 3g and 6g placebo doses/day respectively. Cinnamon and placebo were given in the form of capsules with breakfast, lunch and dinner. The doses were taken for 40 days followed by a 20 days blank period. Fasting blood samples were taken on days 0, 20, 40 and 60; the blood glucose, TGL, cholesterol, HDL and LDL of both the cinnamon and placebo groups were determined. The cinnamon doses significantly ($P < 0.05$) reduced the mean fasting blood glucose, TGL, cholesterol and LDL but did not significantly change the mean fasting HDL levels in Type 2 diabetic individuals when compared with the control values for cinnamon (day 0 values for cinnamon doses). The placebo doses did not affect the blood glucose, TGL, cholesterol, HDL and LDL levels in Type 2 diabetic individuals when compared with the control values for placebo (day 0 values for placebo doses). There was no significant effect of 1g, 3g and 6g cinnamon doses/day on the concentration of glucose, TGL, cholesterol, HDL and LDL in Type 2 diabetic individuals. In the light of their findings, they recommended that Type 2 diabetic individuals should use 1-3g cinnamon in their food preparations on regular basis. The diabetic individuals can use cinnamon shakers for sprinkling of cinnamon powder on the curry in the plate. The patients can prepare cinnamon tea without sugar and can use it after meals. Also diabetics can chew cinnamon bark after meals. This will keep their sugar level near to normal values.

Iyer and Mani (1989) studied the effect of curry leaves (bay leaves) supplementation (Murraya Koenigi) on lipid profile, Glycated protein and amino acids in 30 NIDDM patients. The results indicated a transient reduction in fasting and postprandial blood sugar levels with no appreciable change in other parameters.

Sharma and Rahuram (1990) and Rahuram *et al*. (1994) observed the hypo-glycemic effect of fenugreek seeds in 15 NIDDM subjects. Incorporation of fenugreek in diet produced a significant fall in fasting blood glucose and improvement in glucose tolerance, by improving peripheral glucose utilization. Bijlani *et al*. (1993) studied acute postprandial and long term metabolic responses to a traditional mixture of barley, Bengal gram and wheat mixture on 8 healthy and 6 NIDDM. The subjects who consumed cereal pulse mixture showed reduced plasma glucose, decrease glycosylated hemoglobin levels and carbohydrate tolerance and increased LDL cholesterol level. Sook and Myung (1992) investigated the hypoglycemic effects of Korean wild plants, Capsella Bursa-Pastoris Medicine (CBM), Connective Communis L (CCL), Calystegica Japonia Choicy (CJC), Discoria Japonia Thumb (DJT) and Persicaria Per foliate Gross (PPG), used as a herb or soup in male rats. The results suggested that CCL or DJT alleviate the hyperglycemic state in diabetes mellitus.

Bhardwaj *et al*. (1994) observed the effective reduction of LDL cholesterol by indigenous plant product. A herbal powder containing guar-gum (Cyamopsis tetragonolobr), methi (Trigonella foenumgraaccum, fenugreek), Tumbdika (Cephalandra indica) or meshasringi (Gymnema sylueskre) was administered to 30 control and 30 NIDDM patients for a month. Total and low density lipoprotein cholesterol were reduced significantly after treatment.

Botanical products can improve glucose metabolism and over all condition of persons with diabetes not only by hypoglycemic effect but also by improving lipid metabolism, antioxidant status, and capillary function (Broadhurst, 1997). A number of medicinal/culinary herbs have been reported to yield hypoglycemic effects in subjects with diabetes. These include cinnamon, cloves, bay leaves, turmeric (Khan *et al*., 1990), bitter melon, *Momordica charantia* (Srivastava *et al*., 1993;

Raman and Lau, 1996), gurmar, *Gymnena syluestre* (Basakaran *et al*., 1990; Shanmugasundaram *et al*., 1990; Bishayee and Chatterjee , 1994), Korean ginseng, *Panax ginseng* (Sotaniemi *et al*., 1995), onions, *Allium cepa* and garlic, *Allium sativum* (Koch and Lawson, 1996), holy basil, *Ocimum sanctum* (Rai *et al*., 1997), and flaxseed meal, *Linum usitatissimum* (Cunnane *et al*. 1993).

Broadhurst *et al*. (2000) evaluated the possible effects of 49 herb, spice, and medicinal plants extracts on insulin function in the insulin-dependent utilization of glucose using a rat epididymal adipocyte assay. Cinnamon was the most bioactive product followed by witch hazel, green and black teas, allspice, bay leaves, nutmeg, cloves, mushrooms, and brewer's yeast. The glucose oxidation enhancing bioactivity was lost from cinnamon, tea, witch hazel, cloves, bay leaf and all spice by polyvinylpyrrolidone (PVP) treatment, indicating that the active phytochemicals are likely to be phenolic in nature. They concluded that the extracts of specific plants had improved the glucose and insulin metabolism.

References

Almind, K., C. Bjorbeak, H. Vestergaard, T. Hansen, S. Echwald and O. Pederson, 1993. Amino acid polymorphisms of insulin receptor substrate-1 in non-insulin dependent diabetes mellitus. Lancet, 342: 828-832.

Anderson, J. W., J. A. Zeigler, D. A. Deakins, T. L. Floore, D. W. Dillon, C. L. Wood, P. R. Oeltgen and R. J. Whilley, 1991. Metabolic effects of high carbohydrate, high fiber diet for IDDM individuals. Am. J. Clin. Nutr., 54: 936-943.

Anderson, J. W. and B. Sieling, 1985. Nutrition and diabetes. IN: Nutrition update. (Weinevger, J., Griggs, G., eds). New York, John Wiley and Sons.

Anderson, P. H., S. Lunds, O. Schmitz, S. Junker, B. B. Kahn and Pedersen, 1992. Increased insulin stimulated glucose uptake in athletes: The importance of $glut_4$ mRNA Glut4 protein and fiber type composition of skeletal muscle Acta. Physiol. Scand., 149: 393-404.

Anderson, R. A., 1986. Chromium metabolism and its rolein disease processes in man. Clin. Physiol. Biochem., 4: 31-41.

Anderson, R. A., 1992. Chromium, glucose tolerance and diabetes. Biol. Trace Elem. Res., 32: 19-24.

Anderson, R. A. and N. A. Brydon, 1983. Concentration, insulin potentiation and absorption of chromium in Beer. Agri. Food Chem., 31: 308-311.

Anderson, R. A. and S. A. Kozlousky, 1985. Chromium intake, absorption and excretion of subjects consuming self selected diets. Am. J. Clin. Nutr., 41: 1177-1183.

Anderson, R. A., 1993. Chromium, glucose tolerance and diabetes. Biol. Trace Element. Res., 32: 19-29.

Anderson, R. A., N. Chang, N. Bryda, M. Polansky, N. Chang, J. Chi and J. Feng, 1996. Beneficial effects of chromium for people with type II diabetes. Am. Diab. Assoc. Annual Meeting at San. Francisco, CA.

Anderson, R. A., C. L. Broadhurst, M. M. Polansky, W. F. Schmidt, A. Khan, N. W. Schoene and D. J. Graves, 2001. Isolation and characterization of chalcone polymers from cinnamon with insulin like biological activities. Manuscript in preparation, 2001.

Axelrod, C., 1989. Omega-3-fatty acids in diabetes mellitus. Gift from the Sea? Diabetes, 38: 539-543.

Basakaran, K., B. K. Ahmath, K. R. Shanmugasundaram and E. R. B. Shanmugasundaram, 1990. Antidiabetic effect of a leaf extract from *Gymnema sylvestre* in non-insulin dependent diabetes mellitus patients. J. Ethnopharm., 30: 295-305.

Begum, N., K. E. Sussman and B. Draznin, 1991. Differential effects of diabetes on adipocyte and liver phosphotyrosine and phosphoserine phosphatase activities. Diabetes, 40: 1620-1629.

Bever, O. B. and G. R. Zahnd, 1979. Plants with oral hypoglycemic action. Quart. J. Crude Drug Res., 17: 139-196.

Bhardwaj, P. K., D. J. Dasgupta, B. S. Prashar and S. S. Kaushal, 1994. Effective reduction of LDL cholesterol by indigenous plant product. J. Ind. Med. Assoc., 92: 80-81.

Bijlani, R. L., J. P. Narain, K. Shukla, K. P. Kochhar, P. Puri, M. G. Karmarker and S. Balas, 1993. Int. J. Food Sci. Nutr., 44: 243-251. Glycemic and metabolic responses to a traditional cereal-legume mixture.

Birchwood, B. and A. L. Jenkins, 1988. Fructose and sorbitol in the management of diabetes mellitus. J. Can. Diet. Assoc., 49: 153-157.

Bishayee, A. and M. Chatterjee, 1994. Hypolipidaemic and antiastherosclerotic effects of oral *Gymnema sylvestre* R. Br. Leaf extract in albino rats fed a high fat diet. Phytother. Res., 8: 118-120.

Bonanome, A., A. Visona, L. Lusiani, G. Beltramelleo, L. Confortin, S. Biffanti, F. Sorgato, F. Costa, and A. Pagnan, 1991. Carbohydrate and lipid metabolism in patients with NIDDM: effect of a low fat, high carbohydrate diet vs a diet high in mono-unsaturated fatty acid. Am. J. Clin. Nut., 54: 586-590.

Brand, J. C., S. Colagiure, S. Crossman, A. Allen, Roberts, Dck and A. S. Truswell, 1991. Diabetes care, 14: 95-101.

Broadhurst, C. L., 1997. Nutrition and non-insulin dependent diabetes from an anthropological perspective. Alt. Med. Rev., 2: 378-399.

Broadhurst, C. L., M. M. Polansky and R. A. Anderson, 2000. Insulin-like biological activity of culinary and medicinal plants aqueous extracts *in vitro*. J. Agri. Food chem., 48: 849-852.

Burgers, B. R. B. E., 1982. Rational for changes in the dietary management of diabetes. J. Am. Diet. Assoc., 81: 258-261.

Camerini- Davalos, R. A. and H. S. Cole, 1987. Current concepts in the diet therapy of diabetes mellitus. In: S.L. Halper (ed), Quick reference to clinical Nutrition. Second Ed. pp: 263-269. J.B. Lippincott Comp. Philadelphia, USA.

Cline, G. W., K. F. Oetersen, M. Krssak, J. Shen, R. S. Hundal, Z. Trajanoski, S. Inzucchi, A. Dresner, D. L. Rothman and G. I. Shulman, 1999. Impaired glucose transport as a cause of decreased insulin-stimulated muscle glycogen synthesis in Type 2 diabetes. N. Engl. J. Med., 341: 240-245.

Collier, G. R., J. Kalmusky and Guidicis, 1985. Effect of slowly digested carbohydrates in type I diabetic children. Diabetes, 32: 33A.

Cunnane, S. C., S. Ganguli, C. Menard, A. C. Liede, M. J. Hamadeh, Z. Y. Chen, T. M. S. Wolever and D. J. Jenkins, 1993. A. High a-linoleic flaxseed (*Linum usitaissimum*): some nutritional properties. Br. J. Nutr., 69: 443-453.

Davis, G. K. and W. Mertz, 1987. Copper Trace elements in human and animal nutrition. In: W. Mertz, (eds). Trace Orlando, Academic Press, Vol. I, pp: 301-364.

Dourson, M. L., 1994. The chromium reference dodge IN: Risk Assessment of Essential Elements, W. Mertz, C.O. Abernathy and S.S. Olin, (eds). ISLI Press, Washington, DC, pp: 207-212.

Eldar-Finkelman, H. and E. G. Krebs, 1997. Phosphorylation of insulin receptor substrate-1 by glycogen synthase kinase 3 impairs insulin action. Proc. Natl. Acad. Sci. USA, 94: 9660-9664.

Fernandez, Soto, M. L., Gonzalez, A. Jimenez, L. Navarrete- Lopeg- Cozer,, Lobon, J. A. Hernandez, Aguirri, M. A. Zamorano, Escobar and F. Junenez, 1990. Diet and NIDDM current and historical perspective. Reuista-Clin. Espanola, 186: 131-133.

Fuessle, H. S., Williames, T. E. Adrain and S. R. Bloom, 1987. Guar sprinkled on food effect on glyceramic control, Plasma lipid and gut Harmon in NIDDM subject. Diet. Med., 4: 463-468.

Garg, A., A. Bonanome, S. M. Grundy, Z. Shang and R. H. Unger, 1989. Comparison of high carbohydrate diet with a high monounsaturated fat diet in patients with NIDDM. National Eng. J. Med., 319: 829-34.

Garrow, J. S. and A. M. Ovens, 1990. Dietary fiber food intake and obesity. In: Fiber - is it good for you? Duphar Med. Relation, 37-48.

Griver, K. and R. R. Henry, 1994. Nutrition management of obesity and diabetes. Nutr. Res., 14: 465-483.

Hambidge, K. M., C. E. Cassey and N. F. Krebs, 1987. Zinc, In: Mertz. W. (eds). Trace element in Human and Animal Nutrition, ed. 5 Orlando, Academic Press, pp: 1-138.

Imamura, T., Y. Takata, H. Morioka, T. Haruto, T. Sawa, M. Iwanishi, Y. G. Hu, Y. Suzuki, J. Hamada and M. Kobayashi, 1994. Two naturally occurring mutations in the kinase domain of the insulin receptor accelerate degeneration of the insulin receptor and impair the kinase activity. J. Biol. Chem., 269: 31019-31027.

Ivora, M. D., M. Paya and A. villar, 1989. A review of natural products and plants as potential antidiabetic drugs J. Ethnopharmacol., 27: 243-275.

Iyer, U. M. and U. V. Mani, 1989. Studies on the effect of curry leaves supplementation (Murrya-koenigi) on lipid profile, Glycated protein and amino acid in NIDDM Diabetic patients. Plant Foods for Human Nut., 40: 275-282.

Janjua, 1988. Role of micro minerals on human health: diabetic control and chromium contents of the herb used for diabetic control in Islamic system of medicines: Chromium diabetes, carbohydrates. Pak. J. Sci. Indus Res., 31: 369-370.

Jarvill-Taylor, K. J., R. A. Anderson and D. J. Graves, 2001. A hydroxy chalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J. ACN., 20: 327-336.

Jeejeebhoy, T. N. and R. C. Chu, 1977. Chromium deficiency, glucose intolerance and neuropathy reversed by chromium supplementation in a patient receiving long term total parenteral nutrition. Am. J. Clin. Nut., 30: 531.

Jenkins, A. and R. G. Josse, 1985. Effects of processing/preparation as the blood glucose response to potatoes in diabetic patients. Diabetes (Suppl.), 34: 32A.

Kerin O' Dea, K. Traianedes, P. Ireland and M. Niall, 1989. The effects of diet differing in fat, carbohydrate and fiber on carbohydrate and lipid metabolism in type II diabetes. J. Am. Diet. Assoc., 89: 1076-1086.

Khan, A., I. Ahmad and Z. M. Wazir, 1993a. Prevalence of diabetes mellitus in the North West Frontier Province of Pakistan. J. Med. Sci., 3: 4-12.

Khan, A., I. Ahmad and Z. M. Wazir, 1993b. Epidemiological study of diabetes mellitus in the North West Frontier Province of Pakistan-I. J. Med. Sci., 3: 35-44.

Khan, A. and I. Ahmad, 1994. Risk factors for diabetes mellitus - A Review. Sarhad J. Agri., X: 367-373.

Khan, A. and I. Ahmad, 1993. Biochemical nature of diabetes mellitus. Diabetic J., V: 9-15.

Khan, A., N. A. Bryden, M. M. Polanski and R. A. Anderson, 1990. Insulin potentiating factor and chromium content of selected foods and spices. Bio. Trace. Element Res., 24: 183-188.

Khan, A., M. Safdar, M. A. K. Khattak, K. N. Khattak and R. A. Anderson, 2003a. Effect of cinnamon on blood glucose in diabetic individuals. Submitted to FASEB Journal.

Khan, A., M. Safdar, M. A .K. Khattak, K. N. Khattak and R. A. Anderson, 2003b. Effect of cinnamon on lipid profile in diabetic individuals Submitted to FASEB Journal.

Khan, A., A. Richard, M. Marylin, Polansky, Noella and A. Bayden, 2003c. Insulin potentiating factor (IPF) present in foods, spices and natural products. Submitted to Sarhad J. Agri.

Khana, P., 1985. Insulin from bitter gourd - herbal drug. Eastern Pharmacist. pp: 101-103.

King, M. J., R. P. Sharmr and G. J. Sale, 1991. Site-specific dephosphorylation and deactivation of the human insulin receptor tyrosine kinase by particulate and soluble phosphotyrosyl protein phosphatases. Biochem. J., 275: 413-418.

Koch, H. P. and L. D. Lawson, 1996. Garlic: The Science and Therapeutic Application of *Allium sativum* L. Related Species; Williams and Wilkins: Baltimore, M.D.

Lin, Wen-Han, Chen, Ming-Der, Wang, Jyh-Jain, Tsou, Chung-Tide, Lin and Piyao, 1993. Levels of blood metals in healthy individuals and non-insulin dependent diabetes. Abstracts Book I, XV, Inter. Cong. Nutr. Adelaide, pp: 87.

Maddux, B. A., P. Sbraccia, S. Kumakura, S. Sasson, S. Youngren, A. Fisher, S. Spencer, A. Grupe, W. Henzel, T. A. Stewart, G. M. Reaven and I. D. Goldfine, 1995. Membrane glycoprotein PC-1 and insulin resistance in non-insulin dependent diabetes mellitus. Nature, 373: 448-451.

Madar, Z., 1990. Dietary fiber from legume seed in control of blood lipids and glucose proceedings of the joint CEC - NCRD workshop held in Israel in Jan. 1989 on Lupin production and bioprocessing for feed, food and other by-products EUR publications. 1990. No. 12641, 115-133. 39. Luxembourg, office for official publications of European Community.

Madar, Z. and R. Thorne, 1987. Dietary fiber progression in Food and Nutr. Sci., 11: 153-174.

Martin, D. I. R., G. B. Wyatt, G. R. Griew, T. D. Malthews and H. D. G. Campise, 1981. Diabetic surveys in Papua New Guinea, results and implications. Papua New Guinea Med. J., 24 : 188-194.

McCarty, P. and P. Zimmet, 1997. Diabetes 1994-2010: global estimate and projections. Diabetes Care, 20: 1785-1790.

Mertz, M., 1982. Chromium: An essential micronutrient. Contemporary Nutrition, 7: 1-2.

Mertz, W. and Schwarz, 1959. Relation of glucose tolerance factor to impaired glucose tolerance of rats on stock diets. Am. J. Physiol., 196: 614-619.

Mertz, W., 1969. Chromium occurrence and function in biological system. Phsiol. Rev., 49, 163-239.

Mertz, W., E. R. Marris, J. C. Smith, Velomkes, E. Malee, Jr. , M. Fields, O. A. Levander and R. A. Anderson, 1989. H. N. Munro and D. E. Danford, (eds). Plenum, NY, pp: 222-227.

Moller, D. E. and J.S. Flier, 1991. Insulin resistance-mechanisms, syndromes and implications. N. Engl. J. Med., 325: 938-948.

Moser, E., 1988. Dietary management of diabetes mellitus. Vet. Technician, 9: 451-452.

Mossop, E. R., 1983. Supplementation of Chromium (111) on fasting glucose, cholesterol, and cholesterol HDL levels in diabetics. Cent. Afr. J. Med., 29: 80-82.

Nadiv, O., O. Cohen and Y. Zick, 1992. Defects in insulin's signal transduction in old rat livers. Endocrinology, 130: 1515-1524.

Nadiv, O., M. Shinitzke, H. Manu, D. Hecht, C. T. Roberts, D. LeRoith and Y. Zick, 1994. Elevated protein tyrosine phosphatase activity and increased membrane viscosity are associated with impaired activation of the insulin receptor kinase in old rats. Biochem. J., 298: 443-450.

Nath, R., J. Minocha, V. Iyall, S. Sunder, V. Kumar, S. Kapoor and K. L. Dhar, 1979. Assessment of chromium metabolism in maturity onset and juvenile diabetes using chromium 51 and therapeutic response of chromium administration on plasma lipids, glucose tolerance and insulin levels. In: chromium in nutrition and metabolism, D. Shapcott and J. Hubert, Eds., Elsevier/ North Holland, Amsterdam, pp: 213-222.

National Academy of Sciences, 1989. Recommended dietary allowance ed. 10. Washington, National Academy Press.

Offenbacher, E. G. and F. X. Pi-Sunyer, 1980. Beneficial effect of chromium - rich yeast on glucose tolerance and blood lipids in elderly subjects. Diabetes, 29: 919.

Olefsky, J. M., 1993. Insulin resistance and the pathogenesis of non-insulin dependent diabetes mellitus: Cellular and molecular mechanisms; in Ostenson, C.G., Efendic, S. and Vranic, M. (eds): New concepts in the pathogenesis of NIDM. New York, Plenum Press, 129-150.

Podell, R. N., 1983. Chromium supplementation. Post Grad. Med. 74: 135.

Pun, K. K., Z. Uarghese and J. F. Moorheed, 1988. Effect of diet with high carbohydrate content on diabetic hyperlipidemia and micro albumen urea. Diab. Res. and Clin. Practice, 5: 153-157.

Raal, F. J., W. J. Kalk, M. Lawson, J. D. Esser, R. Buys, L. Fourie and V. R. Panz, 1994. Effect of moderate dietary protein restriction on the progression of over diabetic nephropathy. a 6-mo prospective study. Am. J. Clin. Nutr., 60: 579-585.

Rahuram, T. C., R. D. Sharma, B. Siva Kumar and B. K. Satray, 1994. Effect of fenugreek seed intravenous glucose disposition in NIDDM diabetic patients. Phototherapy Res., 8: 83-86.

Rai, V., U. V. Mani and U. M. Iyer, 1997. Effect of *Ocimum sanctum* leaf powder on blood lipoproteins, Glycated proteins, and total amino acids in patients with non-insulin dependent diabetes mellitus. J. Nutr. Environ. Med., 7: 113-118.

Raman, A. and C. Lau, 1996. Antidiabetic properties and phytochemistry of *Momordica chantaria* L. (Cucurbitaceae). Phytomedicine, 2: 349-362.

Rehman, A. U. and K. Zaman, 1989. Medical plants with hypoglycemic activity. J. Ethnopharmacol., 26: 1-55.

Robinson, C. H., M. R. Lawler, W. L. Chenoweth and A. E. Cawick, 1986. Diabetes mellitus. IN: Normal and therapeutic nutrition. Seven edition, pp: 504-519. MacMillan Publishing Co. New York, U.S.A.

Sabina, Zambon, E. Karen, Friday, Marian, Y. Tchilds Wilfred, Fujimoto, L. Edwin, Biermen, W. John and Ensinck, 1992. Effect of glyburide supplementation on glucose and lipid metabolism in patients with NIDDM. Am. J. Clin. Nutr., 56: 447-454.

Sasson, S., Y. Ashhab, D. Melloul and E. Cerasi, 1993. Autoregulation of glucose transport: Effects of glucose transporter expression and cellular location in muscle; in Ostenson, C.G., Efendic, S. and Vranic, M. (eds): New concept in the pathogenesis of NIDDM. New York, Plenum Press, pp: 113-127.

Satyavati, G. V., A. K. Gupta and N. Tandan, 1987. Medicinal plants of India. Vol. 2: 261, Indian Council of Med. Res. New Delhi.

Sharma, R. D. and T. C. Rahuram, 1990. Effect of fenugreek seed on blood glucose and serum lipids in type I diabetes. Eur. J. Clin. Nutr., 44: 301-306.

Shanmugasundaram, E. R. B., G. Rageswari, K. Baskaran, K. K. Rajesh kumar and B. K. Ahmath, 1990. Use of *Gymnema sylvestre* leaf extract in the control of blood glucose in insulin dependent diabetes mellitus. J. Ethnopharm., 30: 281-294.

Silvis, N., H. H. Vorster, W. F. Mollentze, J. Jager, H. W. de., Huisman and J. Dc-Jager, 1989. Nutrient intakes, metabolic control and coagulation profiles of 40 black South African diabetes mellitus patients. Int. Clin. Nutr. Rev., 9: 197-205.

Sook, J. L. and W. K. Myung, 1992. Hypoglycemic effect of wild korean vegetable. Korean J. Nutr., 25: 511-517.

Sotaniemi, E. A., E. Haapakoski and A. Rautio, 1995. Ginseng therapy in non-insulin dependent diabetic patients. Diabetes Care, 18: 1373-1375.

Srivastava, Y., H. Venkatakrishna-Bhatt, Y. Verma, K. Venkaiah and B. H. Raval, 1993. Antidiabetic and adaptogenic properties of *Momordica charantia* extract: an experimental and clinical evaluation. Phytother. Res., 7: 285-289.

Sun, J. V., H. W. Tepperman and J. A. Tepperman, 1977. J. Lipid Res., 18: 533-539.

Tanphaichitr, V., K. Teganjanavanich, R. Pakpeakitvatama, and P. Leelahagul, 1993. Nutritional Treatment of diabetes mellitus. Abstract book-2, XV International Cong. of Nutr. Adelaide, pp: 499.

Toepfer, E. W., W. Mertz, N. M. Polanski, E. E. Rogenski and W. R. Wolf, 1977. Preparation of chromium containing material of glucose tolerance factor activity from brewers yeast and synthesis. J. Agri. Food Chem., 25: 162-165.

Toma, E. Del., C. Lintas, A. Clementi and M. Marcelli, 1988. Soluble and insoluble dietary fibre in diabetic diets. Eur. J. Clin. Nutr., 42: 313-319.

Turnbull, W. H. and T. Ward, 1995. Mycoprotein reduces glycemic and insulinemia when taken with an oral glucose tolerance test. Am. J. Clin. Nutr., 61: 135-140.

Venik, A. I. and D. J. A. Jenkins, 1988. Dietary fiber in the management of diabetes. Diabetes Care, 11: 160-173.

Viswanathan, 1978. M. J. Ind. Med. Assoc., 70: 275-279.

Vorster, H. H., C. S. Venter, T. S. Eeden, Van, N. Silvis, H. W. Huisman, J. C. J. Van Ryssen and A. R. P. Walker, 1988. Benefits from supplementation of the current recommended diet with jel fiber. Int. Clin. Nutr. Rev., 8: 140-146.

Weinsier, R. L., A. Seeman and G. Herrera, 1978. High and low carbohydrate diets in diabetes mellitus. Ann. Int. Med., 80: 332.

Wilson, B. A., D. R. Hadden, I. D. Merrett and J. A. Weaver, 1988. Dietary management of maturity on set diabetes. Br. Med. J., 7: 367.

Wing, R. R., 1995. Use of very low calorie diets in the treatment of obese persons with non-insulin dependent diabetes mellitus. J. Am. Diet. Assoc., 95: 569-572.