REVIEW OF TYPE 2 DIABETES MELLITUS PREVENTION

F. K. Titty

Department of Medical Biochemistry, SMHS, University of Development Studies, P. O. Box 1350, Tamale, Ghana

Abstract

Prevention of type 2 diabetes has been reviewed to ascertain the factors that reduce the risk of developing the disease. Sustained, modest body weight loss of about 5-7 per cent through reduced energy intake, reduced intake of dietary fat and increased physical activity lower the risk for developing type 2 diabetes. Both moderate and vigorous exercise independently decrease the risk of impaired glucose tolerance and type 2 diabetes. Individuals at risk, especially first degree relatives of type 2 diabetic patients, should engage in regular physical excercise of about 30 min/day to lower the risk of developing the disease. Increased intake of whole grains and dietary fibre, and reduced intake to fat, such as saturated fat, may improve insulin sensitivity and reduce the risk for type 2 diabetes. Increased intake of total vitamin E, α-tocopherol, γ-tocopherol and β-tocotrienol, as well as moderate alcohol intake (6-48 g/day) reduce risk. There is no association between intake of vitamin C and and type 2 diabetes. There is insufficient evidence to support the use of glucose lowering-drugs to prevent the disease.

Résumé

Titty F. K.: *Révision de la prévention de Diabète Mellite Type 2*. La prévention de diabète Type 2 a été révisée pour s'assurer de facteurs qui réduisent le risque de développer le diabète Type 2. Une perte de poids modeste et soutenue d'environ 5-7 % de poids corporel à cause de consommation réduite d' énergie, de consommation de la graisse alimentaire et d'activité physique augmentée, réduisent le risque de développer le diabète Type 2. La gymnastique modérée et vigoureuse diminuent séparément le risque de tolérance détériorée au glucose et le diabète Type 2. Les individus au risque, surtout les malades au premier degré de patients de diabète Type 2, doivent s'engager en exercice physique régulier d'environ 30 min/jour pour diminuer le risque de développer le diabète Type 2. La consommation augmentée de grains complets et de cellulose végétale et la consommation réduite de la graisse totale surtout la graisse saturée, pourraient améliorer la sensibilité à l'insuline et réduire le risque pour le diabéte Type 2. Les consommations augmentées de vitamine E totale, $\propto$- tocophérol, γ-tocophérol et β- tocotriénol, ainsi que la consommation modérée d'alcool (6-48 g/jour) réduisent le risque de diabète Type 2. Il n'y a pas de rapport entre la consommation de vitamine C et le risque de diabète Type 2. Il n'y a pas de preuve suffisante pour soutenir l'utilisation de drogue qui baisse de glucose pour prévenir le diabète Type 2.

Introduction

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by defects in insulin secretion or insulin action, or both. This leads to deficiency of insulin or its inadequate function, resulting in disturbances of carbohydrate, lipid and protein metabolism, which manifest as chronic hyperglycaemia. Diabetes mellitus may present symptoms such as thirst, polyuria, dehydration, weight loss and blurring of vision. Its long term effects include progressive development of complications such as retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, charcot joints, and sexual dysfunction. Diabetic patients are at increased risk of cardiovascular, peripheral vascular and cerebrovascular diseases. Diabetes mellitus may be caused by a defect in the immune system, a flaw that may compromise other disease-fighting mechanisms.

The main aetiological classes of diabetes mellitus are type 1 diabetes, type 2 diabetes and 'other types' diabetes mellitus. In type 1 diabetes there is absolute deficiency of insulin. About 5-10 per cent of all cases of diabetes are in this

class. In type 2 diabetes insulin levels may be normal, decreased or increased. The main defects in type 2 diabetes include insulin resistance, that is decreased ability of insulin to act on peripheral tissues, and also impaired insulin secretion due to β cell defect. The specific aetiology of type 2 diabetes is unknown. Type 2 diabetes comprises about 90 per cent of all diagnosed cases. "Other types" diabetes mellitus is a less common form. It may be due to genetic defects of beta-cell function, or insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced and infections.

The World Health Organization estimated that in 1997 there were 143 million people with diabetes mellitus worldwide (King, Aubert & Herman, 1998a). The two countries with the largest diabetic populations were India (21 million) and China (17 million). The total number of diabetics may reach 300 million by 2025 (King, Aubert & Herman., 1998a;King, Aubert & Herman, 1998b). Most of this increase is anticipated in low- and middle-income countries. Although diabetes mellitus and its associated metabolic diseases have been a feature of the developed countries, it is now emerging as a major health concern in developing countries. The transition from rural to urban lifestyles is associated with adverse changes in dietary habits and physical activity patterns (Solomons & Gross, 1995).

Ghana is a developing low-income country with rapid urbanization, thus, the implications of diabetes mellitus and its associated diseases should be a major public health concern. Data on diabetes mellitus prevalence in the entire Ghanaian population is unavailable. However, the prevalence of diabetes mellitus in the Greater Accra Region of Ghana has been found to be 6.3 per cent (Amoah, Owusu & Adjei, 2002). This review is meant to create awareness in the prevention of diabetes mellitus that will supplement the efforts of other health workers. The review shows that preventive strategies are a result of conclusions drawn from a wide range of research by experts.

Therefore, their authenticity is beyond doubt and must be adhered to if high-risk individuals are to prevent, delay or reduce the magnitude and burden of diabetes mellitus in Ghana.

Type 2 diabetes millitus main risk factors
Genetic susceptibility, a risk factor which cannot be modified, plays an important role in the development of type 2 diabetes. However, since population gene pools shift slowly, the current epidemic reflects marked changes in lifestyles. These changes, characterized by a decrease in physical activity and increased energy consumption, promote obesity, which is a risk factor for type 2 diabetes, and is itself influenced by both genes and behaviour. Obesity is characterized by an increase in the lipid content of the adipocyte as well as an increase in the total number of fat cells. For over 95 per cent of patients the cause of obesity is a caloric intake in excess of caloric expenditure. The association linking obesity to type 2 diabetes is complex. Obesity results in hyperinsulinaemia, leading to down-regulation of insulin receptors and, thus, insulin resistance by the tissues. This means there is a decreased ability of insulin to act on peripheral tissues. This is also the major pathological defect in type 2 diabetes and, hence, provides the link between obesity and type 2 diabetes.

Obesity can be measured by weighing and measuring the height of an individual and calculating basal metabolic index (BMI) as weight in kilograms divided by the square of height in metres. A person having a BMI greater than 30 kg/m^2 is obese. Obesity is characterized by excess body fat and it is probably the most notable modifiable risk factor for the development of type 2 diabetes (Edelstein *et al*., 1997). It is estimated that the risk for type 2 diabetes attributed to obesity is as high as 75 per cent (Manson & Spelsberg, 1994). An increase in the prevalence of type 2 diabetes, as a result of an increase in obesity is evident. It follows that as the prevalence of obesity increases the prevalence of type 2

diabetes in the population will also increase. Major factors that can prevent type 2 diabetes include weight loss, increased physical exercise (activity), increased intake of polyunsaturated fat and dietary fibre, selected micronutrients and moderate alcohol intake as well as pharmacological intervention.

Preventive measures
Weight loss
Weight loss improves insulin sensitivity and leads to a decrease in blood glycated haemoglobin and triglyceride levels, all of which suggest a decrease risk for type 2 diabetes. Numerous interventions focusing on weight loss through hypocaloric, low-fat diets, increased physical activity, and a variety of behaviour change strategies have been investigated (Wing *et al.*, 1998; Wing, 1999). Unfortunately, reducing body weight effectively and, hence, preventing obesity have proven challenging and difficult to achieve by behavioural strategies. Alternatively, phar-macological agents to enhance weight reduction and maintenance of weight loss have recently been recommended for individuals at high risk of obesity-related conditions when other weight loss methods have failed (Apfelbaum *et al.*, 1999; Rossner *et al.*, 2000).

Despite the difficulties, several studies have demonstrated the potential for moderate, sustained weight loss to substantially reduce risk for type 2 diabetes (Pan *et al.*, 1997; Eriksson & Lindgarde, 1991; Viswanathan *et al.*, 1997; Heymsfield *et al.*, 2000; Sjostrom *et al.*, 1999; Moore *et al.*, 2000). Increased risk of type 2 diabetes in men who gained weight over a 12-year period of follow-up has been reported (Wannamethee & Shaper, 1999). Overweight men who lost weight had a reduced risk for type 2 diabetes. In the Framingham Study cohort, sustained weight loss over two consecutive 8-year periods led to a 37 per cent lower risk for type 2 diabetes. However, those who regained weight later failed to experience any reduction in type 2 diabetes incidence (Moore *et al.*, 2000).

Clinical trial data also support the potential for weight loss to reduce risk of type 2 diabetes. In the Malmo Feasibility Study (Eriksson & Lindgarde, 1991), both weight reduction and increased fitness were associated with reduced incidence of type 2 diabetes in a lifestyle intervention group when compared to a control group. In the Da Qing Study, diet, exercise, and diet plus exercise all reduced the incidence of type 2 diabetes compared to the control group (Pan *et al.*, 1997). In the Swedish Obese Subjects Study, obese individuals with sustained weight loss after bariatric surgery demonstrated substantially lower risk of type 2 diabetes and hyperinsulinaemia compared to control subjects after 2 years of follow-up (Sjostrom *et al.*, 1999). Results from a 2-year clinical trial showed reduced risk of progression from impaired glucose tolerance to type 2 diabetes among individuals randomized to orlistat compared to those randomized to behavioural therapy (Heymsfield *et al.*, 2000).

The Finish Diabetes Prevention Study (Tuomilehto *et al.*, 2001) included 522 overweight individuals with impaired glucose tolerance randomized to control or lifestyle intervention, which included weight reduction (5% or more), reduction of total fat intake ($< 30\%$ of energy intake) and saturated fat ($< 10\%$ of energy intake), increased fibre (> 15 g/1,000 kcal), and increased physical activity (> 150 min/week). Success in achieving goals in the intervention group varied from 25 per cent (fibre intake) to 86 per cent (exercise). The cumulative incidence of type 2 diabetes after 4 years was 11 per cent in the intervention group and 23 per cent in the control group. The risk of type 2 diabetes was reduced by 58 per cent in the intervention group. The United State Diabetes Prevention Programme Research Group (2002) study included 3234 individuals of diverse ethnic backgrounds (45% minority inclusion) all of whom had impaired glucose tolerance at study entry.

Participants randomly assigned to lifestyle

intervention reduced their risk of developing type 2 diabetes by 58 per cent over 3 years of follow-up. Much risk reduction was observed across subgroups of ethnicity, age, sex, basal metabolic index (BMI) and different levels of fasting glucose. Among the individuals over 60 years, the risk reduction was 71 per cent. Individuals in the lifestyle intervention group reduced their percentage calories of fat from about 34 to 27.5 per cent; maintained their physical activity at about 30 min/day on moderate physical activity such as walking, and lost 5-7 per cent of their baseline body weight. In this same study, the safety and efficacy of chemotherapy, metformin, was tested. Metformin reduced type 2 diabetes risks by 31 per cent, which was less than the risk reduction observed for the lifestyle intervention.

Although effective in young and overweight men and women in all ethnic groups, metformin was relatively ineffective in the older volunteers and in those who were less obese. Finally, the Nurses' Health Study (Hu *et al*., 2001), in which individuals were categorized as low risk based on a BMI < 25 and a set of lifestyle variables related to the Finish and Diabetic Prevention Programme, experienced reduced risk for type 2 diabetes incidence over 16 years of follow-up. Aqueous extract of *Ocinum canum* decreased body weight, free radicals, fasting plasma glucose, serum total cholesterol and low-density lipoprotein cho-lesterol, but increased high density lipoprotein cholesterol in diabetic mice investigated in Ghana (Nyarko *et al.,* 2002), thus, justifying the use of *O. canum* extract as an anti-diabetic drug. It follows that the use of *O. canum* could help prevent or slow down the onset of type 2 diabetes in high-risk individuals with impaired glucose tolerance as well.

Exercise

Decreased physical activity has also been identified as a type 2 diabetes risk factor, independent of its impact on energy balance. It was observed that societies that had abandoned traditional lifestyles involving large amount of habitual physical activity, subsequently, experienced major increases in rates of type 2 diabetes. The fact that an active lifestyle may prevent or delay the development of type 2 diabetes was demonstrated in a number of studies (Helmrich *et al*., 1991; Frisch *et al*., 1986; Manson *et al*., 1991; Manson *et al.*, 1992; Perry *et al.*, 1995). The mechanism of the protective effect of exercise is thought to be an increased sensitivity to insulin in skeletal muscle and adipose tissue. Exercise also lowers glucose levels, improves lipid profile, blood pressure, fitness and the well-being of an individual independently of other factors. Protection from type 2 diabetes appears to occur from moderate intensity activities, such as brisk walking, as well as from participation in vigorous physical activity. Moreover, physical activity may provide some protection against mortality at all levels of glucose tolerance, as has been demonstrated in middle-aged men (Kohl *et al.*, 1992).

Dietary fat and sugars

Dietary fat intake appears to be an important determinant of type 2 diabetes risk, independent of total caloric intake. Using a case control design, increased intake of dietary fat was associated with occurrence of type 2 diabetes among second-generation Japanese-American men (Tsunehara, Leonetti & Fujimoto, 1990). After adjustment of caloric intake and obesity, increased incidence of diabetes with increased intake of dietary fat was reported (Marshall, Bessesen & Hamman, 1997). However, three large prospective studies that relied on patient-report of physician-diagnosed type 2 diabetes did not detect an effect of dietary fat on type 2 diabetes incidence, or else suggested differential effects of various subtypes of dietary fat (Salmeron *et al*., 1997a; Salmeron *et al*., 1996b; Meyer *et al.*, 2001). Results from two studies (Hughes *et al*., 1995; Louheranta *et al*., 1999) suggest that increased intake of polyunsaturated fat may be associated with reduced risk of type 2

diabetes, independent of basal metabolic index (BMI), total energy intake, physical activity, and other potential confounders.

Several studies have identified dietary fat as a contributor to insulin resistance independent of obesity (Manson & Spelsberg, 1994; Marshall *et al.*, 1997; Feskens, Loeber & Kromhout, 1994; Folsom *et al.*, 1996; Lovejoy & DiGirolamo, 1992; Lovejoy *et al.*, 1998; Mayer *et al.*, 1993; Mayer-Davis *et al.*, 1997; Maron, Fair & Hastell, 1991), but other studies do not support this (Hughes *et al.*, 1995; Louheranta *et al.*, 1999; Sarkkinen *et al.*, 1996).

However, it appears that all types of dietary fat except omega-3 (n-3) polyunsaturated fatty acids such as α-linolenic acid may have an adverse effect on insulin sensitivity. Results are most consistent for an adverse effect of saturated fats. These effects may be enhanced among individuals with obesity (Meyer-Davis *et al.*, 1997) or low levels of physical activity (Meyer *et al.*, 1993; Meyer–Davis *et al.*, 1997). In general, the impact of dietary fat on type 2 diabetes risks appears to lie primarily in the effect of high-fat diets on long-term energy balance. Janket *et al.* (2003) have recently reported that intake of sugars (including sucrose, glucose, fructose and lactose) does not appear to play a deleterious role in primary prevention of type 2 diabetes. This report supports the American Diabetes Association's guideline that a moderate amount of sugar can be incorporated in a healthy diet.

Whole grains / fibre

Basically, the term fibre refers to carbohydrates that cannot be digested. Fibre is present in all plants that are eaten for food, including fruits, vegetables, grains and legumes. A study comparing a diet containing 24 g fibre per day (high usual intake) to a diet containing 50 g fibre per day found that the intake of food high in dietary fibre improved glycaemic control, reduced hyperinsulinaemia, and decreased plasma lipids (Chandalia *et al.*, 2000) and, hence, reduced the risk for type 2 diabetes. Other studies have

provided evidence for reduced risk of type 2 diabetes with increased intake of whole grains and dietary fibre (Liu *et al.*, 2000; Wolever *et al.*, 1997; Meyer *et al.*, 2000). In both the Nurses' Health Study (Liu *et al.*, 2000) and the Iowa Women's Health Study (Meyer *et al.*, 2000), increased intake of whole grain food was associated with significant reductions in incidence of type 2 diabetes.

Micronutrients

Selected micronutrients may affect glucose and insulin metabolism. Total antioxidant status was found to be lower in Ghanaian type 2 diabetic patients as compared to healthy subjects, suggesting the existence of lower antioxidant defence in type 2 diabetes (Dosoo *et al.*, 2001). Another evidence suggested that oxidative stress may contribute to the pathogenesis of type 2 diabetes by increasing insulin resistance or impairing insulin secretion (Oberly, 1988). Further, dietary antioxidants were hypothesized to have a protective effect against the development of type 2 diabetes by inhibiting peroxidation chain reactions (Halliwell & Gutteridge, 1989). In one study, supplementation with total vitamin E (400 i.u./day) for 4.5 years did not result in any significant benefit (Yusuf *et al.*, 2000). However, total vitamin E intake has recently been found to be significantly associated with a reduced risk of type 2 diabetes (Montonen *et al.*, 2004). In the same study intakes of α-tocopherol, γ-tocopherol, and β-tocotrienol were also inversely related to a risk of type 2 diabetes, whilst no association was evident between intake of vitamin C and type 2 diabetes risks.

The results confirm the fact that vitamin E is the most efficient chain breaking antioxidant that protects tissue membranes from oxidative damage (Halliwell & Gutteridge, 1989). This also confirms the observation that men with higher plasma concentrations of α-tocopherol experienced reduced risk for type 2 diabetes compared to men with lower concentrations of α-tocopherol

(Salonen *et al.*, 1995). Insufficient intake of magnesium, zinc and chromium has been implicated as possible risk factors for the development of type 2 diabetes (Salmeron *et al.*, 1995; Meyer *et al.*, 2000; Lukaksi, 2000; Singh *et al.*, 1998; Anderson, 1998; Anderson, 2000). However, neither the efficacy nor the safety of supplemented intake has been established.

Alcohol

Alcohol consumption is a lifestyle factor that has also been suggested to be relevant with respect to the risk of type 2 diabetes. When compared to abstinence and heavy drinking, moderate alcohol intake has been related to improved insulin sensitivity (Meyer *et al.*, 1993; Facchini, Chen & Reaven, 1994; Bill *et al.*, 2000) and reduced risk for type 2 diabetes (Wei *et al.*, 2000). Three other reviews suggested that moderate alcohol consumption is associated with a decreased incidence of type 2 diabetes but were inconclusive about the magnitude of moderate alcohol consumption and the corresponding decreased incidence (Zilkens & Puddey, 2003; Howard, Amsten & Gourevitch, 2004; Wannamethee *et al.*, 2003). Recent evidence from observational studies have suggested about 30 per cent reduced risk of type 2 diabetes in moderate alcohol consumers of 6-48 g/day, whereas no risk reduction was observed in heavier consumers of greater than 48 g/day or abstainers (Koppes *et al.*, 2005).

Pharmacological interventions

The biguanide metformin reduced the risk of type 2 diabetes by 31 per cent in the United States Diabetes Prevention Programme research (2002). In the Troglitazone in prevention of diabetes (TRIPOD) study (Buchaman *et al.*, 2002), troglitazone (now withdrawn) treatment was associated with a 56 per cent relative reduction in progression to type 2 diabetes. After a washout period of more than 8 months, the preventive effects of the drug were still observed. Furthermore, in the STOP–NIDDM trial (Chiasson

et al., 2002), 1429 participants with IGT were randomized in a double-blind fashion to receive either the α– glucosidase inhibitor, acarbose or a placebo. The subjects have a mean of 55 years and a mean BMI of 31 kg/m². After a mean follow–up of 3.3 years, a 25 per cent relative risk reduction in progression to diabetes was observed in the acarbose–treated group compared with the placebo group. Drug therapy used to prevent or delay type 2 diabetes appeared to be much less beneficial for a variety of reasons. First, when compared directly with lifestyle modification, metformin was considerably less effective. Second, all glucose lowering drugs that require monitoring have been associated with significant adverse side effects and are contraindicated in some individuals. Finally, prescribing a medication to delay the onset of type 2 diabtes which is also used for treatment will increase a patient's total years of drug exposure and may increase the likelihood of drug effects.

Conclusion

The greater benefit of weight loss and physical activity strongly suggests that lifestyle modification should be the first choice in the prevention or delay of type 2 diabetes, since drug therapy used in the prevention or delay of type 2 diabetes appears to be less beneficial. There is strong evidence that sustained, modest weight loss of about 5–7 per cent of body weight through reduced energy intake, reduced intake of dietary fat and increased physical activity will reduce the risk for developing type 2 diabetes. Structured programmes that emphasize lifestyle changes are necessary to accomplish these objectives. Both moderate and vigorous exercise independently decrease the risk of impaired glucose tolerance and type 2 diabetes. Thus, there is strong evidence that all individuals (especially family members of individuals with type 2 diabetes) should be encouraged to engage in regular physical exercise of about 30 min/day to decrease the risk of developing type 2 diabetes.

There is some evidence that increased intake of whole grains and dietary fibre may reduce type 2 diabetes risk. There is also some evidence that reduced intake of total fat, particularly saturated fat, may improve insulin sensitivity and reduce risk for type 2 diabetes, independent of weight loss. There is limited evidence that increased intake of polyunsaturated fat, in the context of appropriate total energy intake for weight management, may reduce the risk for type 2 diabetes. Furthermore, recent evidence indicates that increased intakes of total vitamin E, α-tocopherol, γ-tocopherol and β-tocotrienol, as well as moderate alcohol intake (6-48 g/day) would reduce type 2 diabetes risk. Finally, when all factors are considered there is insufficient evidence to support the use of glucose–lowering drugs as a substitute for, or routinely used in addition to, lifestyle modification to prevent type 2 diabetes. Therefore their routine use is not recommended.

Reference

AMOAH, A. G., OWUSU, S-K. & ADJEI, S. (2002) Diabetes in Ghana: a community based prevelance study in Guneater Accra. *Diabetes Res. Clin. Pract.* **56**(3), 197 – 205.

ANDERSON, R. A. (2000) Chromium in the prevention of diabetes. *Diabetes Metab.* **26**, 22 – 27.

ANDERSON, R. A. (1998) Effects of chromium on body composition and weight loss. *Nutr. Rev.* **56**, 266 – 270.

APFELBAUM, M., VAGUE, P., ZIEGLER, O., HANOTIN, C., THOMA, F. & LEUTENEGGER, E. (1999) Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am. J. Med.* **106**, 179 – 184.

BILL, R. A., MAYER-DAVIS, E. J., MARTIAN, M. A., D'AGOSTINO, R. B. & HAFFNER, S. M. (2000) Associations between alcohol consumption and insulin sensitivity and cardiovascular disease risk factors: The Insulin Resistance and Atherosclerosis Study. *Diabetes Care* **23**, 1630 – 1636.

BODINGTON, M. J., MCNALLY, P. G. & BURDEN, A. C. (1994) Cow's milk and type 1 childhood diabetes: no increase in risk. *Diabetes Med.* **11**, 663 – 665.

BROWN, S., UPCHURCH, S., ANDING, T., WINTER, M. & RAMIREZ, G. (1996) Promoting weight loss in type 2 diabetes. *Diabetes Care* **19**, 613 – 624.

BUCHAMAN, T. A., XIANG, A. H., PETERS, R. K., KJOS, S. L., MARROQUIN, A., GOICO, J., OCHOA, C., TAN, S., BERKOWITZ, K., HODIS, H. N. & AZEN, S. P. (2002) Preservation of pancreatic B-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high–risk Hispanic women. *Diabetes* **51**, 2796–2803.

CHANDALIA, M., GARG, A., LUTHOHANN, D., VON BERGMANN, K., GRUNDY, S-M. & BRINKLEY, L. J. (2000) Beneficial effects of a high dietary fibre intake in patients with type 2 diabetes. *N. Engl J. Med.* **342**, 1392 – 1398.

CHIASSON, J. L., JOSSE, R. G., GOMIS, R., HANEFELD, M., KARASIK, A. & LAAKSO, M., (2002) Acarbose for prevention of type 2 diabetes mellitus: the STOP – NIDDM randomized trial. *Lancet* **359**, 2072 – 2077.

DIABETES PREVENTION RESEARCH GROUP (2002) Reduction in the incidence of type 2 diabetes with life-style intervention or metformin. *N. Engl. J. Med.* **346**, 393 –403.

DOSOO, D-K., RANA, S. V., OFFE – AMOYAW, K., TETE – DONKOR, D. & MADDY, S.Q. (2001) Total antioxidant status in non – insulin-dependent diabetes mellitus patients in Ghana. *West Afr. J. Med.* **20**(3), 184-6.

EDELSTEIN, S.L., KNOWLER, W. C., BAIN, R. P., ANDRES, R., BARRETT-CONNOR, E. L., DOWSE, G. K., HAFFNER, S. M., PETTITT, D. J., SORKIN, J. D., MULLER, D. C., COLLINS, V. R. & HAMMAN, R. F. (1997) Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* **46**, 701-710.

ERIKSSON, K. F. & LINDGARDE, F. (1991) Prevention of type 2 (non-insulin dependent) diabetes mellitus by diet and physical exercise. *Diabetologia* **34**, 891-898.

FACCHINI, F., CHEN, Y-D. & REAVEN, G. M. (1994) Light-to-moderate alcohol intake is associated with enhanced insulin sensitivity. *Diabetes Care* **17**, 115 – 119.

FESKENS, E. J., LOEBER, J. G. & KROMHOUT, D. (1994) Diet and physical activity as determinants of hyperinsulinaemia: the Zutphen Elderly Study. *Am. J. Epidemiol.* **140**, 350 –360.

FOLSOM, A. R., MA, J., MCGOVERN, P. G. & ECKFELDT, H. (1996) Relation between plasma phospholipid saturated fatty acids and hyperinsulinaemia.

Metabolism **45**, 223– 228.

Frisch, R. E., Wyshak, G., Albright, E., Albright, N. L. & Schiff, I. (1986) Lower prevalence of diabetes in female former college athletes compared with nonathletes. *Diabetes* **35**, 1101 – 1105.

Halliwell, B. & Gutteridge, J. M.C.(1989) Free radicals in Biology and Medicine. Oxford University Press, New York.

Helmrich, S. P., Ragland, D. R., Leung, R. W. & Paffenbarger, R. S. Jr (1991) Physical activity and reduced occurrence of non – insulin – dependent diabetes mellitus. *N. Engl. J Med.* **325**, 147 – 152.

Heymsfield, S. B., Segal, K. R., Hauptman, J., Lucas, C. P., Boldrin, M. N., Rissanen, A., Wilding, J.P . & Sjostrom, L. (2000) Effects of weight loss with Orlistat on glucose tolerance and progression to type 2 diabetes in obese adults. *Arch. Intern. Med.* **160**, 132–1326.

Howard, A. A., Arnsten, J. H., & Gourevitch, M. N. (2004). Effect of alcohol consumption on diabetes mellitus. *Ann. Intern. Med.* **140**, 211 –219.

Hu, F. B., Manson, J. E., Stampfer, M. J., Colditz, G., Liu, S., Solomon, C. G. & Willett, W. C. (2001) Diet, lifestyle and the risk of type 2 diabetes mellitus in women. *N. Engl. J. Med.* **345**, 790 – 797.

Hughes, V. A., Fiatarone, M. A., Fielding, R. A., Ferrara, C. M., Elahi, D. & Evans, W. J. (1995) Long-term effects of a high-carbohydrate diet and exercise on insulin action in older subjects with impaired glucose tolerance. *Am. J. Clin. Nutr.* **63**, 426–433.

Janket, S., Manson, J. E., Sesso, H., Burring, J. E. & Liu, S. (2003) *Diabetes Care* **26**, 1008 – 1015.

King, H., Aubert, R. E. & Herman, W. H. (1998a) Global burden of diabetes: estimates for 1997. *CVD Prevention* **1**, 43-258.

King, H., Aubert, R. E. & Herman, W. H. (1998b) Global burden of diabetes, 1995 – 2025: prevalence, numerical estimates, and projections. *Diabetes Care* **21**,1414–1431.

Kohl, H. W., Gordon, N. F., Villegas, J. A. & Blair, S. N. (1992) Cardiorespiratory fitness, glycemic status, and mortality risk in men. *Diabetes Care* **15**, 185 –192.

Koppes, L. L. J., Dekker, J. M., Hendricks, H. F. J., Bouter, L. M. & Heine, R. J. (2005) Moderate alcohol consumption lowers the risk of type 2 diabetes. *Diabetes Care* **28**, 719–725.

Liu, S., Manson, J. E., Stampfer, M. J., Hu, F. B.,

Giovannucci, E., Colditz, G. A., Hennekens, C. H. & Willet, W. C. (2000) A prospective study of whole grain intake and risk of type 2 diabetes mellitus in U.S. women. *Am. J. Hlth.* **90**, 1409– 1415.

Louheranta,A. M., Turpeinen, A. K., Vidgren, H. M., Schwab, U. S. & Uusitupa, M. L. (1999) A high-trans fatty acid diet and insulin sensitivity in young healthy women. *Metabolism* **48**, 870 –805.

Lovejoy, J. C. & DiGirolamo, M. (1992) Habitual dietary intake and insulin sensitivity in lean and obese adults. *Am. J. Clin. Nutr.* **55**, 1174 – 1179.

Lovejoy, J. C., Windhauser, M. M., Rood, J. C. & de la Bretonne, J. A. (1998). Effect of a controlled high – fat versus low – fat diet on insulin sensitivity and leptin levels in African – American and Caucasian women. *Metabolism* **47**, 1520–1524.

Lukaksi, H. C. (2000) Magnesium, zinc, and chromium nutriture and physical activity. *Am. J. Clin. Nutr.* **72** (Suppl.), 585S–593S.

Manson, J. E., Nathan, D. M., Krolewski, A. S., Stampfer, M. J., Willett, W. C. & Hennekens, C. H. (1992). A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* **268**, 63–67.

Manson, J. E., Rimm, E. B., Stampfer, M. J., Colditz, G. A., Willett, W. C., Krolewski, A. S., Rosner, B., Hennekens, C. H. & Speizer, F. E. (1991) Physical activity and incidence of non-insulin-dependent diabetes in women. *Lancet* **338**, 774– 778.

Manson, J. E. & Spelsberg, A. (1994) Primary prevention of non-insulin-dependent diabetes mellitus. *Am. J. Prev. Med.* **10**, 172 –184.

Maron, D. J., Fair, J. M. & Haskell, W. L. (1991). Saturated fat intake and insulin resistance in men with coronary artery disease. *Circulation* **84**, 2070 – 2074.

Marshall, J. A., Bessesen, D. H. & Hamman, R. F. (1997). High saturated fat and low starch and fiber are associated with hyperinsulinaemia in a non-diabetic population: the San Luis Valley Diabetes Study. *Diabetologia* **40**, 430–438.

Mayer, E. J., Newman, B., Quesenberry, C. P., Friedman, G. D. & Selby, J. V. (1993) Alcohol consumption and insulin concentrations: role of insulin in associations of alcohol intake with high-density lipoprotein cholesterol and triglycerides. *Circulation* **88**, 2190-2197.

MAYER, E. J., NEWMAN, B., QUESENBERRY, C. P. JR. & SELBY, J. V. (1993) Usual dietary fat intake and insulin concentrations in healthy women twins. *Diabetes Care* **16**,1459–1469.

MEYER, K. A., KUSHI, L. H., JACO BS, D. R. & FOLSOM, A. R. (2001) Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care* **24**, 1528–1535.

MEYER, K. A., KUSHI, L. H., JACOBS, D. R. JR., SLAVIN, J., SELLERS, T. A. & FOLSOM, A. R. (2000) Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am. J. Clin. Nutr.* **71**, 921 – 930.

MAYER-DAVIS, E. J., MANACO, J. H., HOEN, H. M., CARMICHAEL, S., VITOLINS, M. Z., REWERS, M. J., HAFFNER, S. M., AYAD, M. F., BERGMAN, R. N. & KARTER A. J. (1997) Dietary fat and insulin sensitivity in a triethnic population: the role of obesity. The Insulin Resistance Atherosclerosis Study. *Am. J. Clin. Nutr.* **65**, 79 –87.

MONTONEN, J., KNEKT, P. JARVIVEN, R. & REUNANEN, A. (2004) Diefary antioxidant intake and risk of type 2 diabetes. *Diabetes Care* **27**, 362-366.

MOORE, L. L., VISIONI, A. J., WILSON, P. W., D'AGOSTINO, R. B., FINKLE, W. D. & ELLISON, R. C. (2000) Can sustained weight loss in overweight individuals reduce the risk of diabetes mellitus? *Epidemiology* **3**, 269–273.

NYARKO, A. K., ASARE-ANANE, H., OFOSUHENE, M., ADDY, M. E., TEYE, K. & ADDO, P. (2002) Aqueous extract of *Ocimum* decreases levels of fasting blood glucose and fre radicals and increases of antiatherogenic lipic levels in mice. *Vascul. Pharmacol.* **39**(6),273- 9.

OBERLEY, L.-W. (1998) Free radicals and diabetes. *Free Radic. Biol. Med.* **5**, 113-124.

PAN, X. R., LI, G. W., HU, Y. H., WANG, J. X., YANG, W. Y., AN, Z. X., HU, Z. X., LIN, J., XIAO, J. Z., CAO, H. B., LIU, P. A., JIANG, X. G., JIANG, Y. Y., WANG, J. P., ZHENG, H., ZHANG, H. & BENNETT, P. H. & HOWARD, B. V. (1997) Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. *Diabetes Care* **20**, 537-544.

PERRY, I. J., WANNAMETHEE, M., WALKER, M. K., THOMSON, A. G., WHINCUP, P. H. & SHAPER, A. G. (1995) Prospective study of risk factors for development of non- insulin-dependent diabetes in middle aged British men. *Brit. Med. J.* **310**, 560-564.

ROSSNER, S., SJOSTROM, L., NOACK, R., MEINDERS, A. E. & NOSEDA, G. (2000) Weight loss, weight maintenance, and improved cardiovascular risk factors after 2 years treatment with orlistat for obesity: European Orlistat Obesity Study Group. *Obes. Res.* **8**, 49-61.

SALMERON, J., ASCHERIO, A., RIMM, E. B., COLDITZ, G. A., SPIEGELMAN, D., JENKINS, D. J., STAMPFER, M. J., WING, A. L. & WILLET, W. C. (1997) Dietary fiber, glycaemic load, and risk of NIDDM in men. *Diabetes Care* **20**, 545 –550.

SALMERON, J., MANSON, J. E., STAMPFER, M. J., COLDITZ, G. A., WING, A. L. & WILLET, W. C. (1997) Dietary fiber, glycaemic load, and risk of NIDDM in women *J. Am.Med. Ass.* **277**, 472 –477.

SALONEN, J. T. NYYSSONEN, K., TUOMAINEN, T. P., MAENPAA, P. H., KORPELA, H., KAPLAN, G. A., LYNCH, J., HELMRICH, S. P. & SALONEN R. (1995) Increased risk of NIDDM at low plasma vitamin E concentrations: a four-year study in men. *Brit. Med. J.* **311**, 1124-1127.

SARKKINEN, E., SCHWAB, U., NISKANEN, L., HANNUKSELA, M., SAVOLAINEN, M., KERVINEN, K., KESNIEMI, A. & UUSITUPA, M. I. (1996) The effects of monounsaturated-fat enriched diet and polyunsaturated-fat enriched diet on lipid and glucose metabolism in subjects with IGT. *Euro. J. Clin. Nutr.* **50**, 592–598.

SINGH, R. B., NIAZ, M. A., RASTOGI, S. S., BAJAJ, S., GAOLI, Z. & SHOUMIN, Z. (1998) Current zinc intake and risk of diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of North India. *J. Am. Coll. Nutr.* **17**, 564-570.

SJOSTROM, C. D., LISSNER, L., WEEDEL, H. & SJOSTROM, L. (1999) Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. *Obes. Res.* **5**, 477– 484.

SOLOMONS, N. W. & GROSS, R. (1995) Urban nutrition in developing countries. *Nutr. Rev.* **53**, 90 –95.

TSUNEHARA, C. H., LEONETTI, D. L. & FUJIMOTO, W. Y. (1990) Diet of second-generation Japanese-American men with and without non-insulin-dependent diabetes. *Am. J. Clin. Nutr.* **52**, 731-738.

TUOMILEHTO, J., LRINDSTROM, J., ERIKSSON, J. G., VALLE, T. T., HAMALAINEN, H., ILANNE-PARIKKA, P., KEINANEN- KIUKAANNIEMI, S., LAAKSO, M., LOUHERANTA, A., & RASTAS, M. (2001) Prevention of type 2 diabetes mellitus by changes in lifestyle

among subjects with impaired glucose tolerance. *N. Eng. J. Med.* **344**, 1343-1350.

VISWANATHAN, M., SNEHALATHA, C., VISWANATHAN, V., VIDYAVATHI, P., INDU, J. & RAMACHANDRAN, A. (1997) Reduction in body weight helps to delay the onset of diabetes even in non-obese with strong family history of the disease. *Diabetes Res. Clin. Pract.* **35**, 107-112.

WANNAMETHEE, S. G., CAMARGO, C. A. J., MANSON J.E., WILLET, W. C. & RIMM, E. B. (2003) Alcohol drinking patterns and risk of type 2 diabetes mellitus among younger women. *Arch. Intern. Med.* **163**,1329–1336.

WANNAMETHEE, S. G. & SHAPER, A. G. (1999) Weight change and duration of overweight and obesity in the incidence of type 2 diabetes. *Diabetes Care* **22**, 1266-1272.

WEI, M., GIBBON, L. W., MITCHELL, T. L., KAMPERT, J.B. & BLAIR, S. N. (2000) Alcohol intake and incidence of type 2 diabetes in men. *Diabetes Care* **23**, 18– 22.

WING, R. R. (1999) Physical activity in the treatment of adulthood overweight and obesity: current evidence and research issues. *Med. Sci. Sports Exerc.* **31** (Suppl.), S547-S552.

WING, R. R., VENDITTI, E., JAKICIC, J. M., POLLEY, B. A. & LANG, W. (1998) Lifestyle intervention in overweight individuals with a family history of diabetes. *Diabetes Care* **21**, 350–359.

WOLEVER, T. M., HAMAD, S., GITTELSOHN, J., GAO, A. J., HANLEY, A. J., HARRIS, S. B. & ZINMAN, B. (1997) Low dietary fiber and high protein intakes associated with newly diagnosed diabetes in a remote aboriginal community. *Am. J. Clin. Nutr.* **66**, 1470-1474.

YUSUF, S., DAGENAIS, G., POGUE, J., BOSCH, J., & SCEIGHT, P. (2000) Vitamin E Supplementation and cardiovascular events in high-risk patients: the Heart Outcomes Prevention Evaluation Study Investigators. *W. Engl. J. Med.* **342**, 154–160.

ZILKENS, R. R. & PUDDEY, I. B. (2003) Alcohol and type 2 diabetes: another paradox? *J. cardiovasc. Risk* **10**,25 – 30.