

Introduction

INTRODUCTION

NON COMMUNICABLE DISEASES: SCENARIO AND RISK FACTORS

Non Communicable diseases (NCDs) is a term used to distinguish a group of diseases mostly chronic in nature such as cardiovascular diseases, diabetes cancer and chronic respiratory diseases. The cause of most of these diseases is often complex and multi factorial. Globally, NCDs are increasingly recognized as major causes of morbidity and mortality. NCDs account for most of the global burden of disease. Around 60% of all deaths globally in 2005 were caused by NCDs and mortality by 2015 is projected to increase by 17% (WHO 2005).

Globally, majority (80%) of deaths due to chronic diseases are projected to occur in low and middle income countries. Further in these countries, chronic disease mortality tends to affect younger individuals compared to higher income countries (WHO 2005). Indians succumb to diabetes, high blood pressure and heart attacks 5–10 years earlier than their Western counterparts, in their most productive years (Goenka et al 2009).

The rapidly increasing burden of these diseases is affecting poor and disadvantaged populations disproportionately, contributing to widening health gaps between and within countries (Alwan and MacLean 2009).

India is experiencing a rapid health transition with large and rising burden of chronic diseases, which are estimated to account for 53% of all deaths and 44% of disability adjusted life years (DALY'S) lost in 2005. Earlier, estimates from the global burden of disease study, projected the number of deaths attributable to chronic disease would rise from 3.78 million in 1990 i.e. 40.4% of all deaths to 7.63 million in 2020 i.e. 66.7% of all deaths (Reddy et al 2005)

The World Health Organization reported that for non-communicable diseases the most important risk factors are high blood pressure, high concentrations of blood cholesterol, inadequate intake of fruit and vegetables,

overweight/obesity, physical inactivity and tobacco use (WHO, 2002). Thus, the burden of NCDs may be prevented, in part, by addressing certain associated lifestyle risk factors.

Results of a recent community-based study in Kerala found a high prevalence of NCD risk factors. Prevalence of tobacco use, alcohol use, low fruit and vegetable intake, physical inactivity, overweight, abdominal obesity, hypertension, diabetes, hypercholesterolemia, low HDL-C, hypertriglyceridemia was 28%, 15.4%, 47%, 6.8%, 30.8%, 39.4%, 32.7%, 16.2%, 56.8%, 39.5%, 19.2% respectively (Thankappan et al 2010).

Risk factors associated with NCDs are seen in various states of India, due to nutrition health transitions with advancement of technology and the agricultural revolution.

NCDs-WORKPLACE

With lifestyle behavioral choices contributing to a significant proportion of chronic diseases globally, evidence-based strategies to improve behavioral risk factors such as healthier eating and regular physical activity should be considered in a variety of settings. The workplace has been identified as a likely setting in which a large section of the adult population can be reached and can positively have an impact on the health risk profile of individuals.

In a study by Kuriyama et al (2004) it was found that physical inactivity, smoking and obesity were associated with an 8.0%, 8.35% and 7.1% increase in health care charges, respectively. In addition, employees having a combination of all three modifiable risk factors had the highest percentage increase (42.6%) in health care expenditure compared to their lower risk counterparts. Serxner et al (2001) found that employees who had high blood pressure, high cholesterol and were overweight had higher rates of absenteeism along with related medical costs.

Upon identification of employee health risk profiles, targeted and relevant intervention strategies can be designed and implemented. Reducing the

number of risk factors can have important implications in the worksite setting, reducing both direct and indirect costs associated with absenteeism.

Workplace programs may be especially important because the imbalance between physical activity and energy intake at work may contribute to the obesity epidemic (Engbers et al 2005). The focus of occupational health has shifted in recent years from occupational exposures to non-communicable diseases, and the consequent impact on individual health, and economic costs to companies (Matos et al 2004, Mills 2005).

Workplace health promotion has generally focused on promoting worker health through reduction of individual risk-related behaviors such as tobacco use, substance use, a sedentary lifestyle, poor nutrition, stressors and reactions to them, reproductive risks, and other preventable health behaviors (Quintiliani et al 2008).

DIABETES MELLITUS

Diabetes is an “iceberg” disease. According to recent estimates, the human population worldwide appears to be in the midst of an epidemic of diabetes. Diabetes is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and post prandial blood glucose levels. If this imbalanced homeostasis does not return to normalcy and continues for a protracted period of time, it leads to hyperglycemia which in due course turns into a syndrome called diabetes mellitus (Tiwari and Rao, 2002). There are two main categories of this disease-Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM).

PREVALENCE

The impact of the worldwide explosion of T2DM would remain centred in the developing countries, since by the year 2025, 75% of all the people would be in the developing countries as compared to 62% in 1995. The majority (59%) would be in the Indian subcontinent (King et al, 1998). In 2010, it is estimated that there will be 285 million people with diabetes in the age group of 20-79

years in the seven regions of the International Diabetes Federation (IDF 2009). The number of people with diabetes is expected to rise to 438 million by the year 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries (IDF 2009).

The prevalence of diabetes in low and middle income countries is increasing faster than in high income countries. In the urban population of Chennai, the prevalence is reported to have increased by 72% in only 14 years (Mohan et al 2006). Similarly, population-based surveys in China have shown that the prevalence of diabetes has risen substantially within a relatively short period of time (Gu et al 2003).

India gives shelter to the maximum number of people with diabetes mellitus worldwide. From 31.7 million in the year 2000, the number of persons with diabetes mellitus in India would register a 2.5 fold increase over the next 30 years so as to reach an alarming level of estimated 79.4 million by the year 2030 (Wild et al 2004). According to the Diabetes Atlas 2009, in the year 2010 India had an estimated 50.8 million diabetic people. This figure is slated to rise to 87 million by 2030.

The Prevalence of Diabetes in India Study (PODIS), a multi-centric study (49 urban and 59 rural) was carried out in different parts of India to look at the urban-rural differences in type 2 diabetes and glucose intolerance in the year 2004. According to American Diabetes Association criteria, the prevalence of diabetes was 4.7% in the urban and 1.9% in the rural areas. The prevalence of diabetes according to WHO criteria was 5.6% and 2.7% among urban and rural areas respectively (Sadikot et al 2004 and Sadikot et al 2004).

A recent study conducted in rural Kerala found the age-adjusted prevalence of diabetes mellitus and impaired fasting glucose to be 12.5 % and 4.6 % respectively. Adjusted for age and sex, diabetes was significantly associated with positive family history of diabetes, high socioeconomic status, central obesity, hypercholesterolemia, and hypertension (Vijayakumar et al 2009).

Recently Mohan et al (2008) conducted a national NCD risk factor surveillance in six different geographical locations in India. The centres in the southern states had a higher prevalence [Trivandrum (9.2%); Chennai (6.4%)] as compared to north [Delhi (6.0%); Ballabgarh (2.7%)], east [Dibrugargh (2.4%)] and west/central India [Nagpur (1.5%)] for self-reported diabetes.

This marked escalation in diabetes may be attributed to rapid changes in lifestyle and economic progress in India. Obesity is known to be a major risk factor for diabetes. India is currently passing through an epidemiological transition, with increasing urbanization, and industrialization. One of the consequences of urbanization is nutritional transition which put simply translates to food inadequacy being replaced with food surplus. This is accompanied by a dramatic reduction in physical activity consequent to change from jobs that are associated with manual labour to that are more sedentary. This is the basis for the rapid weight gain and obesity seen in several parts of the subcontinent (Deepa et al 2007).

The third largest increase in the number of people with diabetes (20-79 y) from the period 2010-2030 is projected to occur in the South-East Asian region (IDF 2009). In the seventies, migrant Asian living in different parts of the world had shown a higher prevalence of diabetes than other ethnic groups living in the same countries. This was attributed to the changes in the environmental factors such as increased affluence that may unmask a genetic or racial tendency for diabetes (Ramchandran 2005).

Hyperglycemia not sufficient to meet the diagnostic criteria for diabetes is categorized as either impaired fasting glucose (IFG= FPG 100 mg/dl to 125 mg/dl) or impaired glucose tolerance (IGT= 2-h plasma glucose 140 mg/dl to 199 mg/dl), depending on whether it is identified through the FPG or the oral glucose tolerance test (OGTT). IFG and IGT have been officially termed "pre-diabetes." Both categories of prediabetes are risk factors for future diabetes and for cardiovascular disease (ADA 2009).

The prevalence of diabetes in Southern India increased from 13.9 % to 18.6 % in 6 years and IGT decreased significantly. The towns and the cities had the same prevalence. However there was an increase in the prevalence in the peri urban villages, attributing it to urbanization (Ramchandran et al 2008).

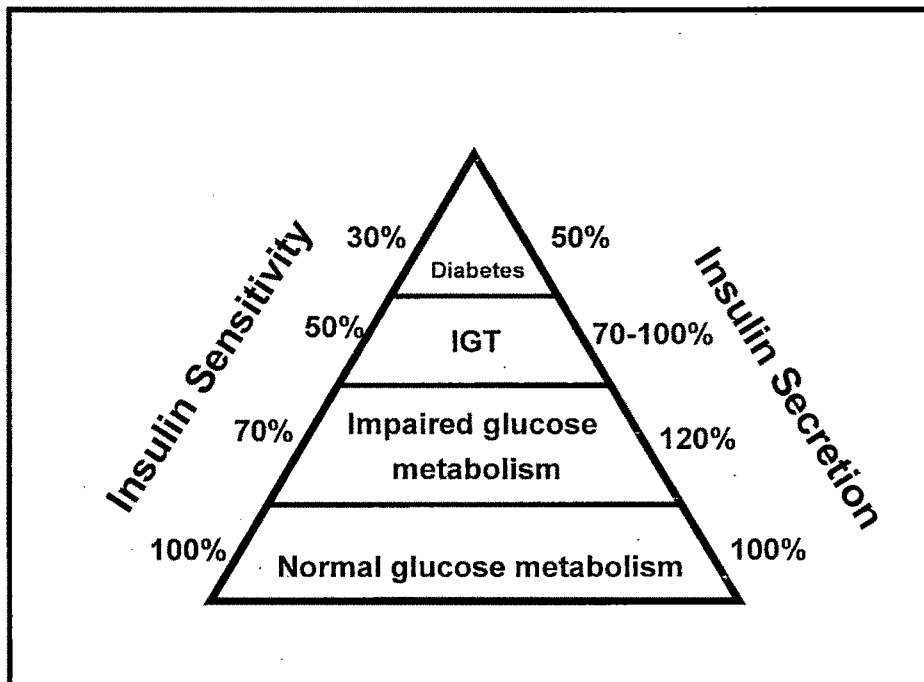
PATHOGENESIS OF DIABETES

A number of factors have been linked to an increased propensity to develop type 2 diabetes. The main risk factors independently associated with diabetes are classified as acquired risk factors and environmental risk factors. The acquired risk factors are age and family history of diabetes and the environmental risk factors are central obesity, body mass index, insulin resistance, physical inactivity, sedentary occupation, urbanization, gestational diabetes and stress.

Type 2 diabetes is a dual chronic disorder that, in the majority of patients, arises from defects in both peripheral insulin action (insulin resistance) and insulin secretion (β -cell dysfunction). The endogenous insulin levels may be normal, depressed or elevated but they are inadequate to overcome the concomitant insulin resistance. As a result hyperglycemia develops. Insulin resistance is first demonstrated in the target tissues, mainly muscle, liver and adipose cells. Initially there is a compensatory increase in insulin secretion which maintains normal glucose concentrations but as the disease progresses insulin production gradually decreases (Figure 1.1). Hyperglycemia is first exhibited as an elevation of post prandial blood glucose caused by insulin resistance at the cellular level and is followed by an elevation in fasting glucose concentrations. As insulin secretion decreases hepatic glucose production increases causing the increase in pre prandial blood glucose levels (Mahan and Escott-Stump 2008).

Epidemiologic data have shown that obesity, sedentary lifestyle and high calorie, high fat diets all correlate with the development of insulin resistance (Fagot et al 2000). Physical inactivity along with other risk factors is a significant contributor to global burden of disease. During physical exercise,

FIGURE 1.1
β CELL DYSFUNCTION AND INSULIN RESISTANCE
IN THE PATHOGENESIS OF T2DM



glucose uptake by the working muscles rises 7 to 20 times over the basal level, depending on the intensity of the work performed. However, intense exercise provokes the release of insulin-counter regulatory hormones such as glucagons and catecholamines, which ultimately cause a reduction in the insulin action. Continued physical training improves the reduced peripheral tissue sensitivity to insulin in IGT and Type II diabetes, along with regularization of abnormal lipid metabolism (Sato et al 2003).

Type 2 diabetes is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities, including reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglycerides (Krauss 2004).

COMPLICATIONS OF DIABETES MELLITUS

Epidemiological and prospective studies in T2DM have suggested a relationship between the degree of metabolic control and diabetic complications. It is one of the most common chronic disorders associated with devastating secondary complications. Vascular disorders are the major long term complications of diabetes that result in morbidity and mortality. These disorders can be broadly classified as micro-vascular (retinopathy, nephropathy and neuropathy) and macro-vascular or cardiovascular (coronary, peripheral and cerebrovascular disease) (Shamoon, 1996).

Stratton et al (2000) have suggested the role of hyperglycemia per se along with hypertension, dyslipidemia and abdominal obesity in the development of diabetic complications. If a tight control of blood glucose can be achieved earlier in the progression of T2DM, the greater will be the reduction in long-term complications (Wright et al 2006).

Cardiovascular events occur 2 to 4 times more frequently, while cardiovascular mortality is 1.5–4.5 times higher in diabetes than in individuals without diabetes (Haffner et al 1998). Diabetic individuals have significantly higher risk for atherosclerosis than non diabetic individuals. They have significantly increased serum triglycerides and decreased HDL cholesterol. Since T2DM subjects also have a decreased lipoprotein lipase activity that

might cause decreased clearance of triglycerides, it may lead to its accumulation in the plasma (Fontbonne et al 1989). In T2DM subjects, enhanced LDL oxidation occurs in vivo, which leads to foam cell formation. This is the earliest lesion of atherosclerosis (Fuster et al 1992).

The metabolic syndrome (MS) is common among subjects with diabetes and is a very important risk factor for macrovascular complications. The MS is characterized by aggregation of obesity (mainly central), dyslipidemia and hypertension. Oversecretion of insulin with peripheral insulin resistance underlies this syndrome (Reaven 1988, DeFronzo 1991). Around 70–80% of diabetic subjects are diagnosed with the syndrome using the NCEP-III or World Health Organization criteria (Marchesini et al 2004, Bonora et al 1998, Alexander et al 2003).

A study by Costa et al (2004) found that patients with the MS (85%) had a higher prevalence of peripheral vascular disease (35% vs. 18%), retinopathy (44% vs. 20%), distal sensory neuropathy (44% vs. 24%), micro- and macroalbuminuria (38% vs. 28%) and coronary artery disease (53% vs. 36%). It was observed that more the number of MS features higher was the proportion of diabetes complications.

DIABETIC NEPHROPATHY

Diabetic nephropathy is the most frequent complication in patients with T2DM. Diabetic nephropathy is a progressive condition and as it evolves, the risk of cardiovascular complications increases. Diabetic nephropathy progresses in a relatively predictable manner through the stages of normoalbuminuria, microalbuminuria and macroalbuminuria, which often heralds increasing creatinine as the final manifestation of overt diabetic nephropathy. In patients with T2DM annual death rates were 0.7%, 2.0%, 3.5% and 12.1% for patients with normoalbuminuria, microalbuminuria, macroalbuminuria and elevated creatinine respectively (Adler 2003).

Kidney biopsies of diabetic patients reveal classic glomerulosclerosis characterized by increased glomerular basement membrane width, diffuse

mesangial sclerosis, microaneurysms, and the presence of interstitial inflammation, possibly caused by excessive passage of protein through the glomerulus. Kimmelsteil Wilson nodes (nodular glomerulosclerosis) are one classic feature of diabetic damage to the kidney. If present on biopsy, the test is positive for diabetic nephropathy. However, lack of these nodes does not preclude diabetic kidney disease (Ossman 2006).

MICROALBUMINURIA

Microalbuminuria (MAU) represents the simplest and most sensitive prognostic factor to evaluate the risk of overt nephropathy in diabetes, representing the first stage of progressive diabetic renal disease (Tobe et al 2002).

The Developing Education on Microalbuminuria for Awareness of renal and cardiovascular risk in Diabetes Study (DEMAND) found the prevalence of MAU to be 19.1% and that of macroalbuminuria to be 3.5%. Abdominal obesity, elevated blood pressure levels and low HDLcholesterol levels were found to increase the risk of MAU (Rossi 2008).

In a study in native Asian Indians the prevalence of MAU was found to be 25.5% and macroproteinuria to be 16.2%. In patients with a diabetes duration of less than 1 year, the prevalence of MAU was 24.7%, and that of macroproteinuria was 6.2%. The risk factors associated with MAU and macroproteinuria were glycated hemoglobin, retinopathy, and calcium channel blocker intake (Kanakamani et al 2010).

Detecting MAU (<300 mg but >30 mg albuminuria per day) in diabetic patients holds significant importance because MAU, as well as heralding the onset of diabetic nephropathy, is a risk factor for cardiovascular events in both diabetic and non-diabetic patients.

A study by Taskiran et al (2010) evaluated the long-term effect of MAU on mortality among patients with acute myocardial infarction. MAU, defined as a urinary albumin/creatinine concentration ratio (ACR) above 0.65 mg/mmol, L,

occurred in 50% of the patients and was associated with increased all-cause mortality. Around 68% of the patients with MAU as compared to 48% of the patients without MAU died during the 10 years of follow-up. The gender and age adjusted hazard ratio for death associated with MAU was 1.71.

MAU was chosen as a clinical criterion for MS by the WHO classification and as an additional metabolic measurement for research in the IDF definition (Grundy et al 2004, www.idf.org).

The risk for the development and progression of MAU is highly dependent on blood pressure (Ritz and Orth 1999). There is evidence to suggest that lowering blood pressure reduces the risk for new onset or progressive nephropathy. In the recently published INNOVATION trial 527 Japanese diabetic patients with MAU were randomised to 40 or 80 mg of telmisartan or placebo with a short followup of 1.3 years. There was reduced transition to overt nephropathy and increased remission to normoalbuminuria seen in both hypertensive and normotensive patients in the telmisartan treated patient groups (Makino et al 2007).

Shih-Te et al (2010) evaluated the effect of tightly controlling multiple factors (HbA_{1c}, SBP, DBP, LDL-C, TG and HDL-C) recommended by the American Diabetes Association (ADA) on the development and prevention of diabetic nephropathy in Chinese patients with T2DM and normoalbuminuria during a 4½-year period. During the study period, 16.4% patients developed new-onset MAU. A significant association was found between the achievement of ADA goals, including HbA_{1c} level, SBP and HDL-C and the development of new-onset MAU. The authors concluded that multifactorial intervention should be started in patients with diabetes and normoalbuminuria in order to delay diabetic nephropathy.

The American Diabetes Association (ADA 2004) recommends annual screening for MAU as a high proportion of patients with T2DM are found to have MAU or overt nephropathy shortly after diagnosis of their diabetes. MAU in T2DM patients is associated with enhanced renal and cardiovascular risk.

Therefore early detection, monitoring of vascular complications and more aggressive multifactorial treatment aiming at renal and vascular protection is recommended.

MANAGEMENT OF DIABETES MELLITUS

Type 2 diabetes is the most common form of diabetes constituting about 90% of the diabetic population in any country. Since its pathogenesis involves β cell failure, the ideal treatment of T2DM requires

1. Arrest of the progressive β cell dysfunction
2. Stabilization of glucose concentrations at non diabetic levels and
3. Reversal or delay of long term complications

Thus Diabetes Management Therapy includes:

1. Medical Nutrition Therapy (MNT)
2. Exercise
3. Oral Hypoglycemic agents
4. Insulin Therapy

Diabetes mellitus is a chronic disease that requires long term medical attention both to limit the development of its devastating complications and to manage them when they do occur. Life style management including diet control and adequate exercise is essential for the successful treatment of T2DM. However many times these measures may be insufficient or patient compliance difficult rendering conventional drug therapies necessary in many patients. The limitations of currently-available oral antidiabetic agents either in terms of efficacy or safety coupled with the emergence of diabetes as a global epidemic have revealed a clear need for the development of indigenous, inexpensive botanical sources for anti-diabetic crude or purified drugs (Jarald et al 2008). Thus, as an alternative approach, medicinal herbs with anti hyperglycemic activities are increasingly being sought after by diabetic individuals and health care professionals.

During the past decade, traditional systems of medicine have become a topic of global importance. In the last few years there has been an exponential

growth in the field of herbal medicine and these drugs are gaining popularity both in developing and developed countries because of their natural origin and less side effects. Traditional medicines derived from medicinal plants are used by about 60% of the world's population (Modak et al 2007).

Plant-based medicinal products have been known since ancient times, and several medicinal plants and their products (active natural principles and crude extracts) have been used to control diabetes in the traditional medicinal systems of many cultures worldwide, including those of the Asian Indians, Chinese and South Americans.

Many people in developed countries have begun to turn to alternative or complementary therapies, including medicinal herbs. Ayurveda, a science that uses herbal medicines extensively, originated in India. Of considerable interest is the adoption of Ayurveda by the mainstream medical system in some European countries (e.g., Hungary), emphasizing this modality is increasing worldwide recognition.

The World Health Organization (WHO) has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. The World Health Organization Expert Committee on diabetes has recommended that traditional medicinal herbs be further investigated (Modak et al 2007).

A limited number of these plant species have been studied and validated for their possible medical application. Safety and efficacy data are available for even fewer plants, their extracts and active ingredients, and the preparations containing them.

India has an ancient heritage of traditional medicine. *Materia Medica of India* provides information on the folklore practices and traditional aspects of therapeutically important natural products. Indian traditional medicine is based on various systems including Ayurveda, Siddha and Unani.

As many of these plants were used for many centuries and some times as regular constituents of the diet, it is assumed that they do not have many side effects. However caution must be exerted in chronic consumption of large amounts of these traditional remedies as toxicity studies have not been conducted for most of these plants

Botanicals have been in use for medicinal purposes since the dawn of civilization. Many modern pharmaceuticals used in conventional medicine today also have natural plant origins. Metformin was derived from the flowering plant, *Galega officinalis* (Goat's Rue or French Lilac), which was a common traditional remedy for diabetes (Yeh et al 2003).

Technically, a herbal product is made from the leaves and roots of a plant, whereas a botanical product includes parts or pieces from the whole plant. However, these terms are often used interchangeably in discussions of complementary therapies (Shane-McWhorter 2001).

Since ancient times, plants have been an exemplary source of medicine. Indian literature like the Rigveda and Ayurveda (4500-1600BC) reveal that ancient Indians had a rich knowledge of the use of medicinal plants. India occupies the topmost position in the use of herbal drugs since the ancient times utilizing nearly 600 plant species in different formulations.

Since the time of Charaka and Susruta many herbal medicines in different oral formulations have been recommended for Madhumeha and many claims of cure have been recorded (Mahdi et al 2003).

The antidiabetic activity of herbs depends upon variety of mechanisms (Jarald et al 2008). The mechanism of action of herbal anti-diabetics could be grouped as:

- Adrenomimeticism, pancreatic beta cell potassium channel blocking, cAMP (2nd messenger) stimulation
- Inhibition in renal glucose reabsorption

- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes
- Reduction in insulin resistance
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells
- Regenerating and/or repairing pancreatic beta cells
- Increasing the size and number of cells in the islets of Langerhans
- Stimulation of insulin secretion
- Stimulation of glycogenesis and hepatic glycolysis
- Protective effect on the destruction of the betacells
- Improvement in digestion along with reduction in blood sugar and urea
- Prevention of pathological conversion of starch to glucose
- Inhibition of β -galactocidase and α -glucocidase
- Cortisol lowering activities
- Inhibition of alpha-amylase
- Preventing oxidative stress that is possibly involved in pancreatic β -cell dysfunction found in diabetes

Thus plant-based herbal drugs or botanicals are emerging as the primary components of holistic approaches to diabetes management. However a major hindrance in amalgamation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their efficacy and safety. One such under researched plant product is barley grass.

BARLEY GRASS POWDER

Barley grass (*Hordeum Vulgare*) consists of the young green leaves of the barley plant. A myriad of vitamins, minerals and amino acids have been isolated from barley grass. Barley grass contains abundant chlorophyll, antioxidants, antioxidant enzymes, and other phytochemicals that neutralize free radicals. Barley grass supplements are purported to have many health benefits. Suggested benefits of barley grass include prevention and cure of cancer, treatment of HIV infection, cholesterol lowering, detoxification of

pollutants, protection against solar and other forms of radiation, and boosting energy and immunity (www.drugs.com).

A potent bioflavonoid antioxidant, named 2"-O-glycosylisovitexin or 2"-O-GIV was isolated, identified, and studied in young barley grass. 2"-O-GIV was found to be very effective in preventing the formation of two toxic by-products, acetaldehyde and malonaldehyde, in horse blood plasma oxidized with Fenton's reagent and in a sample of beer (Miyake and Shibamoto 1998, Nakajima et al 1998).

In a study by Yu et al (2002) it was found that the plasma levels of serum triacylglycerol, total cholesterol, and low-density lipoprotein cholesterol decreased in rabbits receiving a barley leaf essence supplement in combination with an atherogenic diet as compared with animals on the atherogenic diet alone.

In a study on type 2 diabetics, supplementation with barley leaf extract (15g) for four weeks reduced the plasma levels of TC and LDL-C, increased the vitamin E contents and lag times of large, buoyant LDL molecules and small, dense LDL molecules and decreased lucigenin-chemiluminescence and luminol- chemiluminescence levels in blood (Yu et al 2002). In another study on hyperlipidemic subjects, supplementation with 15 g of young barley leaf extract for four weeks substantiated the previous observations (Yu et al 2004).

Thus, from the literature it is clear that diabetes mellitus is a complex metabolic disorder having devastating secondary complications. Therefore it is of utmost important to monitor the risk factors and the biochemical indicators to assess the progression of the disease. Existing literature on efficacy of complementary and alternative medicine in the treatment of diabetes is relatively sparse and heterogenous. More research needs to be carried out on various indigenous plants in order to assess their beneficial effects on health and also the toxic effects, if any.

Thus, there are some research questions which need to be addressed. They are:

1. The extent of metabolic alterations and prevalence of microalbuminuria in T2DM subjects in a pathological lab setting.
2. Risk factor analysis in an industrial diabetic population and trends over years with regard to dyslipidemia and hypertension.
3. Development of functional foods for optimizing health using BGP.
4. Management of T2DM using BGP.

With this background the present study was planned with the following objectives:

1. To study the metabolic alterations in stable T2DM subjects, and to map the prevalence of microalbuminuria.
2. To study the risk factors for diabetes in an industrial population of Vadodara and to track glycemic and lipemic levels over a period of four years.
3. To develop functional food products incorporating Barley Grass Powder.
4. To determine the acceptable level of Barley Grass Powder incorporation in the developed food products by sensory evaluation.
5. To analyze the nutrient composition of Barley Grass Powder.
6. To study the impact of Barley Grass Powder supplementation in the form of capsules for a period of 60 days on the carbohydrate and lipid metabolism of T2DM subjects.
7. To determine the feasibility of scaling up Barley Grass Powder Khakhra as a functional food.

Review of Literature

REVIEW OF LITERATURE

ABOUT DIABETES MELLITUS

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β -cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action.

Type 1 Diabetes Mellitus (T1DM)

This form of diabetes, accounts for only 5–10% of those with diabetes. The primary defect is a cellular-mediated autoimmune destruction of the β -cells of the pancreas usually leading to absolute insulin deficiency and resulting in hyperglycemia, polyuria, polydipsia, weight loss, dehydration, electrolyte disturbance and ketoacidosis. The rate of β -cell destruction is quite variable, being rapid in some individuals (mainly infants and children) and slow in others (mainly adults). Persons with Type 1 diabetes are dependent on exogenous insulin to prevent ketoacidosis and death. Hyperglycemia and symptoms develop only after >90% of the secretory capacity of the β -cell mass has been destroyed. Autoimmune destruction of β -cells has multiple genetic predispositions and is also related to environmental factors that are still poorly defined. Markers of the immune destruction of the β -cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2 β . One and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected (ADA 2009, Mahan and Escott-Stump 2008).

Type 2 Diabetes Mellitus (T2DM)

T2DM may account for 90–95% of all diagnosed cases of diabetes. It is a progressive disease that in many cases is present long before it is diagnosed because the hyperglycemia develops gradually and at earlier stages is often

not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications. T2DM encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. Insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Although persons with T2DM do not require exogenous insulin for survival, around 40% or more will eventually require exogenous insulin for adequate blood glucose control. Autoimmune destruction of β -cells does not occur in this form of diabetes (ADA 2009, Mahan and Escott-Stump 2008).

Gestational Diabetes Mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. GDM is usually diagnosed during the second or third trimester of pregnancy. At this point insulin-antagonist hormone levels increase and insulin resistance normally occurs. The prevalence may range from 1 to 14% of pregnancies, depending on the population studied. GDM represents nearly 90% of all pregnancies complicated by diabetes. During pregnancy GDM requires treatment to normalize maternal blood glucose levels to avoid complications in the infant. Repeated pregnancy may increase the risk of developing irreversible diabetes, particularly in obese women (ADA 2009, Mahan and Escott-Stump 2008, Gupta et al 2009).

Other Types of Diabetes

This category includes diabetes associated with specific genetic syndromes (such as MODY), surgery, drugs, malnutrition, infections and other illnesses. This may account for 1 to 5% of all diagnosed cases of diabetes (ADA 2009).

PREVALENCE OF DIABETES MELLITUS

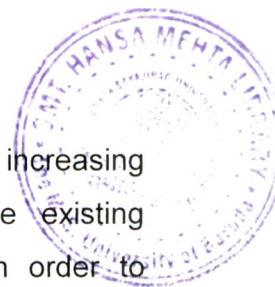
Global Scenario

Diabetes Mellitus is a serious condition which is rapidly increasing in prevalence across the globe. (Table 2.1). The number of people with diabetes

TABLE 2.1
GLOBAL PREVALENCE OF DIABETES MELLITUS

Rank	2000		2030	
	Country	People with diabetes (millions)	Country	People with diabetes (millions)
1.	INDIA	31.7	INDIA	79.4
2.	China	20.8	China	42.3
3.	U.S	17.7	U.S	30.3
4.	Indonesia	8.4	Indonesia	21.3
5.	Japan	6.8	Pakistan	13.9
6.	Pakistan	5.2	Brazil	11.3
7.	Russian Federation	4.6	Bangladesh	11.1
8.	Brazil	4.6	Japan	8.9
9.	Italy	4.3	Philippines	7.8
10.	Bangladesh	3.2	Egypt	6.7

Source: Wild et al, 2004



is rising due to population growth, aging, urbanization, and increasing prevalence of obesity and physical inactivity. Quantifying the existing prevalence of diabetes and future predictions are important in order to develop effective strategies for the prevention and management of the diabetes epidemic.

In the newest edition of the IDF Diabetes Atlas, it is estimated that approximately 285 million people worldwide, or 6.6%, in the age group 20-79, will have diabetes in 2010, some 70% of whom would live in low- and middle-income countries. This number is expected to increase by more than 50% in the next 20 years if preventive programmes are not put in place. By 2030, some 438 million people, or 7.8% of the adult population, are projected to have diabetes. The largest increases would take place in the regions dominated by developing economies (IDF 2009).

The potential impact of diabetes as a development issue was recognized by the United Nations in 2006 in Resolution 61/225 when it stated that **“diabetes is a chronic, debilitating and costly disease associated with severe complications, which poses severe risks for families, Member States and the entire world and serious challenges to the achievement of internationally agreed development goals including the Millennium Development Goals”**.

The global burden of diabetes has been estimated several times. In 1994, the International Diabetes Federation Directory included type 1 and T2DM estimates supplied by member nations. Using this data IDF estimated that over 100 million people worldwide had diabetes. Also in 1994, McCarty et al used data from population-based epidemiological studies and estimated that the global burden of diabetes was 110 million in 1994 and that it would likely more than double to 239 million by 2010 (<http://da3.diabetesatlas.org/indexd9bd.html>).

In 1997, Amos et al estimated the global burden of diabetes to be 124 million people, 97% of them having NIDDM. They projected that this would increase

to 221 million people by the year 2010 (Amos et al 1997). Despite using different methodologies, and at times showing large differences in country-specific estimates, these reports have arrived at remarkably similar global figures of diabetes.

Assuming that age specific prevalence remains constant, the number of people with diabetes in the world is expected to approximately double between 2000 and 2030, based solely upon demographic changes. The greatest relative changes have been predicted to occur in Middle Eastern Crescent, sub Saharan Africa and India. The greatest absolute increase in the number of people would be in India. Most of the expected population growth between 2000 and 2030 would be concentrated in the urban areas of the world. The most striking demographic change in global terms would be the increase in the proportion of the population >65 years of age (Wild et al 2004).

According to the estimates by King et al (1998), approximately 135 million people throughout the world had diabetes in 1995 and the number was predicted to increase to 300 million (122% increment) by the year 2025, with the majority of cases being T2DM. In the developed countries, a 42% increase from 51 million to 72 million was estimated while in developing countries, the predicted increase was over 170% from 84 million to 228 million. This indicates that by the year 2025, over 75% of the population with diabetes will be from the developing countries as compared to 62% in 1995.

According to Gupta et al (2008) prevalence rates in South Asian countries were 5% to 16% in urban areas and 2% to 8% in rural areas.

In addition to Diabetes, the condition of Impaired Glucose Tolerance (IGT) also constitutes a major public health problem, because of its association with an increased risk of development of cardiovascular diseases (CVD). IGT is recognized as being a stage in the transition from normality to diabetes. Thus individuals with IGT are at high risk of progressing to T2DM, although such progression is not inevitable. Around 70 % of these individuals are expected to develop the disease.

It is estimated that some 344 million people worldwide, or 7.9% in the age group 20-79, will have IGT in 2010 and a vast majority of them would be living in low and middle income countries. By 2030 the number of people with IGT is projected to increase to 472 million, or 8.4% of the adult population (IDF 2009).

Thus the global prevalence of diabetes is increasing markedly and projected trends for the future are also grim.

Indian Scenario

Increased urbanization, westernization and economic development in developing countries has contributed to a substantial rise in diabetes. The process of industrialization and urbanization has brought about advancements at all fronts and has altered the lifestyle of the population from activity ridden to a more sedentary one. There is a change in the dietary pattern too. Majority of the Indian population is also undergoing transition in their lifestyle. Though all these changes have benefited the population for a better living, the darker side of the advancements seems to be an increase in the incidence of lifestyle related diseases especially T2DM.

The number of people with diabetes is expected to rise by 195% in India during the period 1995-2025 and is likely to reach 57.2 million in 2025 (King et al 1998).

A multicentric study carried out by the Indian Council of Medical Research (ICMR) in the early seventies, reported the prevalence of diabetes to be 1.5% in the rural areas (Ahuja 1991). A significantly increasing trend for diabetes has been observed in urban populations in India (exponential trend $R^2 = 0.74$), whereas the increase is slower ($R^2 = 0.29$) in rural populations (Gupta et al 2008). This urban rural difference in the prevalence of diabetes may indicate a major role for urbanization in the causation of the disease (Ramchandran 2002).

Far from being a disease of higher income nations, diabetes is very much a disease associated with poverty, with the major burden borne by the low and middle income countries and disproportionately affecting the lower socio-economic groups, the disadvantaged and the minorities in the richer countries.

Until the 1970s it was believed that India had a low prevalence of diabetes compared to many western countries. However reports of migrant Asian Indians living in different parts of the world showed that these populations had a higher prevalence of diabetes than other ethnic groups living in the same countries. T2DM among migrant Asian Indian populations in several countries was high compared with the host population and other migrant ethnic groups (Zimmet 1999).

The Indian population is undergoing a change in its lifestyle pattern which is thought to contribute to the incidence of diabetes. Today, India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the **“diabetes capital of the world”**. India leads the global top ten in terms of the highest number of people with diabetes with a figure of 50.8 million for 2010 and 87 million for 2030 (IDF 2009) (Table 2.2).

There have been several studies from various parts of India, revealing a rising trend in the prevalence of T2DM in the urban population (Table 2.3 and Figure 2.1).

A series of studies from Chennai showed that the percentage of adult urban subjects affected had increased from 5.2% in 1984 to 8.2% in 1989, 11.6% in 1995 and 13.9% in 2000 (Ramchandran et al 2002) which further increased to 14.3% in 2004 (Mohan et al 2006). A National Urban Survey in 2000 showed that the prevalence of diabetes was 12.1% in urban areas in subjects aged > 20 years (Ramachandran et al 2001). The prevalence in all the cities was more than 9% (9.3- 16.6%). The same study revealed that the prevalence of diabetes in the southern parts was higher than the other parts of the country

TABLE 2.2
TOP 10 COUNTRIES WITH DIABETES IN 2010 AND 2030
(NUMBER OF PEOPLE)

2010		2030	
Country/Territory	Millions	Country/Territory	Millions
1 India	50.8	1 India	87.0
2 China	43.2	2 China	62.6
3 United States of America	26.8	3 United States of America	36.0
4 Russian Federation	9.6	4 Russian Federation	13.8
5 Brazil	7.6	5 Brazil	12.7
6 Germany	7.5	6 Germany	12.0
7 Pakistan	7.1	7 Pakistan	11.9
8 Japan	7.1	8 Japan	10.4
9 Indonesia	7.0	9 Indonesia	10.3
10 Mexico	6.8	10 Mexico	8.6

Source: IDF (2009)

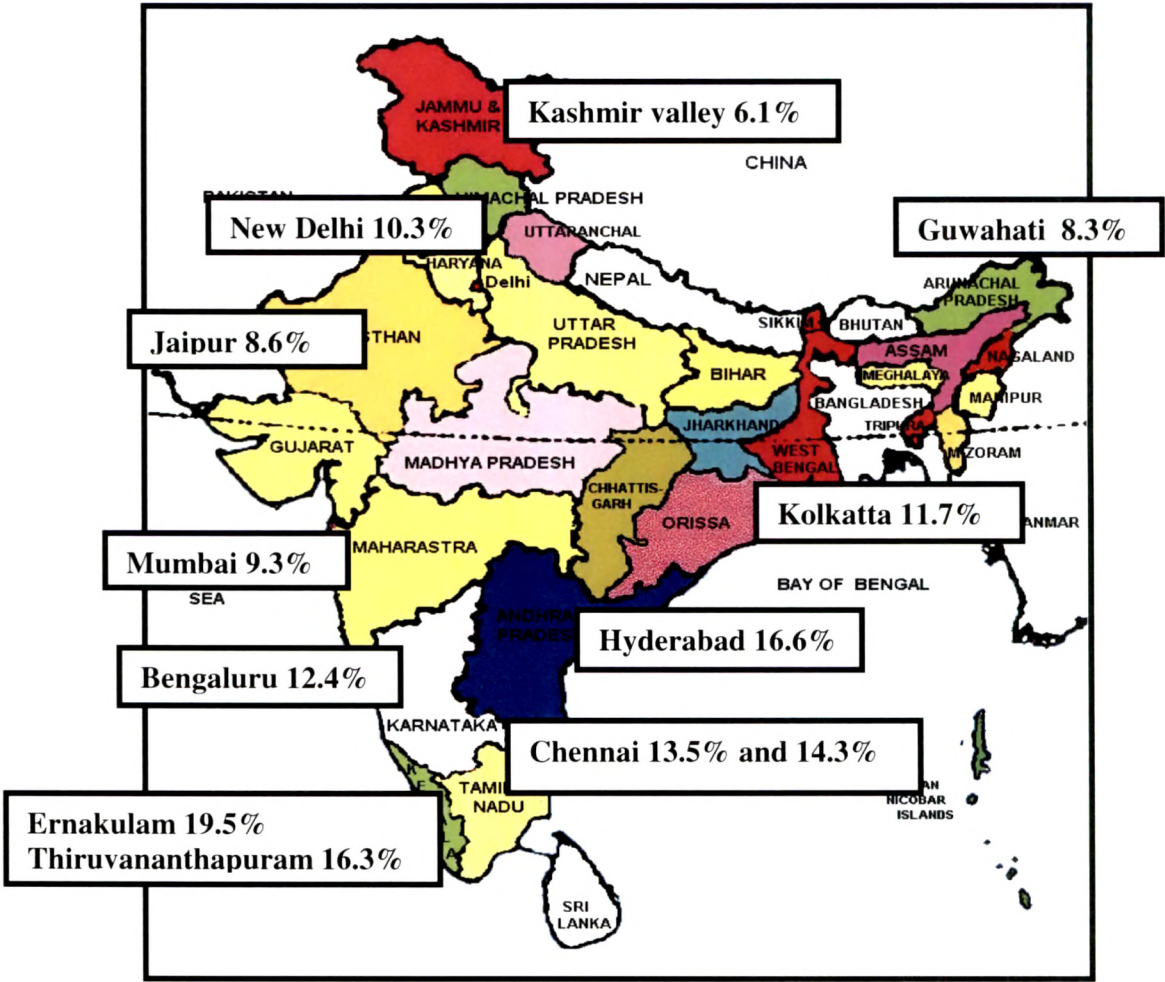
TABLE 2.3
PREVALENCE OF TYPE 2 DIABETES IN INDIA

Year	Author	Place	Prevalence (%)	
			Urban	Rural
1971	Tripathy et al.	Cuttack	1.2	
1972	Ahuja et al.	New Delhi	2.3	
1979	Gupta et al.	Multicentre	3.0	1.3
1984	Murthy et al.	Tenali	4.7	
1986	Patel	Bhadran	3.8	
1988	Ramachandran et al.	Kudremukh	5.0	
1989	Kodali et al.	Gangavathi		2.2
1989	Rao et al.	Eluru		1.6
1991	Ahuja et al.	New Delhi	6.7	
1992	Ramachandran et al.	Madras	8.2	2.4
1997	Ramachandran et al.	Madras	11.6	
2000	Ramankutty et al.	Kerala	12.4	2.5
2001	Ramachandran et al.	National Urban	12.1	
2001	Misra et al	New Delhi	10.3	
2001	Mohan et al.	Chennai	12.1	
2001	Indian Task Force on Diabetes	PODIS	9.6	
2004*	Sadikot et al.	National	5.6	2.7

* Different sample selection criteria (The subjects were aged 25 years and above. The study was carried out in 77 centers (40 urban and 37 rural). 18363 (9008 males and 9355 females) subjects were studied. 10617 (5379 males and 5238 females) were from urban areas and 7746 (3629 males and 4117 females) from rural areas)

Source: Ramachandran et al (2007) and Munichoodapa (2002)

FIGURE 2.1
PREVALENCE OF TYPE 2 DIABETES IN DIFFERENT PARTS OF INDIA



Source: Mohan et al 2007

(Chennai -13.5%, Bangalore -12.4%, Hyderabad -16.6%, Kolkata-11.7%, New Delhi -11.6% and Mumbai -9.3%).

A Study done on North Eastern population of India showed that the age adjusted prevalence of T2DM was 8.2 % and for IGT it was 4 % (Shah et al 1998). Results of the population based studies such as the Chennai Urban Population Study (CUPS) and Chennai Urban Rural Epidemiological Study (CURES) revealed that the recent prevalence of diabetes in Chennai in adults ≥ 20 y was 14.3. The CUP Study also showed that higher income group who consumed excess fat and calorie rich food had an increased prevalence of diabetes as compared to low income group (Mohan et al 2007).

Departmental Studies

Many studies have been carried out in the department to study the prevalence of diabetes mellitus in different places and populations. Table 2.4 shows some of the prevalence studies carried out in the department. The prevalence of DM in and around Vadodara ranges from 5.3 to 18.8%.

Thus the information pertaining to the prevalence of diabetes signifies that

- a) The prevalence of diabetes is on the rise
- b) Diabetes is prevalent across the country
- c) The magnitude of the problem reflects that it is a public health problem in India

PATHOGENESIS OF TYPE 2 DIABETES

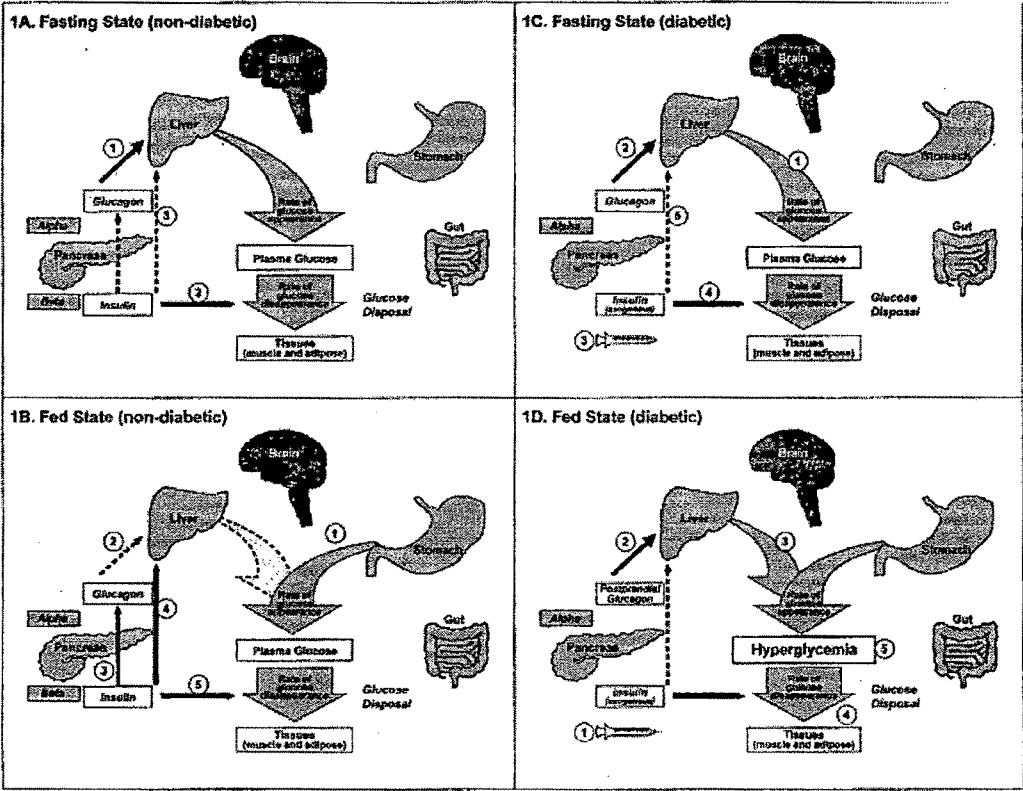
Nearly unlimited supplies of energy-dense foods and technologies that encourage sedentary behaviour have introduced a new threat to the survival of our species: obesity and its co-morbidities. Foremost among the co-morbidities is T2DM.

In the bi-hormonal model of glucose homeostasis (Figure 2.2), insulin is the key regulatory hormone of glucose disappearance, and glucagon is a major regulator of glucose appearance. Insulin is derived from the β - cells of the

TABLE 2.4
DEPARTMENTAL STUDIES ON PREVALENCE OF DIABETES

Year	Author	Place	Type of population	Prevalence (%)
2010	Desai & Iyer	Godhra	Urban	18.8
2007	Mathur & Iyer	Vadodara	Industrial	6.4
2005	Kantharia & Mehan	Vadodara	Industrial	15.3
2004	Pandya & Mehan	Vadodara	Industrial	10.4
2002.	Dholakia & Iyer	Vadodara	Urban	9.5
2002	Gujarati & Mani	V.V.Nagar	Urban	5.3
2002	Khan & Mani	Vadodara	Urban	8.8
2000	Desai & Mani	Vadodara	Industrial	7.4

FIGURE 2.2
GLUCOSE HOMEOSTASIS: ROLES OF INSULIN AND GLUCAGON



Source: Aronoff et al (2004)

pancreas and glucagon is derived from the α -cells of the pancreas (Aronoff et al 2004).

1A. (1) For nondiabetic individuals in the fasting state, plasma glucose is derived from glycogenolysis under the direction of glucagon. (2) Basal levels of insulin control glucose disposal. (3) Insulin's role in suppressing gluconeogenesis and glycogenolysis is minimal due to low insulin secretion in the fasting state.

1B. (1) For nondiabetic individuals in the fed state, plasma glucose is derived from ingestion of nutrients. (2) In the bi-hormonal model, glucagon secretion is suppressed through the action of endogenous insulin secretion. (3) This action is facilitated through the paracrine route (communication within the islet cells). Additionally, in the fed state, (4) insulin suppresses gluconeogenesis and glycogenolysis in the liver and (5) promotes glucose disposal in the periphery.

1C. For individuals with diabetes in the fasting state, (1) plasma glucose is derived from glycogenolysis and gluconeogenesis (2) under the direction of glucagon. (3) Exogenous insulin influences the rate of (4) peripheral glucose disappearance and, because of its deficiency in the portal circulation, (5) does not properly regulate the degree to which hepatic gluconeogenesis and glycogenolysis occur.

1D. (1) For individuals with diabetes in the fed state, exogenous insulin is ineffective in suppressing (2) glucagon secretion through the physiological paracrine route, (3) resulting in elevated hepatic glucose production. As a result, the appearance of glucose in the circulation exceeds the rate of (4) glucose disappearance. (5) The net effect is postprandial hyperglycemia.

A combination of insulin resistance and loss of β -cell function is known to be involved in the development of T2DM. Genetic and environmental factors have been implicated in the development of insulin resistance and β -cell

dysfunction (Figure 2.3). Insulin resistance at the tissue level is primarily due to abnormalities in the way that the effects of insulin are carried from the receptor on the cell's surface to intracellular proteins that regulate glucose transport.

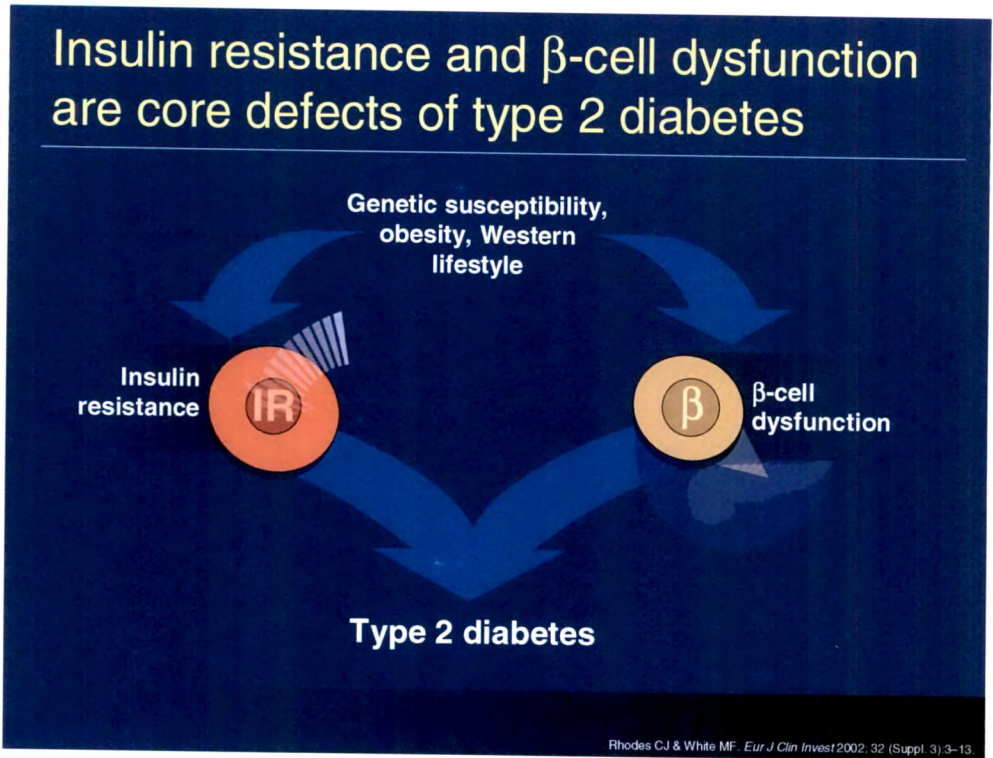
Insulin resistance is said to precede the development of hyperglycemia in subjects that eventually develop T2DM. Insulin resistance may lead to IGT and eventually to the development of T2DM. More than 80% of individuals with T2DM are found to be insulin resistant.

T2DM is said to develop in insulin resistant subjects only with the onset of β cell dysfunction. The normal pancreatic β cell response to a chronic fuel surfeit and obesity-associated insulin resistance is compensatory insulin hypersecretion in order to maintain normoglycemia leading to β -cell dysfunction as the disease progresses. In the long term, as the β -cells begin to fail, insulin secretion falls, IGT and hyperglycemia become apparent and frank T2DM develops. Fasting and post-prandial glucose levels increase steadily as the individual progresses from normoglycemia to IGT and, finally, T2DM. T2DM only develops in subjects who are unable to sustain the β cell compensatory response (Figure 2.4 & 2.5).

Many affected persons who initially have adequate control of their disease with lifestyle changes alone eventually require insulin therapy in the later stage of the disease. The time point in T2DM development when β cell dysfunction first appears is less certain. The recent evidence points to it being early, long before the diagnosis of diabetes with mean β -cell function already less than 50% at diagnosis. On an average, β -cell function declines by 1% per year with normal aging, compared with 4% per year in diabetes (Figure 2.6).

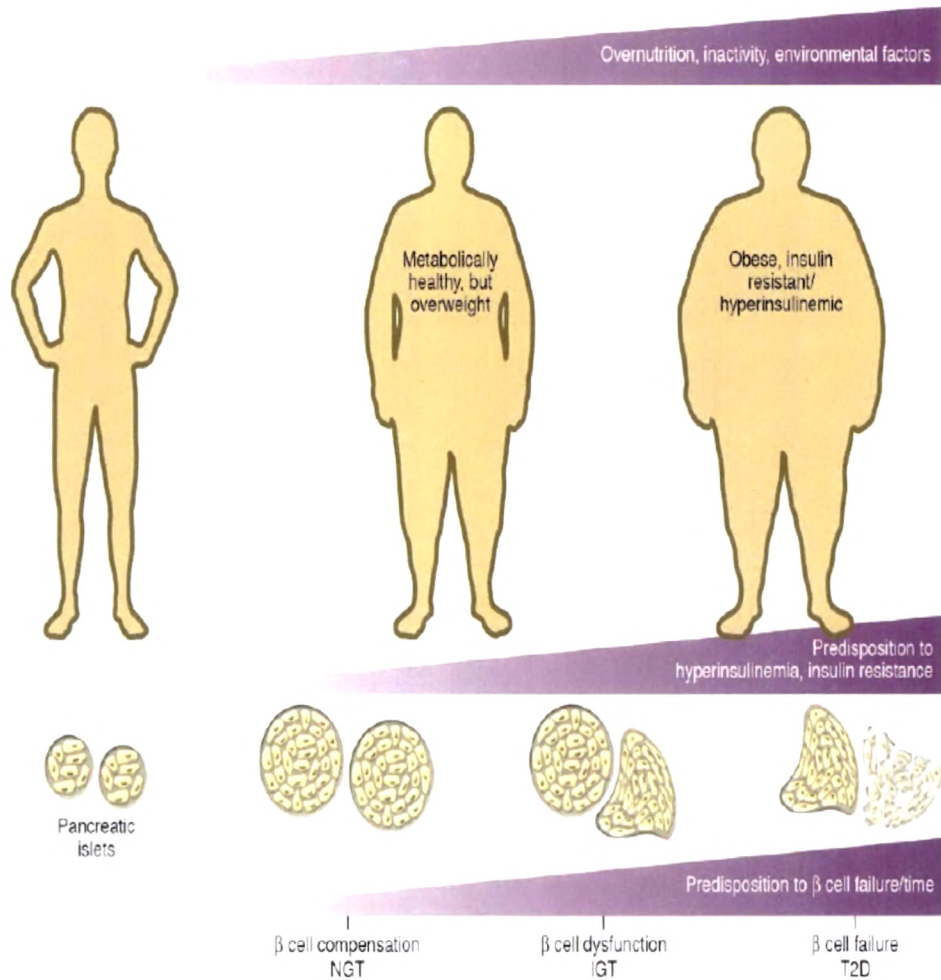
Apart from genetic factors and β cell compensation, failure of the β cell has been attributed to certain other factors. At physiological levels, both glucose and free fatty acids stimulate insulin secretion. Chronic hyperglycemia, may negatively affect the β -cell through a process known as glucotoxicity.

FIGURE 2.3



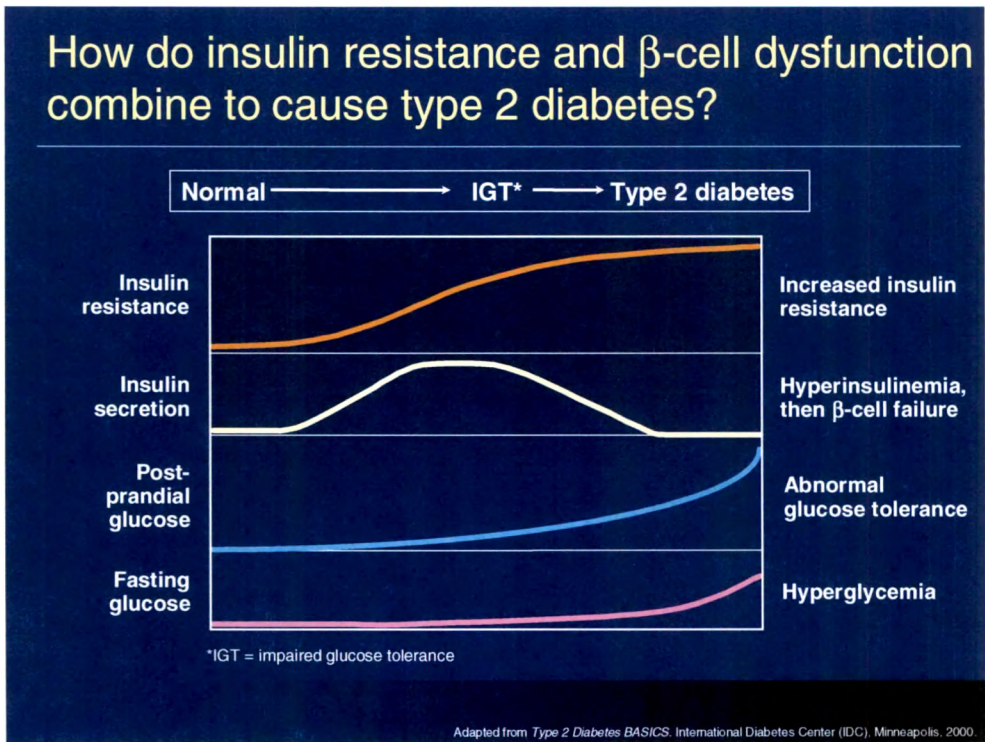
Source: www.idf.org

FIGURE 2.4
ISLET β CELL FAILURE AND THE NATURAL HISTORY OF T2D



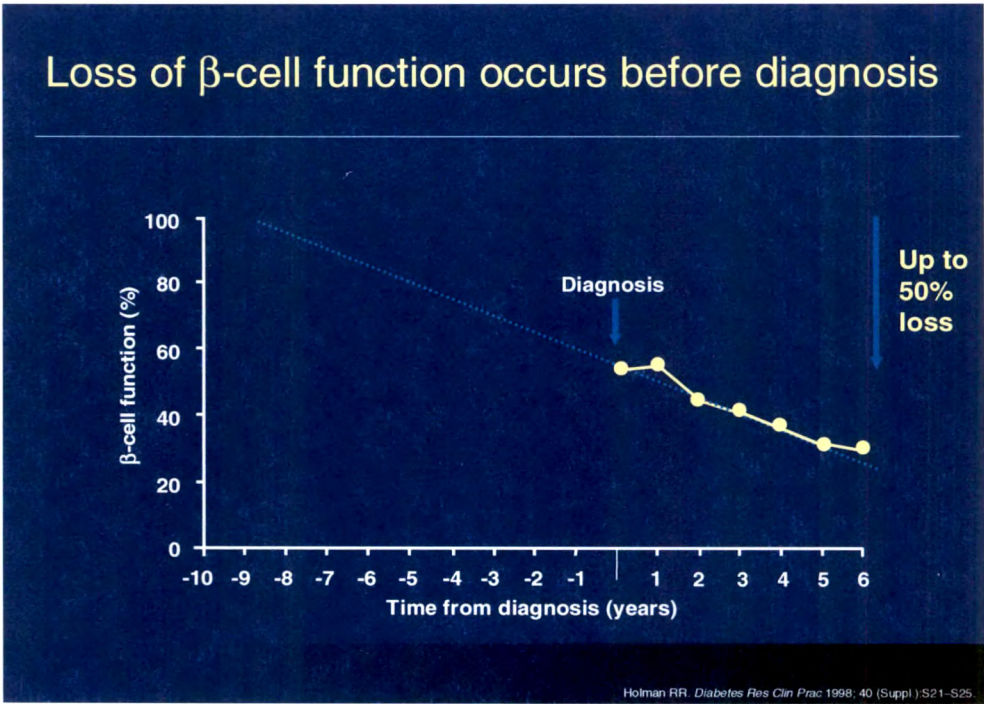
Source: Prentki and Nolan (2006)

FIGURE 2.5



Source: www.idf.org

FIGURE 2.6



Source: www.idf.org

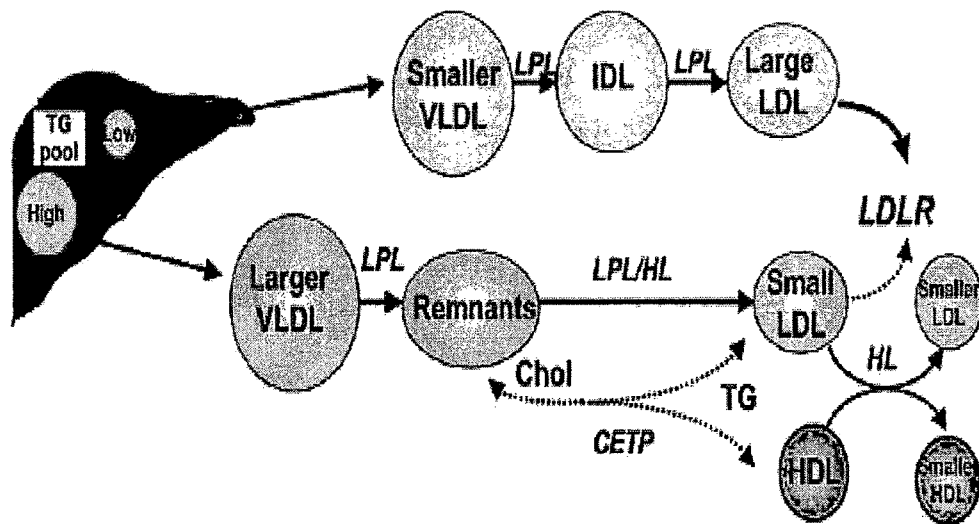
Similarly, chronically elevated free fatty acids have a lipotoxic effect upon the pancreas, inducing β -cell dysfunction. Compensation involves expansion of β cell mass, enhanced insulin biosynthesis, and increased responsiveness of nutrient-secretion coupling. Compensation fails in subjects that have “susceptible” as opposed to “robust” islets (Prentki and Nolan 2006, www.idf.org).

DIABETIC DYSLIPIDEMIA

T2DM is associated with a cluster of interrelated plasma lipid and lipoprotein abnormalities, including reduced HDL cholesterol, a predominance of small dense LDL particles, and elevated triglycerides. These abnormalities occur in many patients despite normal LDL cholesterol levels. These changes are also a feature of the insulin resistance syndrome or the metabolic syndrome, which underlies many cases of T2DM. In fact, pre-diabetic individuals often exhibit an atherogenic pattern of risk factors that includes higher levels of total cholesterol, LDL cholesterol, and triglycerides and lower levels of HDL cholesterol than individuals who do not develop diabetes. Each of these dyslipidemic features is associated with increased risk of cardiovascular disease, the leading cause of death in patients with T2DM. An important feature of the pathophysiology of the atherogenic dyslipidemia of diabetes is the altered metabolism of triglyceride rich lipoproteins. Alterations include both increased hepatic secretion of VLDL and impaired clearance of VLDL and intestinally derived chylomicrons. As a result of this impaired clearance there is prolonged plasma retention of both VLDL and postprandial chylomicrons as partially lipolyzed remnant particles (Figure 2.7). These remnants, which include cholesterol enriched intermediate density lipoproteins (IDLs), have been found to be atherogenic in humans and in a number of animal models.

Another consequence of the increased hepatic production and/or impaired clearance of large VLDL from plasma is the increased production of precursors of small dense LDL particles. LDL size and density are inversely related to plasma levels of HDL, especially the HDL₂ subclass. Small dense

FIGURE 2.7
HYPOTHETICAL SCHEME: RELATION OF ALTERED METABOLISM OF
TRIGLYCERIDE-RICH LIPOPROTEINS TO THE DEVELOPMENT OF AN
ATHEROGENIC LIPOPROTEIN PHENOTYPE



CETP- Cholesterol Ester Transfer Protein; Chol-Cholesterol; HL- Hepatic Lipase; LDLR- LDL Receptor; LPL- Lipoprotein Lipase; TG-Triglyceride

Source: Krauss (2004)

LDL particles appear to arise from the intravascular processing of specific larger VLDL precursors through a series of steps, including lipolysis. Further triglyceride enrichment of the lipolytic products through the action of cholesteryl ester transfer protein, together with hydrolysis of triglyceride and phospholipids by hepatic lipase, leads to increased production of small dense LDL particles. Plasma residence time of small dense LDL particles may be prolonged because of their relatively reduced affinity for LDL receptors.

The increased transfer of cholesterol from HDL to triglyceride rich lipoproteins, with reciprocal transfer of triglyceride to HDL appears to be a prominent factor in the reduction in HDL associated with T2DM and insulin resistance. Hepatic lipase hydrolyzes the triglyceride-rich HDL particles and, as a result, they are rapidly catabolized and cleared from plasma. Typically, the reduced HDL levels in plasma of patients with T2DM are manifested as reductions in the HDL_{2b} subspecies and relative or absolute increases in smaller denser HDL_{3b} and HDL_{3c}.

The development of diabetic dyslipidemia also involves the role of insulin resistance. In insulin resistance and T2DM, increased efflux of free fatty acids from adipose tissue and impaired insulin mediated skeletal muscle uptake of free fatty acids increase fatty acid flux to the liver. In particular, excess intraabdominal obesity, characterized by an excess accumulation of visceral fat around and inside abdominal organs, results in an increased flux of free fatty acids to the liver, leading to an increase in insulin resistance. Increased fatty acids also cause a further decrease in insulin sensitivity at the cellular level, impair pancreatic insulin secretion, and augment hepatic glucose production. In the presence of insulin resistance, free fatty acids in the form of triglycerides are deposited in muscle, liver, heart, and pancreas. Insulin resistance also increases hepatic lipase activity, which is responsible for hydrolysis of phospholipids in LDL and HDL particles and leads to smaller and denser LDL particles and a decrease in HDL₂ (Krauss 2004, Mahan and Escott-Stump 2008).

DIABETES MELLITUS: ETIOLOGY

T2DM is an extremely heterogeneous disorder. Clinical expression of the disorder requires the interaction of genetic, environmental, nutritional and hormonal factors (DeFronzo et al 1992)

Non Modifiable Risk Factors

Age

Although diabetes may occur at any age, surveys indicate that prevalence rises steeply with age. T2DM usually comes to light in the middle years of life and thereafter begins to rise in frequency. Studies from India have shown a much younger age at onset of diabetes compared to the western population (Bhatia et al 2004, Vikram et al 2005).

The recent DECODE study has made a comparative analysis of age at diagnosis of diabetes in different races (DECODE study group 2003). The overall effect of age on prevalence of diabetes differed considerably between ethnic groups even after correcting for other confounding factors such as BMI. The association between age and diabetes was higher in the Indian and Maltese populations compared to all the other populations (Europeans, Chinese and Japanese) studied.

Genetic Factors

The genetic nature of diabetes is undisputed. In unbiased studies, the concordance in identical twins was ~70%, whereas the lifetime risk to siblings was only half this rate (Gerich 1998). A history of T2DM in first degree relative doubles the risk of diabetes and has insulin resistance many years before T2DM development (Elbein 1997).

The wide prevalence and incidence of T2DM among the different ethnic groups also suggest the role of genetics. Diabetes susceptibility genes identified in Mexican Indians (NIDDM 1) was different from the gene identified in Finnish families (Gerich 1998). Pima Indians had nearly 50% prevalence marked by a degree of Insulin resistance which was not seen in Caucasians (Kenny et al 1995).

Chowdhry et al (2006) carried out a study on 1162 European men and 912 Bangladeshis. The groups were equivalent in age, sex and duration of diabetes. Compared with the Europeans, the Bangladeshis had more macrovascular diseases (19.5 vs. 11.9%, $p < 0.01$), sight threatening retinopathy (7.2% vs. 3.8%, $p < 0.01$), and nephropathy (15.3% vs. 9.1%, $p < 0.01$). In addition the Bangladeshis had poorer glycaemic control (mean HbA_{1c}, 8.6% vs. 8.1%), greater proportion with uncontrolled hypercholesterolaemia and poorer control of blood pressure.

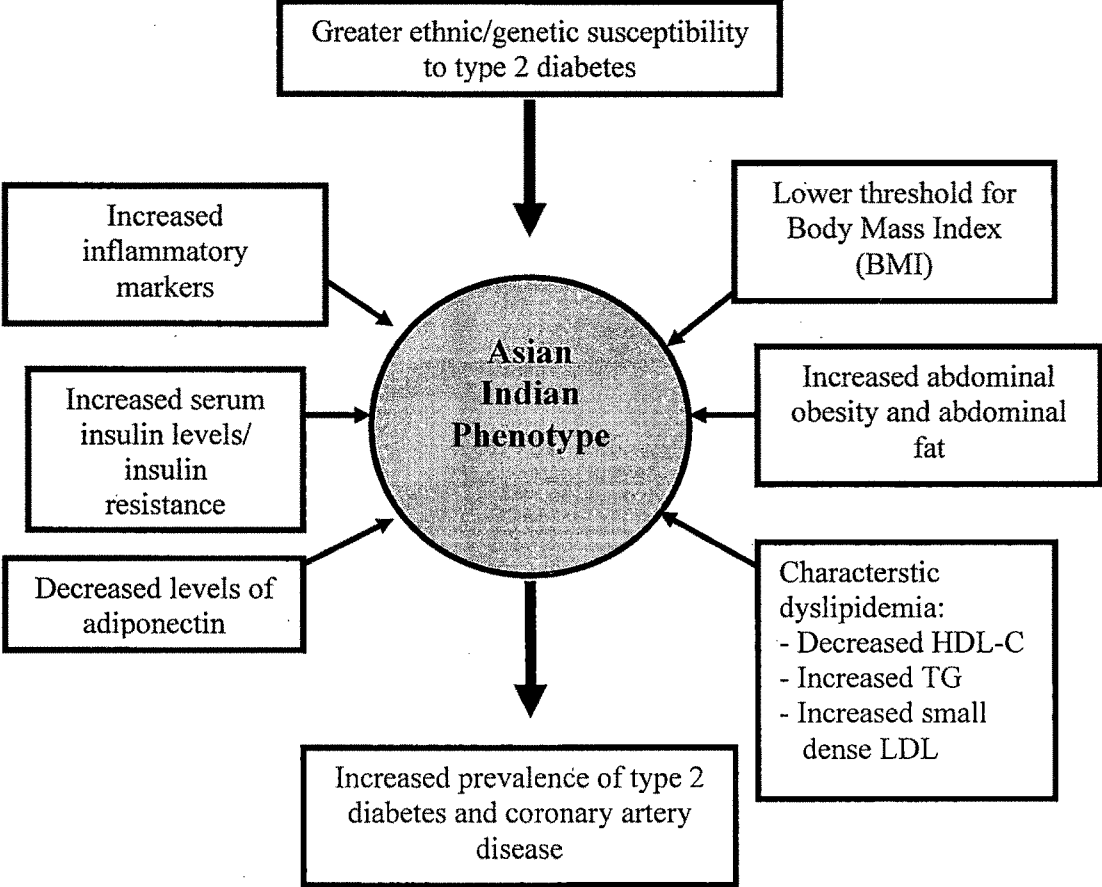
Mohan et al have demonstrated that genetic factors are stronger in Indians compared to Europeans. In their cohort, nearly 10% of the Asian Indian diabetics had family history of diabetes compared to 1 % Europeans. In CUPS study prevalence of glucose intolerance (diabetes +IGT) was significantly higher among subjects with both parents diabetic (55%) compared to those with only one parent diabetic (22%, $p < 0.005$) and those with no family history (15.6%, $p < 0.0001$, Mohan et al 2003).

Asian Indian Phenotype

The 'Asian Indian Phenotype' refers to a peculiar phenotype observed in Asian Indians characterized by increased waist circumference and increased visceral fat despite low body mass index (Figure 2.8). This has been associated with metabolic abnormalities inclusive of greater degree of insulin resistance, high prevalence rates of diabetes and cardiovascular disease. Abdominal obesity and fat modulate the metabolic derangements via insulin resistance (Lele et al 2006).

Indians have lower levels of the protective adipokine adiponectin and have increased levels of adipose tissue metabolites. Studies on neonates suggested that Indian babies are born smaller but relatively fatter compared to Caucasian babies and are referred to as "the thin fat Indian baby". It has been suggested that the "thin fat phenotype" in neonates persists in childhood and could be a forerunner of the diabetogenic adult phenotype (Mohan et al 2007). These findings suggest that Asian Indians are more prone to diabetes and related metabolic abnormalities.

FIGURE 2.8
CHARACTERISTICS OF ASIAN INDIAN PHENOTYPE



Source: Deepa et al (2007)

Modifiable Risk Factors

Overweight and Obesity

Obesity has long been recognized as one of the strongest risk factors for development of diabetes. Obesity measured as Body Mass Index (BMI) is a standard predictor of diabetic status, plasma glucose and HbA_{1c} concentrations in population at risk for T2DM (Daniel et al 1999).

The prevalence of diabetes is 2.9 times higher in overweight (BMI > 27.8 in men and > 27.3 in women) than in non overweight subjects of 20 to 75 years of age (AACE/ACE 1998). The findings from the NHANES survey showed a large increase in fasting concentrations of insulin in those who were overweight compared with those who were not, which reiterates some of the negative physiological consequences of overweight. In addition, the significant increase in concentrations of insulin among those who were at risk for being overweight showed that even this degree of excess weight produces unfavourable physiological changes (Ford et al 2006).

Overweight and Obesity lead to adverse metabolic changes such as insulin resistance, increasing blood pressure and cholesterol. Gender specific multiple logistic regression analysis demonstrated a significant dose response relationship between BMI and obesity related metabolic disorders (one of the following: hypertension, insulin resistance, high plasma triacylglycerol, LDL-C or glucose) (Weng 2006). Haffner et al in 2000 in their study indicated that obesity and adverse body-fat distribution predict the development of both hypertension and type 2 diabetes.

Despite having lower prevalence of obesity as defined by body mass index (BMI), Asian Indians tend to have greater waist circumference and waist to hip ratios thus having a greater degree of central obesity. Again, Asian Indians have more total abdominal and visceral fat for any given BMI and for any given body fat they have increased insulin resistance (Mohan et al 2007).

People with a high waist/ hip ratio indicating that fat is largely in the abdominal cavity have a greater risk of diabetes than people with similar amount of fat distributed peripherally (Colditz et al 1990, Despres et al 2001, Boyko et al 2000).

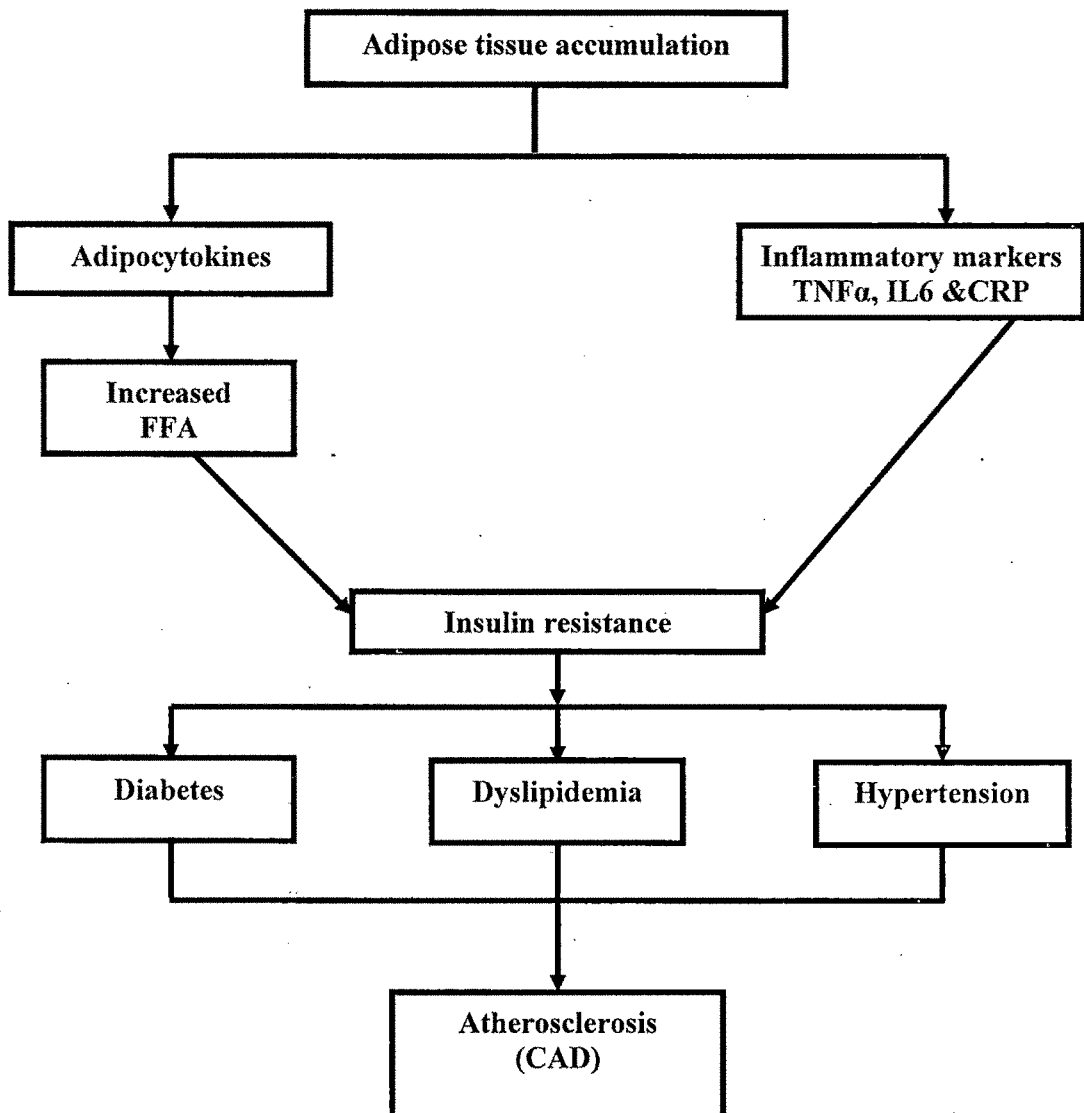
Several cross sectional epidemiological studies suggest that obesity and abdominal obesity are strongly linked to diabetes (Whincup et al 2005, Razak et al 2005). Obesity is considered to be the link between insulin resistance and metabolic abnormalities which include diabetes, hypertension and dyslipidemia, all of which are risk factors for Coronary Artery Disease (CAD) (Figure 2.9, Razak et al 2005, Deepa et al 2007)

In the Chennai Urban Population Study (CUPS study), the prevalence of diabetes increased with increase in the quartiles of BMI, the prevalence being 2.9%, 8.1%, 17.6%, and 19.5% in the first, second, third and fourth quartiles of BMI respectively. Prevalence of diabetes was significantly higher in subjects with abdominal obesity as compared to those without abdominal obesity (27.8% vs 9.0%). The prevalence of IGT also increased with increase in the quartiles of Body Mass Index (Mohan et al 2003).

Voluntary weight loss has shown to improve insulin sensitivity and lipid profile (McAuley et al 2002) and in several randomized control trials (RCTs) it has shown to reduce the risk of progression from IGT to DM (Tuomilehto et al 2002). Prospective studies of sustained weight loss and development of diabetes suggest that even modest weight loss is associated with significantly reduced risk of diabetes (Resnick et al 2000 and Moore et al 2000). Hence, even minor weight reductions may have major beneficial effects on subsequent diabetes risk of overweight persons.

Dengel et al (2006) examined the effects of weight loss on insulin sensitivity and arterial stiffness in overweight adults. In overweight adults, 6 months of weight loss resulted in improvements in body composition, insulin sensitivity, lipid profile and brachial artery compliance and distensibility. Brook et al (2004) showed that 3 months of weight loss improved the metabolic profile of

FIGURE 2.9
ADVERSE EFFECTS OF EXCESS ADIPOSE TISSUE



Source: Deepa et al (2007)

diabetics but failed to improve endothelial function or vascular compliance. The Diabetes Prevention Program (DPP) demonstrated that a 7% reduction in body weight by exercise and diet could prevent diabetes in subjects with IGT by as much as 58% (Quio et al, 2003).

Lifestyle related Risk Factors

DM is considered a major lifestyle disorder today. Changes in the lifestyle and habits of people have influenced health to a great extent. Behaviours (lifestyle related factors), apart from family history and obesity are among the strongest risk factors for T2DM. Environmental and lifestyle changes resulting from industrialization and migration to urban environment from rural settings may be responsible for the increasing incidence of diabetes to a large extent. Availability of improved modes of transport has resulted in decreased physical activities. Better economic conditions have produced changes in dietary habits. The conditions are more favorable for expression of diabetes in the population, which already has a racial and genetic susceptibility to the disease. The rapid pace of industrialization, urbanization and globalization is resulting in high prevalence of common risk factors, namely, tobacco use, alcohol abuse, unhealthy diet, obesity and physical inactivity in the South-East Asia Region (WHO; www.searo.who.int).

Epidemiological studies have shown that reduced physical activity and low fibre diets with high glycemic index affect the incidence of T2DM (Lindquist et al 2000, Hu et al 2001).

Physical Inactivity

Physical inactivity, now recognized as an increasingly important determinant of health, is a result of a progressive shift of lifestyle towards more sedentary patterns, in the developing countries as much as developed ones. Helmrigh and colleagues examined leisure-time physical activity and development of diabetes among 5,990 male alumni of the University of Pennsylvania over 14 years. They discovered that men who exercised regularly, at moderate or vigorous intensity, had a 35% lower risk of developing T2DM than men who were sedentary (Helmrigh et al 1991). In Fiji among Malaysian and Indian

men, the prevalence of diabetes was more than twice as high in those graded as sedentary or undertaking light activity as in those classified as performing moderate or heavy exercise (Taylor 1984).

Thus various studies have identified a number of risk factors which need to be addressed from both prevention and management point of view.

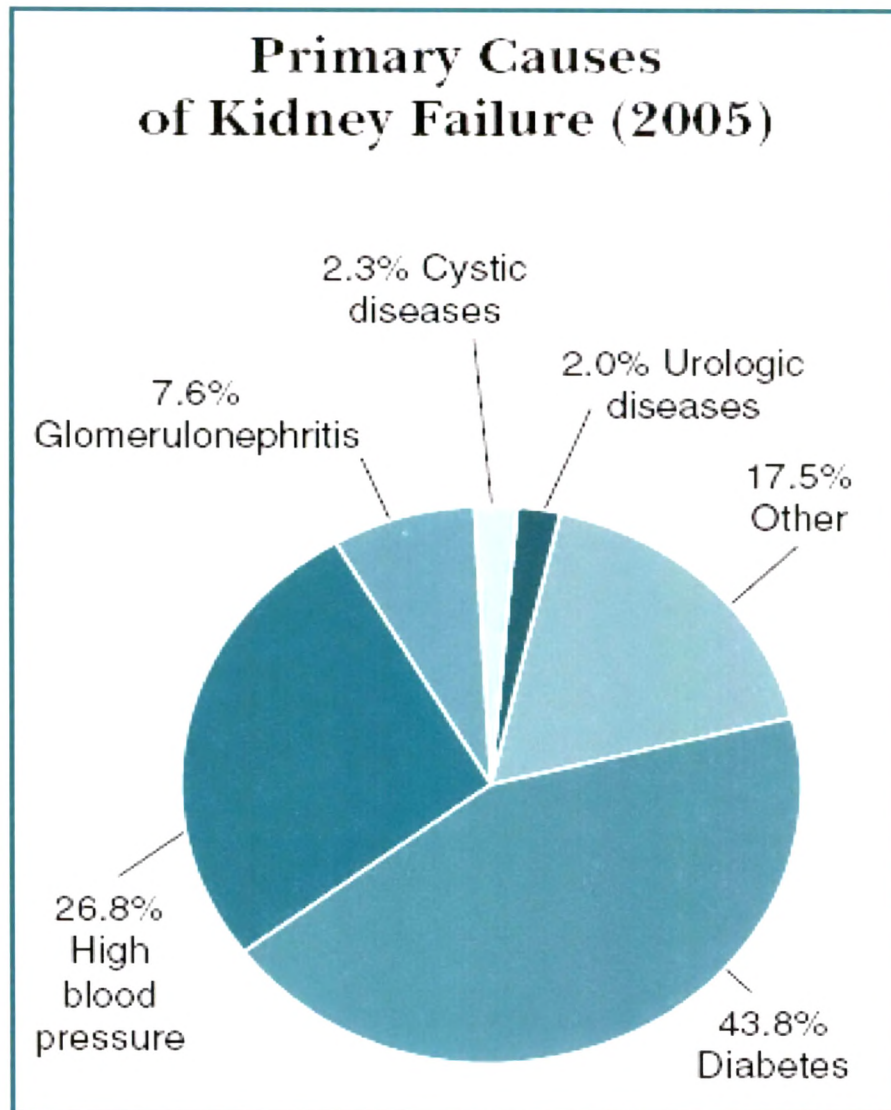
COMPLICATIONS IN DIABETES MELLITUS

Diabetes, a life long progressive disease, is the result of body's inability to produce insulin or use insulin to its full potential, and is characterized by high circulating glucose. The prevalence of diabetes is increasing globally and the maximum increase is expected to be in developing countries like India. India is facing a major health care burden due to the high prevalence of T2DM and there are indications that this would increase further in the next few decades.

Diabetes mellitus is a major health problem and causes considerable morbidity and mortality primarily due to micro and macro vascular complications. While macrovascular complications are associated with significant morbidity and mortality in diabetic subjects, microvascular complications also contribute significantly. About 30–45% of diabetic subjects suffer from microvascular complications, and T2DM has become the principal cause for blindness and end-stage renal disease in western countries (Rainor 2001).

One such microvascular complication of diabetes is diabetic nephropathy. With a worldwide increase in diabetes, it is inevitable that diabetic nephropathy will also become a major issue in the future. Diabetic nephropathy occurs in 20–40% of patients with diabetes and is the single leading cause of end-stage renal disease (ESRD) (ADA 2009). Nearly 30% of chronic renal failures in India are due to diabetic nephropathy (Agarwal and Dash 2000). According to the United States Renal Data System report diabetes is the most common cause of kidney failure, accounting for nearly 44 percent of new cases (Figure 2.10, NKUDIC 2008). Diabetic renal disease is

FIGURE 2.10



Source: NKUDIC (2008)

underdiagnosed and undertreated even now, when detection of the early stages is simple through routinely available laboratory testing.

NATURAL HISTORY OF DIABETIC NEPHROPATHY

Kidney disease in diabetic patients is clinically characterized by increasing rates of urinary albumin excretion, starting from normoalbuminuria, which progresses to microalbuminuria (MAU), macroalbuminuria, and eventually to ESRD.

The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (≥ 30 mg/day or $20 \mu\text{g}/\text{min}$) of albumin in the urine, referred to as MAU, and patients with MAU are referred to as having incipient nephropathy. A higher proportion of individuals with T2DM are found to have MAU and overt nephropathy shortly after the diagnosis of their diabetes, because diabetes is actually present for many years before the diagnosis is made. Without specific interventions, 20–40% of type 2 diabetic patients with MAU progress to overt nephropathy, but by 20 years after onset of overt nephropathy, only ~20% would have progressed to ESRD. However, the greater risk of dying from associated CAD in the older population with T2DM may prevent many with earlier stages of nephropathy from progressing to ESRD. As therapies and interventions for coronary artery disease continue to improve, more patients with T2DM may be expected to survive long enough to develop renal failure (ADA 2004).

MAU is a well-known predictor of poor renal outcomes in patients with T2DM and in essential hypertension. MAU is also a well-established marker of increased CVD risk.

A study by Araki et al in 2007 reported that either remission or a 50% reduction of MAU in type 2 diabetic patients was related to risk reduction of future renal and cardiovascular events. Furthermore, reducing the degree of albuminuria also led to a preservation of kidney function.

The risk for CVD was 3 fold higher in South Indian NIDDM subjects with nephropathy when compared with their non-nephropathic counterparts (Viswanathan et al 1998). Thus, in T2DM, many patients may not reach ESRD due to premature death from CVD.

Early detection of MAU allows the implementation of individualised and aggressive intervention programmes to reduce cardiovascular risk factors. MAU is therefore considered to be an important therapeutic target for the protection against renal and cardiovascular complications. Unfortunately, the implementation of routine screening for renal disease is still far below recommended goals. Attention towards diabetic nephropathy is not directed until the patient has progressed towards the stage of renal failure. Nephropathy due to diabetes can be diagnosed very easily and can be prevented.

PATHOGENESIS

The pathogenesis of diabetic nephropathy is multifactorial and genetic susceptibility has been proposed to be an important factor in the development and progression of diabetic nephropathy. According to Viswanathan (2004) three major histologic changes occur in the glomeruli in diabetic nephropathy (1) mesangial expansion is directly induced by hyperglycemia, via increased matrix production or glycosylation of matrix proteins, (2) thickening of glomerular basement membrane occurs, (3) glomerular sclerosis is caused by intraglomerular hypertension. These different histologic patterns appear to have similar prognostic significance. Diabetes produces qualitative and quantitative changes in the composition of the capillary basement membrane and this altered material undergoes accelerated glycosylation and further rearrangement to form advanced glycosylation end-products (AGE), which stimulate protein synthesis, further decrease degradability of the basement membrane, increase its permeability and causes endothelial dysfunction.

SCREENING FOR MAU

MAU is defined as a urinary albumin excretion rate ≥ 30 mg/24 h which is equivalent to 20 μ g/min on a timed specimen or 30 mg/g creatinine on a

random sample (ADA 2004). Abnormalities of albumin excretion are defined in Table 2.5. Because of the adverse impact of MAU on survival in patients with T2DM and the renal risk of macroalbuminuria, screening and intervention programmes should be implemented early, at the stage of MAU.

As there is difficulty in precise dating of the onset of T2DM, screening for MAU should begin at the time of diagnosis. After the initial screening and in the absence of previously demonstrated MAU, a test for the presence of microalbumin should be performed annually (ADA 2004). Screening for MAU can be performed in three ways (ADA 2004):

- 1) Measurement of the albumin-to-creatinine (ACR) ratio in a random spot collection
- 2) 24-h collection with creatinine, allowing the simultaneous measurement of creatinine clearance
- 3) timed (e.g., 4-h or overnight) collection

The first method is often found to be the easiest to carry out in an office setting, generally provides accurate information, and is therefore preferred; first-void or other morning collections are best because of the known diurnal variation in albumin excretion. The Kidney Disease Outcomes Quality Initiative guidelines (2002) state that ACR measurement in a first-morning spot urine collection is adequate and a timed urine collection is not necessary. Figure 2.11 gives an algorithm for MAU screening (ADA 2004).

FAMILIAL AGGREGATION OF DIABETIC NEPHROPATHY

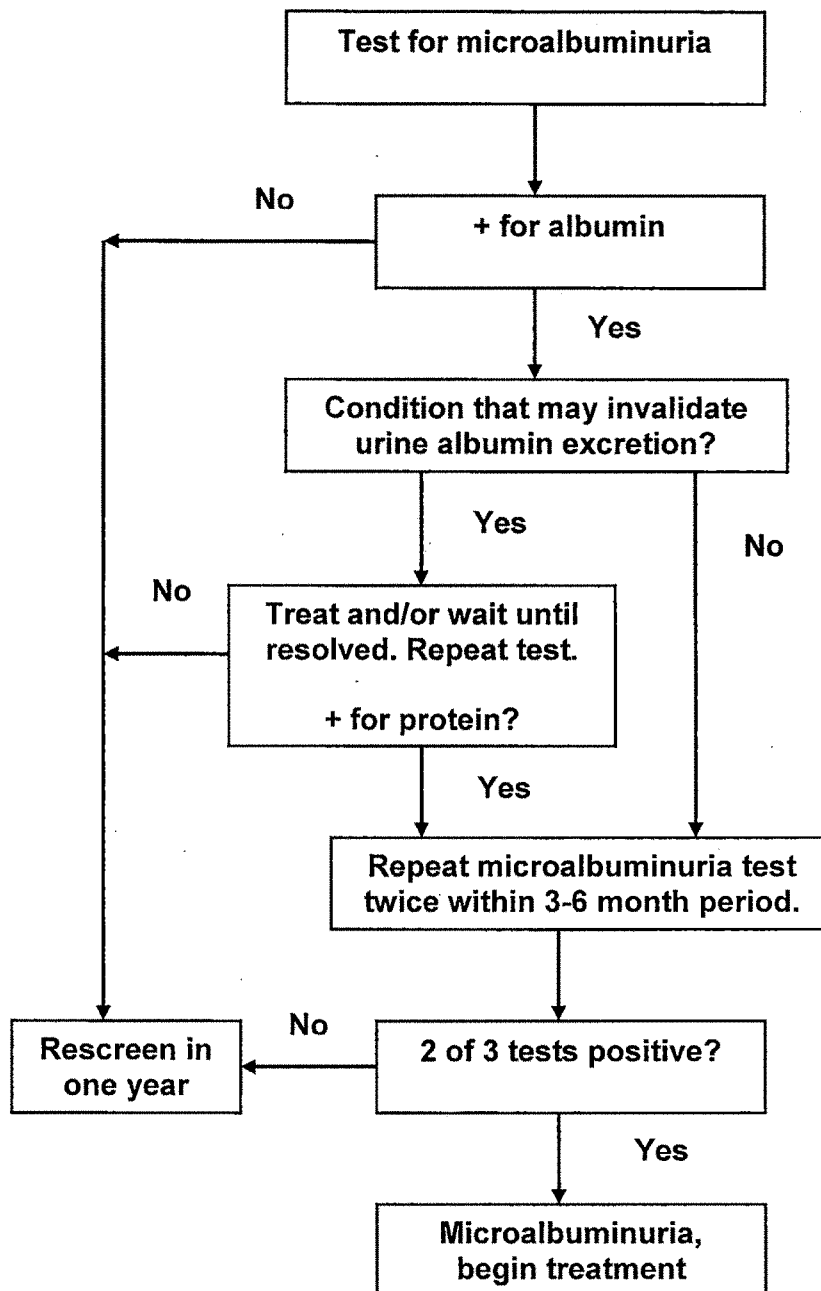
The role of familial factors has been implicated in the development of diabetic nephropathy. In a study by Vijay et al (1999) in South Indian type 2 diabetic subjects it was found that proteinuria was present in 50% and MAU in 26.7% of the diabetic siblings of probands with diabetic nephropathy. In contrast, the prevalence of proteinuria and MAU among diabetic siblings of probands with normoalbuminuria was 0% and 3.3% respectively. Certain ethnic groups,

TABLE 2.5
MEASUREMENT OF ALBUMINURIA

	Normal	Microalb	Macroalb	Advantages	Disadvantages
Dipstick for Protein	-	-	+	Convenience	Dependent on level of hydration
24-h protein (mg)	<150	<500	≥ 500	Overcomes problem of diurnal variation in excretion	Subject to collection errors
24-hour alb (mg)	<30	30-299	≥ 300	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Timed collection (µg/min)	<20	20-199	≥ 200	Overcomes problem of diurnal variation in excretion	Subject to collection errors
Spot collection (µg alb/mg Cr)	<30	30-299	≥ 300	Convenience Not dependent on hydration level Most reproducible	Ratios vary based on sex

Source: ADA 2004, Basi et al 2008

FIGURE 2.11
SCREENING FOR MICROALBUMINURIA



Source: ADA 2004

particularly American blacks, Hispanics, and Native Americans, may be particularly pre disposed to renal involvement as a complication of diabetes (Viswanathan 2004)

PREVALENCE OF MAU

In an Asian study, MAU was detected in 36.3% of type 2 diabetics at a diabetes centre in southern India (Varghese et al 2001). A high prevalence of MAU in non-Caucasians has also been observed in the Pima Indians of North America, where T2DM is very common, and more than 50% develop proteinuria within 20 years (Pettitt et al 1990).

A prospective, long-term follow-up study conducted on T2DM patients who were followed up for 2 to 9 years found that at the end of the study period 19% had MAU (30-300 mg/24 h), and 16% had overt albuminuria (>300 mg/24 h) (Ravid et al 1998).

In a referred cohort of type 2 diabetic patients in the Developing Education on MAU for Awareness of renal and cardiovascular risk in Diabetes study evaluating the global prevalence and determinants of MAU one single random urinary ACR was obtained in 24 151 patients without known albuminuria from 33 countries. The overall global prevalence of MAU and macroalbuminuria was 39% and 10%, respectively. The Asian and Hispanic patients had the highest prevalence of a raised urinary ACR (55%) and Caucasians the lowest (40.6%) (Parving et al 2006).

The UKPDS 74 report shows that over a median of 15 years after diagnosis of T2DM, 38% of UKPDS participants developed albuminuria and 29% developed renal impairment (Retnakaran et al 2006).

The CURES 45 study on urban Asian Indian type 2 diabetic subjects found the prevalence of overt nephropathy and MAU to be 2.2 and 26.9%, respectively (Unnikrishnan et al 2007).

In a study from Seychelles, at age 25-64 years, the prevalence of MAU was 20% in persons with either diabetes or hypertension and 41% in persons with

both conditions (Prujm et al 2008). In multivariate analysis, MAU was associated with age [odds ratio (OR) 1.24 for a 10-year increase; 95% confidence interval (CI): 1.02-1.52], hypertension stage I (2.0; 1.1-3.8) and stage II (4.5; 2.3-8.6), obesity (1.7; 1.0-2.8) and diabetes (3.0; 1.9-4.9).

Gupta et al in 1991 found a 26.6% prevalence of MAU (albumin excretion rate > 20 µg/min) in 64 NIDDM subjects. They also observed that glycated hemoglobin was significantly higher in microalbuminurics in the NIDDM group ($P < 0.05$).

The wide range in the prevalence of MAU in type 2 diabetics is probably due to genetic and cardiovascular risk factors (blood pressure, cholesterol, salt intake, etc.). Albuminuria can also be present at the time of diagnosis of diabetes. An increased prevalence of MAU has been observed among those with impaired fasting glucose before developing clinically diagnosed diabetes (Damsgaard and Mogensen 1986). Mykkanen et al (1994) reported that MAU predicted the development of diabetes independently of blood pressure level.

In a study in Aboriginal people, the presence of MAU [OR-1.90 (95% CI 0.88–4.06)] and macroalbuminuria [OR-2.51 (95% CI 1.08–5.87)] predicted diabetes independent of other known risk markers of development of T2DM. The baseline level of ACR was significantly higher among participants who developed diabetes over a 11 year follow-up period than among controls (Wang Z and Hoy 2006).

In another study MAU (20-200 mg/l) was independently associated with age, gender, hypertension, diabetes, smoking, previous myocardial infarction and stroke. Although MAU and macroalbuminuria were found more frequently in the diabetic (16.4%) and hypertensive (11.5%) subgroup, MAU was still prevalent in 6.6% of the nondiabetic, nonhypertensive subjects. The authors concluded that urinary albumin measurements may be useful in early risk profiling and prevention of cardiovascular disease in the population at large (Hillege et al 2001).

Another study by the same group found a positive dose-response relationship between increasing urinary albumin concentration and mortality. A higher urinary albumin concentration increased the risk of both cardiovascular and non-cardiovascular death after adjustment for other well-recognized cardiovascular risk factors. A 2-fold increase in urinary albumin concentration was found to be associated with a relative risk of 1.29 for cardiovascular mortality (95% CI 1.18 to 1.40) and 1.12 (95% CI 1.04 to 1.21) for non-cardiovascular mortality (Hillege et al 2002).

Increased prevalence of diabetic nephropathy in South Asians

Migrant Asian Indians had 40 times greater risk of developing ESRD when compared with the Caucasians (Chandie et al 2002). Indian-Asian ethnicity is independently associated with the development of both albuminuria and renal insufficiency in T2DM. An increased incidence of renal failure has been estimated previously in U.K. Indian-Asian patients with T2DM (Burden et al 1992). In addition, cross sectional studies have shown a higher prevalence of MAU in Indian Asians compared with Caucasians in both T2DM and population cohorts (Mather et al 1998, Fischbacher et al 2003).

In the United Kingdom Asian Diabetes Study the prevalence of MAU was significantly higher in the South Asian patients compared with the white European patients (31% versus 20%) (Dixon et al 2006).

MAU- RISK FACTOR SCENARIO

Previous studies have confirmed the multifactorial nature of the risk profile underlying albuminuria.

In a cross-sectional study of patients with T2DM, urinary albumin excretion was positively associated with hyperglycemia (Suraniti et al 1992). The Oklahoma Indian Diabetes Study of patients with T2DM also found that hyperglycemia and elevated blood pressure were associated with an increased risk for renal failure (Lee et al 1994).

In a study by Ravid et al (1998) multiple logistic regression analysis indicated that levels of total cholesterol, mean blood pressure, and hemoglobin A1c were the main factors associated with the decrease in renal function and with the increase in albuminuria. Low levels of high-density lipoprotein, body mass index, cigarette smoking, low socioeconomic status, and male sex were all significantly associated with diabetic nephropathy, as well as with the manifestations of arteriosclerosis.

According to Parving et al (2006), HbA1c, systolic blood pressure (BP), ethnicity, retinopathy, duration of diabetes, kidney function, body height, and smoking were all independent risk factors of MAU.

Similarly Retnakaran et al (2006) identified risk factors for albuminuria. They were systolic blood pressure, Indian-Asian ethnicity, urinary albumin excretion, plasma creatinine, male sex, increased waist circumference, plasma triglycerides, LDL cholesterol, HbA1c (A1C), increased white cell count, ever having smoked, and previous retinopathy.

In another study by Varghese et al (2001) multivariate regression analysis revealed age, diastolic blood pressure, glycated haemoglobin, fasting plasma glucose, and duration of diabetes to be associated with MAU. In multivariate analysis, MAU was associated with age, hypertension stage I and stage II, obesity and diabetes (Prujm et al 2008).

A 6-year follow-up study from Finland found that the subsequent development of albuminuria was best predicted by the initial values of serum insulin (Wirta et al 1996). In a study by Unnikrishnan et al (2007) risk factors for diabetic nephropathy included A1C, duration of diabetes, and systolic blood pressure, while for MAU, smoking and diastolic blood pressure were also risk factors.

Using data of the Prevention of Renal and Vascular End stage Disease (PREVEND) Study, Brantsma et al (2007) hypothesized that, lowering glucose concentration and BP, including the start of antihypertensive

medication were the most important ways to reduce urinary albumin excretion in the general population, even in normotensive, nondiabetic individuals.

MAU & METABOLIC SYNDROME

In T2DM, MAU is often associated with clustering of cardiovascular risk factors to form the metabolic syndrome (Kuusisto et al 1995). Using the NCEP-III or World Health Organization criteria, 70–80% of diabetic subjects were diagnosed with the metabolic syndrome (Marchesini et al 2004, Bonora et al 1998, Alexander et al 2003). The metabolic syndrome is a significant risk factor for the development of microvascular complications in diabetic subjects.

Diabetic subjects with the metabolic syndrome were found to have a significantly higher (46.6%) frequency of microvascular-related complications than diabetic subjects without the syndrome (26.8%). These include MAU (41.5% vs. 23.9%), neuropathy (10.4% vs. 7.5%), retinopathy (9.6% vs. 4.1%) and leg ulcers (7.9% vs. 2.8%) (Abdul-Ghani et al 2006).

MANAGEMENT OF DIABETIC NEPHROPATHY

Early screening for MAU is the key for early detection of the devastating complication. A number of interventions have been demonstrated to reduce the risk and slow the progression of renal disease. Optimal blood pressure, tight glycaemic control and pharmacological blockade of the renin–angiotensin system with ACE inhibitors or ARB have been shown to decrease albumin excretion rate and decrease progression from incipient to overt nephropathy.

There is emerging data that reduction of albuminuria leads to reduced risk of adverse renal and cardiovascular events. It has become increasingly clear that albuminuria should not only be measured in all patients with T2DM but also steps should be taken to suppress albuminuria to prevent future renal and cardiovascular adverse events.

The Irbestartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA-2) study compared 150 and 300 mg irbesartan daily to placebo in 590

hypertensive patients with T2DM and microalbuminuria. The hazard ratio for progressing to overt nephropathy was found to be 0.56 in the 150 mg group (95% CI 0.31– 0.99) and 0.32 in the 300 mg group (95% CI 0.15– 0.65) (Parving et al 2001).

In a study by Herman et al (2003), it was shown that treatment with losartan in type 2 diabetic patients with nephropathy reduced the incidence of ESRD and resulted in decrease in cost associated with ESRD. Losartan significantly reduced the number of days with ESRD over 3.5 years when compared with the placebo and conventional therapy group.

Patients with type 2 diabetes and microalbuminuria (N=332) were administered 80 mg/day valsartan or 5 mg/day amlodipine in the Microalbuminuria Reduction with Valsartan (MARVAL) trial. The urinary albumin excretion rate at 24 weeks was 56% of baseline with valsartan and 92% of baseline with amlodipine (Viberti and Wheeldon 2002).

Glycemic control

Intensive diabetes management with the goal of achieving near normoglycemia has been shown in large prospective randomized studies to delay the onset of microalbuminuria and the progression of micro- to macroalbuminuria in patients with both type 1 and type 2 diabetes. In the UKPDS 33 study (1998), more than 4000 patients with freshly diagnosed T2DM were observed over 15 years, either under a conventional or under a more intensive treatment with oral antidiabetics and / or insulin. The study showed that with 12 years of blood glucose control, the reduction in risk for the onset of MAU, proteinuria and two-fold increase of plasma creatinine was 33%, 34% and 74% respectively.

In the KUMAMOTO study, HbA1C values averaged 7.2% in the intensively treated group as compared to 9.4% in the conventionally treated group. The development of diabetic nephropathy was lesser (11.5%) in the group that received intensive treatment as compared to the conventionally treated group (43.5%) (Shichiri et al 2000).

Protein Intake

Studies in patients with varying stages of nephropathy have shown that protein restriction helps slow the progression of albuminuria, GFR decline, and occurrence of ESRD (Pijls et al 1999, Pedrini et al 1996, Hansen et al 2002 and Kasiske et al 1998).

Reduction of protein intake to 0.8 –1.0 g/kg body wt/day in individuals with diabetes and the earlier stages of CKD and to 0.8 g/kg body wt/day in the later stages of CKD may improve measures of renal function and is recommended (ADA 2009).

A high prevalence of MAU thus necessitates early detection, monitoring of vascular complications, and more aggressive multifactorial treatment aiming at renal and vascular protection.

NON COMMUNICABLE DISEASES IN THE INDUSTRIAL POPULATION

Non communicable diseases (NCDs), especially cardiovascular disease, cancer and T2DM, account for 53 and 44% of all deaths and disability adjusted life years (DALYs) respectively in India (WHO 2005). Prevalence of diabetes is rising unabated globally. India is the worldwide leader with the maximum number of diabetics in the world. Disturbing is the fact that while the majority of persons with diabetes in developed countries are at an age of 65 years and above, most diabetics in the South-East Asia Region belong to the young and economically productive age groups (45-64 years) (www.searo.who.int).

The comparatively high number of deaths in developing countries at younger adult ages (15-59 years) is a matter of concern. In India, based on current trends, it has been projected that the number of deaths from these conditions would rise from 3.78 million in 1990 (40.4% of all deaths) to 7.63 million in 2020 (66.7% of all deaths) thus putting an enormous load on the country's health care infrastructure (Mathur 2006).

Risk factors as highlighted in the World Health Report 2002 include tobacco use, alcohol consumption, raised blood pressure, raised lipid levels, overweight, low fruit/vegetable intake, physical inactivity, and diabetes. These risk factors are the focus of the STEPs approach to NCD risk factor surveillance. Most of the major NCDs are linked through a cluster of risk factors, and are responsible for the causation of disease. These factors are linked to each other so much so that occurrence of one factor paves the way for the other, thereby leading to the development of NCDs (WHO 2002). Risk operates in continuum with adverse events in persons with modest elevation of many risk factors, having a multiplicative effect (Bahl 2001). Knowledge about the distribution of these risk factors vital to promoting disease prevention and control programmes. Therefore, primary prevention of occurrence of risk factors along with their early identification and management can help delay the progress to NCDs.

THE WORKPLACE AS A HEALTH PROMOTION SETTING

The workplace has been internationally recognized as an appropriate setting for health promotion. Benefits of health promotion in a workplace setting include improving the health status of workers, staff morale and productivity, and reductions in staff turnover, absenteeism and sick leave. The workplace is a natural setting to work with groups, where collegial and social support for behavioural change can be provided and for putting in place sustainable environmental change (Carenethon 2009).

The importance of workplace health promotion was addressed in 1950 and later updated in 1995 in a joint International Labour Organization/World Health Organization session on occupational health. Since then, workplace health promotion has been recommended by international bodies through numerous charters and declarations, including the 1986 Ottawa Charter for Health Promotion, the 1997 Jakarta Declaration on Leading Health Promotion into the 21st Century and the 2005 Bangkok Charter for Health Promotion in a Globalized World (WHO 2008).

Health interventions can be of value to the employee and employer alike with employers potentially benefiting from a reduction in direct medical and indirect or lost productivity costs as indicated by diabetes cost estimates developed by the ADA (2003).

The goal of the WHO Global Strategy on Diet, Physical Activity and Health is to promote health by guiding the development of an enabling environment for sustainable actions at individual, community, national and global levels which, when taken together, will lead to reduced disease and death rates related to unhealthy diet and physical inactivity. The workplace environment was clearly identified as an important area of action for health promotion and disease prevention (WHO 2004)

Industrial units have captive population and therefore provide an opportunity to establish sentinel surveillance for diabetes risk factors. The workplace also appears to be a promising focal point for conducting disease screening and prevention programmes based on the proximity of medical services to the employee and the requirements for conducting routine occupational health examinations.

RISK FACTOR PROFILE IN INDUSTRIES

Tenkanen et al (1998) studied the joint effect of shift work and certain adverse life-style factors on coronary heart disease and found that for the shift workers the relative risk for CHD rose gradually with increasing numbers of adverse life-style factors, but for the day workers there was no clear dose-response pattern.

In a study to evaluate the prevalence of metabolic syndrome in a mixed working population 1,594 employees were screened. The study-population consisted of 1,075 men and 519 women, aged 17–64 y. The prevalence of the metabolic syndrome was found to be 23.5%. Subjects with metabolic syndrome had higher BMI ($P < 0.01$), blood pressure ($P < 0.01$), heart rate ($P < 0.01$), liver enzymes ($P < 0.01$), uric acid ($P < 0.01$) and LDL ($P < 0.01$), while HDL was significantly lower ($P < 0.01$). (Pre)-Diabetes and CVD were

found more frequently in subjects with metabolic syndrome (Oberlinner et al 2008).

Ajay et al (2008) carried out a cross-sectional survey among the employees and their family members (10930 individuals) of eleven medium-to-large industries from diverse sites in India, to highlight the regional difference in the prevalence of diabetes mellitus (DM) and to explore determinants in variability in the Indian industrial population. The study found wide regional variations in the prevalence of DM in India. The crude prevalence of DM and impaired fasting glucose was found to be 10.1 and 5.3%, respectively. Urban sites had a higher prevalence and awareness of DM status. In diabetic subjects, 38.4% were unaware that they had diabetes. The risk factors associated with overall prevalence of DM were: age, sex, low-education level, family history of DM, hypertension and overweight/obesity.

Mehan et al in (2006) identified the non communicable disease risk factor profile in an industry using a pre tested WHO STEPS questionnaire. A universal prevalence was observed for low (< 500 g) daily intake of vegetables and fruits. High blood pressure and high BMI were reported in 65.9% and 65.5% of the subjects respectively. Central obesity was present in 72.7% of the subjects as defined by a high waist hip ratio and 32.3% of the subjects as defined by high waist circumference. Tobacco usage, inactivity and alcohol usage was prevalent in 31.4%, 17.3% and 5% of the study subjects respectively. Around 34.1% of the subjects had > 3 risk factors and were identified as being "at risk". The prevalence of diabetes, hypercholesterolemia and hypertension was found to be 19.1%, 40.5% and 38.2% respectively.

A prospective mortality study included 20 years of follow up of 7139 middle aged industrial workers at Shell Oil Company's manufacturing and research facilities. Compared with employees with BMI between 18.5 and 24.9 kg/m², those with BMI of 30 kg/m² or greater had a statistically increased RR for all causes (1.25), coronary heart diseases (2.29), cardiovascular diseases (2.22), diabetes (16.97), and accidental deaths (2.64). After adjusting for additional

covariates, coronary heart diseases and cardiovascular diseases remained statistically significant (Tsai et al 2006).

A study by Mohan et al (2008) found that the industrial population, in spite of having better access to healthcare facilities had a higher prevalence of cardiovascular risk factors in comparison with the general population of Chennai. In the study 1167 subjects residing in the residential areas of 2 industries (Indian Airlines and Integral Coach Factory) in Chennai in southern India were recruited. The subjects were employees (n = 440) and their family members (n = 727) in the age group of 20-69 years. Age-adjusted prevalence of diabetes, hypertension, dyslipidaemia, hypertriglyceridaemia, overweight and metabolic syndrome was 11.9%, 25.4%, 40.2%, 28.3%, 60.2% and 34.1% respectively. Tobacco usage in any form was present in 22.9% of men and 0.5% of women; 79% of the subjects followed a sedentary lifestyle. Among subjects receiving medication, 42.1% of subjects with diabetes and 55.3% of subjects with hypertension had their disease under adequate control.

In a cross-sectional study, employees of a research center at Petrobras were assessed clinically and by laboratory testing to determine the prevalence of risk factors for cardiovascular diseases. Around 970 subjects were studied, with a mean age of 42.2 years. The risk factors were lack of exercise (67.3%), cholesterol > 200 mg/dL (56.6%), overweight (42%), obesity (17%), blood hypertension (18.2%), smoking (12.4%), and diabetes mellitus (2.5%) (Matos et al 2004).

The Praeford study (Schneider et al 2007) sought to provide contemporary data on the prevalence of cardiovascular risk factors in middle-aged diabetic automobile industry employees in Germany. Among 4234 employees, 91 employees with diabetes were identified with a mean age of 52 years. Only a negligible proportion of the diabetic subjects achieved the recommended target values. Blood pressure targets were achieved by 26%, HbA1c target value by 54%, and LDL target value by 31% of employees. Only 7 of 91 (8%) diabetic employees achieved all three recommended target values.

The profile of noncommunicable disease (NCD) risk factors was identified by Mehan et al (2007) in an industrial productive population of Baroda city using WHO's STEPS questionnaire. A total of 190 males were taken as the study subjects. The results revealed that majority (93.2%) of the subjects had low daily intake of vegetables and fruits. 79.4%, 78.1% and 48.1% of the subjects had high BMI (≥ 23 kg/m²), high waist-to-hip ratio and high waist circumference respectively. History of hypertension and diabetes was present in 19.5% and 15.3% of subjects, respectively. 19% of the subjects were found to be physically inactive. Tobacco usage (32.1%) and alcohol consumption (18.4%) were also prevalent among the study subjects. About 74.4% of the subjects were identified as being 'at risk' (i.e., had ≥ 3 risk factors).

The costs attributed to employee health problems are usually measured by employers in terms of direct health care costs, such as medical plan claims. Although it has been understood that employee health problems also produce indirect costs for employers, their measurement has been far less frequent.

Pelletier and colleagues (2004) examined the relationship between changes in various health risks and changes in work productivity. Pre and post analysis was conducted on 500 subjects who participated in a wellness program at a large national employer. Based on the baseline analyses, it was reported that those with a poor diet, unhealthy BMI, and physical inactivity had higher levels of productivity loss in terms of both lower absenteeism and presenteeism, than those without these health risks. To examine the possible improvement in productivity due to a reduction in health risk, the mean absenteeism and presenteeism for workers who reduced the health risk was compared. The authors reported that Individuals who reduced one health risk improved their presenteeism by 9% and reduced absenteeism by 2%. The overall conclusion of the authors was that reductions in health risks are associated with positive changes in work productivity.

In a study by Burton et al (1999) three measures i.e. the actual decrease in the productivity of employees while they are on the job, absenteeism and disability were combined to produce a Worker Productivity Index (WPI). The

WPIs of 564 telephone customer-service agents were correlated with the employees' number and type of health risks. It was observed that as the number of health risks increased, an employee's productivity decreased.

A study by Van den Heuvel et al (2005) applied data from a prospective cohort with a follow up period of 3 years. The authors investigated the effect of sporting activities on absenteeism of employees. Registered data on illness related absenteeism covering a period of 4 years were collected from 1,228 workers from 21 Dutch companies. Sporting activities were found to have a favourable effect on absenteeism with those participating in sports taking sick leave significantly less often than their colleagues not practicing sports. A statistically significant higher mean duration of absenteeism was observed among employees not practicing sports, of approximately 20 days over a period of 4 years as compared to their sporting colleagues.

The relation between aerobic physical activity and absenteeism was confirmed by a study of Jacobson and Aldana (2001). Frequency of weekly aerobic activity was compared with annual illness-related absenteeism in 79,070 US adult workers. Weekly exercise, days per week of aerobic activity (≥ 20 minutes), and absenteeism consisting of days per year and grouped as 1 to 3, 4 to 6, and 7+ days were recorded. A significant relationship was found between absenteeism and exercise. Differences ($P < 0.05$) in absenteeism were found between no exercise and all frequencies of weekly exercise. One day of exercise was associated with lower absenteeism when compared with no exercise, and 2 days of exercise was more favorable than one.

HEALTH PROMOTION IN THE WORKPLACE

Historically, interest in workplace diseases and their complications has focused on the level of occupational exposure leading to work-related health risks. In recent years, the emphasis has changed to non contagious chronic diseases, and the workplace has attracted attention as a potential place for causal studies and interventions. These interventional studies aim at changing triggering behaviors of diseases, nonspecific to occupational function, such as diet, exercise, and smoking.

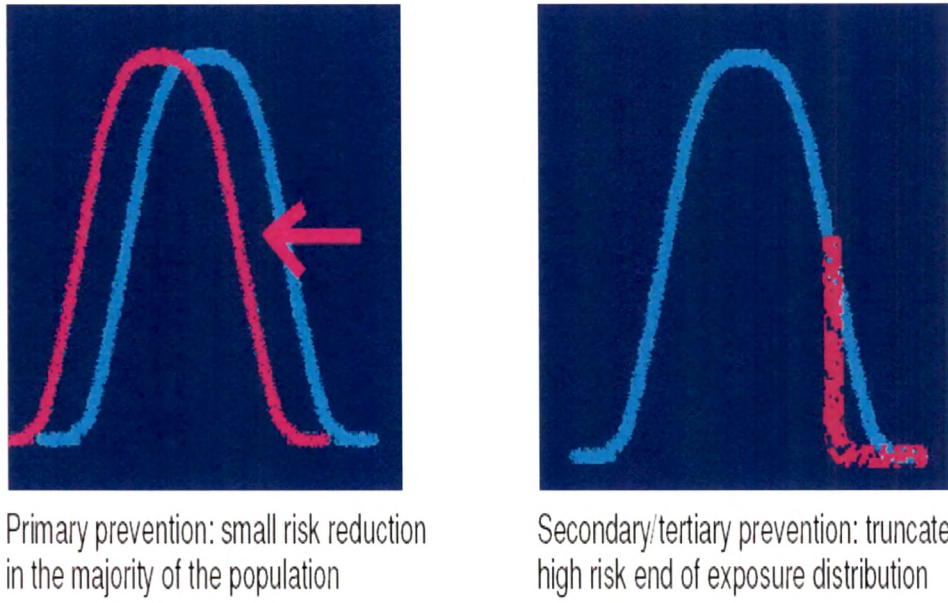
Primary Prevention versus Secondary or Tertiary Prevention

Two broad approaches to reducing risk have been defined. The first approach seeks to reduce risks in the entire population irrespective of each individual's risk level and potential benefits. This is referred to as primary prevention. Primary prevention interventions intend to move the profile of the whole population in a healthier direction. Population attributable risk of death and disability can be influenced by small changes in risk factors in the majority who are at small to moderate risk. By preventing disease in large populations, small reductions in blood pressure, blood cholesterol and so on can dramatically reduce health costs (Figure 2.12). This can be done by interventions that intend to impact the individual directly and by interventions aiming at the environment of the individual.

The second category of interventions focusses on people likely to benefit, or benefit the most from it. These secondary/tertiary prevention interventions are based on screening exposed populations for the early onset of sub-clinical illnesses and then treating them. Secondary prevention intervention in the occupational setting aims at facilitating early return-to-work for those who are off work because of some or other form of disability. Costs at the population level are reduced when focussing on high-risk individuals because an intervention is provided to fewer people, but on the other hand, it might also increase the costs of identifying the group of people most likely to benefit. Population-wide (primary prevention) interventions are generally considered to have the greatest potential for prevention. By reducing risks from blood pressure and cholesterol, shifting the mean of whole populations will be more cost-effective in avoiding future heart attacks and strokes than screening programmes that aim to identify and treat all those people with defined hypertension or raised cholesterol levels (Proper and van Mechelen 2008).

In another study a controlled field trial compared workers at one intervention (N=132) and one control (N=121) worksite. The intervention comprised nutrition displays in the cafeteria and monthly 30-minute workshops for six months. Self-reported dietary and lifestyle behaviours, nutrition knowledge, body mass index (BMI), waist circumference and blood pressure were the key

FIGURE 2.12
PREVENTION STRATEGIES:
HIGH RISK VERSUS POPULATION STRATEGY



Source: Proper and van Mechelen (2008)

outcome measures at six and twelve-months. At baseline, 40% of the total sample (253) was obese, 30% had elevated blood pressure, 59% indicated an excessive fat intake and 92% did not meet the recommended vegetable and fruit intake. Results revealed that a high retention rate (94% at 6-months and 89% at 12-months) was achieved. The intervention reduced fat intake, increased vegetable intake and physical activity, improved nutrition knowledge and reduced systolic blood pressure when compared to the control site. There was no difference in change in mean BMI or waist circumference (Cook et al 2001).

In a study to evaluate the effectiveness of individual-based counselling intervention addressing physical activity and diet (Proper et al 2003) 299 workers of three municipal services were randomised over either a control group (n=168) or an intervention group (n=131) receiving a 9 months intervention. Over the 9 month period, the intervention group subjects were offered seven counseling sessions. Subjects in both the intervention and control group received written information about several lifestyle factors. Primary outcome measures were physical activity, cardiorespiratory fitness and prevalence of musculoskeletal symptoms. Secondary outcome measures were body composition as given by BMI and percentage of body fat, blood pressure and blood cholesterol. Significant positive effects were found on total energy expenditure, physical activity during sports, cardiorespiratory fitness, percentage of body fat, and blood cholesterol. No effects were found for the proportion of subjects meeting the public health recommendation of moderate-intensity physical activity, physical activity during leisure time other than sports, prevalence of musculoskeletal symptoms, body mass index, and blood pressure.

Most of the studies have focussed on optimizing health of the industrial population to control non communicable diseases. However very few studies have focussed on the risk profile of the diabetic industrial population.

DIETARY MANAGEMENT OF DIABETES

Dietary management is frequently referred to as the cornerstone, or the initial step, in the treatment of T2DM. Medical nutrition therapy (MNT) is important at all levels of diabetes prevention (Table 2.6). It is important to prevent diabetes, manage existing diabetes, and prevent, or at least slow, the rate of development of diabetes complications.

TABLE 2.6
NUTRITION AND MNT

Primary prevention to prevent diabetes	Secondary prevention to prevent complications	Tertiary prevention to prevent morbidity and mortality
<ul style="list-style-type: none">• Use MNT and public health interventions in those with obesity and pre-diabetes	<ul style="list-style-type: none">• Use MNT for metabolic control of diabetes	<ul style="list-style-type: none">• Use MNT to delay and manage complications of diabetes

Goals of dietary management for patients with diabetes mellitus as given by ADA, 2008 are as follows:

1. Achieving and maintaining blood glucose levels in the normal range or as close to normal as is safely possible.
2. Achieving and maintaining a lipid and lipoprotein profile that reduces the risk for vascular disease
3. Achieving and maintaining blood pressure levels in the normal range or as close to normal as is safely possible.
4. Preventing, or at least slowing, the rate of development of chronic complications of diabetes by modifying nutrient intake and lifestyle
5. Addressing individual nutrition needs, taking into account personal and cultural preferences and willingness to change
6. Maintaining the pleasure of eating by only limiting food choices when indicated by scientific evidence

Dietary modifications should be implemented by prioritizing these goals. Modifications are generally made in diet composition, amounts, distribution and timings.

Carbohydrates (CHO)

Carbohydrate plays a very important role in control of diabetes. In the management of diabetes, higher complex 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 (Khan and Safdar 2003).

In individuals with T2DM, postprandial glucose levels and insulin responses to a variety of starches and sucrose are similar if the amount of carbohydrate is constant (Malerbi et al 1996 & Bantle et al 1993).

Anderson et al (1991) studied the metabolic effects of high carbohydrate (70%), high fiber (70g) (HCHF) and low carbohydrate (37%) and low fibre (10 g) (LCLF) 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 a period of four weeks. After a 6 weeks washout period, subjects were re-entered to the metabolic ward for a period of four 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 cholesterol ($p < 0.0004$) and high density lipoprotein cholesterol ($p < 0.0013$). Glycemic control and other lipid fractions did not differ significantly.

In weight-maintaining diets for T2DM, replacing carbohydrate with monounsaturated fat reduces postprandial glycemia and triglyceridemia (Garg et al 1998, 1994).

Glycemic Index

Glycemic Index (GI) is defined as the incremental blood glucose area (0-2 hr) following ingestion of 50g of available carbohydrates (CHO) as a percentage of the corresponding area following an equivalent amount of carbohydrate from a standard reference product.

A diet with low GI has been associated with lower risks of T2DM and CHD in prospective studies (Bazzano 2004). A recent review identified at least 15 studies demonstrating increased satiety, delayed return of hunger, or decreased food intake after consumption of foods with low rather than high GI (Ludwig 2000).

Metabolic and epidemiologic evidence suggested that replacing high GI forms of CHO with low GI CHO would improve glycemic control and reduce the risk of T2DM (Willett et al 2002).

Our department has evaluated a number of traditional Indian diets for their GI which is depicted in Table 2.7. This helps to manage the condition of diabetes mellitus in a better way.

Glycemic Load (GL) assesses the impact of CHO consumption that takes the GI into account, but gives a more accurate picture than does GI alone (Miller 2001). It is defined as the product of the amount of available CHO in that serving and the GI of that food. The higher the glycemic load, the greater the expected rise in blood glucose and in the insulinogenic effect of the food.

Data from many epidemiologic studies have suggested that a high dietary glycemic load from refined CHO increases the risk of CHD, independent of known coronary disease risk factors (Willett et al 2000).

Dietary Fiber

Dietary fibre promotes satiety and weight loss in diabetic patients and thus help in controlling diabetes (Khan and Safdar M 2003). Giacco et al (2000) showed improved measures of glycaemic control in people with diabetes by increasing the dietary fibre content.

TABLE 2.7
GLYCEMIC INDEX OF TRADITIONAL INDIAN RECIPES

No	GI (>80)	GI (60-79)	GI (<60)
1.	Rice Puffed rice	Rice flakes Rice + Peas Rice + Green gram dal	Rice + Bengal gram Rice + Green gram dal (whole) Rice + Red gram
2.	Wheat bhakri Dalia	Wheat bhakri + Fenugreek Wheat bhakri + Spinach	
3.	Rava dhokla Rava + Green gram dal Rava + Bengal gram Rava + Upma	Rava + Green gram dal	
4.	Ragi	Kodri, Jowar Kodri + Green gram dal	Bajra Kodri + Green gram (whole)
5.	Idli, Dosa, Sambhar, Rice	Uttapam, Adai	Pongal, Bisibele bhat, Muthiya, Samosa, Dhebra
6.	Gujarati meal	South Indian, Punjabi, Bengali meals	

Source: Mani et al (1993-1997)

Most soluble fibres (psyllium, oats, oat bran, guar, pectin, and konjac-mannan fibre) are also reported to have hypocholesterolemic effects. Chandalia et al in 2000 illustrated that about 50g of fibre per day improved glycemic control, reduced hyperinsulinemia and decreased plasma lipids (Chandalia et al 2000). In addition, several large prospective cohort studies showed inverse associations between dietary fiber intake and risk of developing T2DM (Marshall et al 1997, Meyer et al 2000, Stevens et al 2002).

Jenkins et al 1977 (Jenkins 1977) have shown that postprandial rise in serum glucose and insulin is reduced with the intake of a high fibre diet. Dietary fibre has a blood-glucose reducing effect as is manifested by a diminished GI. Guar gum possesses distinct hypoglycemic properties (Track et al 1985).

Abnormal glucose tolerance and insulin resistance are related to multiple cardiovascular risk factors, especially reduced HDL cholesterol, elevated serum triglycerides and hypertension (Liese et al 1998). When clustered these abnormalities increase the risk of coronary heart disease morbidity and mortality. In a study by Vuksan et al (2000), a diet rich in konjac-mannan improves glycemic control and lipid profile, suggesting a therapeutic potential in the treatment of insulin resistance syndrome.

Protein

Diabetes Mellitus is basically a disorder of carbohydrate metabolism, but with progression of the disease, protein metabolism is also affected.

People with T2DM have an increased need for protein during moderate hyperglycemia and an altered adaptive mechanism for protein sparing during weight loss. Thus with energy restriction, the protein requirements of people with diabetes may be greater than the recommended dietary allowance (RDA) of 0.8 g protein/kg body weight, although not greater than usual intake, which is ~1.0 g protein/kg body weight (Eely et al 1996). However, individuals consuming very low energy intakes may have a deficiency in protein intake and require an assessment of protein adequacy.

An association between dietary protein intake and the development of renal disease have been suggested. Raal et al (1994), studied the effect of moderate dietary protein restriction on progression of diabetic nephropathy on 22 IDDM subjects. The subjects were randomly assigned to unrestricted protein diet ($>1.6\text{g/kg body wt/d}$) and moderately restricted protein diet (0.8g/kg/body wt/d) for 6 months. The results showed a progressive decline in glomerular filtration rate in subjects with unrestricted protein diet with no change in proteinuria. In the moderately restricted protein diet group there was marked decline in proteinuria and stabilization of glomerular filtration rate. Thus suggesting that protein restriction could ameliorate progression of diabetic nephropathy.

Dietary Fat

Type and amount of fat and fatty acids may have an effect on diabetic complications. Food sources of n-3 polyunsaturated fatty acids include fish, especially fatty fish, as well as plant sources such as flaxseed and flaxseed oil, canola oil, soybean oil, and nuts. N-3 fatty acid supplements have been shown to reduce plasma triglyceride levels, especially in hyper triglyceridemic individuals (Philipson et al 1985), and to have beneficial effects on platelet aggregation and thrombogenicity (Harris et al 1990). Increasing the intake of n-3 polyunsaturated fatty acids has been shown to be beneficial in subjects with diabetes (Montori et al 2000 & Friedberg et al 1998).

The type and amount of dietary fat intake has been associated with insulin sensitivity in animal studies (Storlien et al 1991). Monounsaturated or polyunsaturated fats appear to have beneficial effects on insulin action, whereas saturated fats and diets with high total-fat content appear to decrease insulin sensitivity in animal studies (Storlien et al 1991 and Lardinois and Starich 1991). Several clinical studies have shown a decrease in insulin sensitivity with high fat diets (Hu et al 2001, Swinburn 1993).

Trans fats—unsaturated fatty acids formed when vegetable oils are processed and made more solid (hydrogenation)—are found in some margarine and in food prepared or fried in hydrogenated vegetable oils. When studied

independently of other fatty acids, the effect of trans fatty acids is similar to that of saturated fats in raising plasma LDL cholesterol. Trans fatty acids also lower plasma HDL cholesterol (Ascherio et al 1999 and Judd et al 1994).

LIFESTYLE INTERVENTIONS

The major environmental factors that increase the risk of T2DM are overnutrition and a sedentary lifestyle, with consequent overweight and obesity. Interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycaemia in established T2DM (Look AHEAD Research Group 2007). Weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity (Look AHEAD Research Group 2007, Hadden et al 1975). In lieu of these beneficial effects, a lifestyle intervention programme, promoting weight loss and increasing activity levels should, with rare exceptions, be included as a part of diabetes management.

Various studies like Diabetes prevention Programme (DPP) demonstrated that both medication and lifestyle interventions can delay or prevent progression from IGT to diabetes (Knowler 2002). The study also demonstrated that an intensive lifestyle intervention reduced the incidence of diabetes by 58% compared to 31% reduction by metformin intervention. The Da Qing study (Pan et al 1997) compared diet, exercise and diet plus exercise with a no treatment control group and found that all three lifestyle approaches reduced the risk of developing diabetes by 31-46%. The Finnish Diabetes Prevention Study (Tuomilhto et al 2001) of 522 overweight subjects with IGT showed that a lifestyle intervention designed to produce weight loss by improved dietary intake and physical activity reduced the risk of diabetes by 58%. The prospective study on the association between regular exercise and the subsequent development of diabetes in the US male physicians demonstrates that exercise reduces the development of diabetes even after adjusting for BMI (Manson et al 1992). In the Malmö study (Eriksson and Lindgarde 1991), BMI decreased by 2.4% in the intervention group and only

10.6% of the intervention group developed diabetes over 5 years compared with 28.6% of the control group.

PHYSICAL ACTIVITY / EXERCISE

Physical inactivity which is now recognized as an increasingly important determinant of health, is a result of a progressive shift of lifestyle towards more sedentary patterns, in the developing countries as much as developed ones. Exercise has many benefits and many studies have shown that regular physical activity improves quality of life from psychological to physical with weight stability and reduces the risk of mortality from all causes (Klein 2004) and is particularly advantageous in subjects with impaired glucose tolerance (Knowler 2002, Tuomilhto 2001). Physical activity is an effective cost saving tool in the care of diabetes (Loreto Di 2003).

Helmrich and colleagues examined leisure-time physical activity and development of diabetes among 5,990 male alumni of the University of Pennsylvania over 14 years. They discovered that men who exercised regularly, at moderate or vigorous intensity, had a 35% lower risk of developing T2DM than men who were sedentary (Helmrich et al 1991).

INDIGENOUS FOODS IN THE MANAGEMENT OF DIABETES

Fenugreek Seeds (*Trigonella foenum graecum*)

Trigonella foenum graecum is a commonly used herb in Ayurveda. Defatted seeds of fenugreek, which are rich in fiber, saponins, and protein, have been described in early Greek and Latin pharmacopoeias for hyperglycemia. Purported mechanisms include delay of gastric emptying, slowing carbohydrate absorption, and inhibition of glucose transport from the fiber content, as well as increased erythrocyte insulin receptors and modulation of peripheral glucose utilization.

Kuppu et al (1998) & Sharma (1996) studied the impact of fenugreek supplementation on diabetic subjects. The results showed a significant reduction in blood glucose levels indicating improvement in glucose tolerance.

Fenugreek seeds also has antioxidant property as seen in diabetic rats (Ravikumar & Anuradha 1999).

In another study in diabetics by Neeraja and Rajyalaxmi in 1996, raw and germinated seeds confirmed the hypoglycemic effect (Neeraja and Rajyalaxmi, 1996).

Bharadwaj et al (1994) observed the effective reduction of LDL cholesterol by indigenous plant product. A herbal powder containing guar-gum (*Cyamopsis tetragonoloba*), methi (*Trigonella foenum-graecum*), tumbdika (*Cephalandra indica*) was administered to 30 control and 30 NIDDM patients for a month. Total and LDL cholesterol were significantly lower after treatment.

Bitter Melon (*Momordica charantia*)

Welhinda et al (1986) reported that when *Momordica charantia* (Bitter gourd) was given to newly diagnosed Type 2 diabetics in the form of a juice, as a single experimental dose prior to glucose tolerance test, a fall in the post prandial glucose was observed.

Theoretical mechanisms include increased insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis.

Srivastava et al (1993) reported that 3-7 weeks treatment of diabetics with powdered fruit, led to a mean fall of 25% (range 11-48%) in post-prandial blood glucose levels. There was a marked fall in both blood and urine sugar over 7 weeks in a group treated with an aqueous extract of the fruit. Glycosylated haemoglobin showed a significant reduction by the end of the trial. Oral administration of powdered karela seeds produced a significant reduction in post-prandial blood sugar values in 14 NIDDM and 6 IDDM patients (Grover and Gupta 1990).

Curry Leaves

Iyer & Mani (1989) studied the effects of curry leaves on the lipid profile, glycated proteins and amino acid profile in 30 NIDDM patients. The results depicted a transient decrease in fasting and post prandial sugars without much change in the other parameters.

Spirulina

In a study on NIDDM subjects, Spirulina supplementation for a period of two months at a level of 2g/day brought about a significant reduction in fasting and post prandial glucose levels. It also brought about a lowering in HbA1c levels, total cholesterol and LDL cholesterol. There was a favourable increase in the ratio of apolipoprotein A1:B with reduction in the atherogenic indices (Parikh et al 2001).

Tulsi Leaves (*Ocimum sanctum*)

Ocimum sanctum (holy basil) is another commonly used herb in Ayurveda. Tulsi or basil is used as antidepressant, anti-inflammatory, antimicrobial and anti spasmodic since many years. It is an aromatic herb and is often used for culinary purposes.

Studies in animal models suggest hypoglycemic effects (Chattopadhyay 1993). Supplementation of Tulsi powder at 1% level to diabetic rats for a period of 1 month brought about a significant reduction in FBS, Uronic acid, Total aminoacids, Plasma lipids and TC levels thus indicating hypoglycemic and hypolipemic effects of Tulsi (Rai et al 1997).

Postulated effects include enhanced β -cell function and insulin secretion. A controlled clinical trial of *Ocimum sanctum* (n = 40) showed positive effects on both fasting and postprandial glucose in patients with T2DM using a local preparation of fresh leaf powder mixed in water for 4 weeks (Agrawal et al 1996).

In an experimental model of isoproterenol (ISP) induced myocardial necrosis in wistar rats, supplementation with *Ocimum sanctum* showed a cardioprotective effect against myocardial necrosis (Arya et al 2006).

Allium Species

Allium sativum (garlic) is most commonly used worldwide for flavorful cooking. Moderate reductions in blood glucose have been found with experiments in animal models with alloxan-induced diabetes (Sheela et al 1992). Reported mechanisms of allium species include increased secretion or slowed degradation of insulin, increased glutathione peroxidase activity, and improved liver glycogen storage (Shane-McWhorter 2001, Bailey and Day 1989). A trial of garlic in patients with T2DM (n=33) did not find consistent glucose or insulin responses after 1 month of supplementation (Sitprija et al 1987). In a RCT of *Allium sativum* in humans that was actually designed to examine thrombocyte aggregation in nondiabetic individuals (n = 60), the investigators found significant decreases in fasting serum glucose (Keisewetter et al 1991).

In a study by Campos et al (2003), streptozotocin induced rats were treated with *Allium cepa* (onion). The findings of the study showed that hypoglycemic and hypolipemic actions of onion were associated with antioxidant activity. Onion also brought about an increase in HDL cholesterol.

Gymnema Sylvestre

Gymnema sylvestre is another commonly used herb in Ayurveda. According to common folklore, chewing the leaves causes a loss of sweet taste, hence the popular Hindi name of the plant "gurmar," meaning "destroyer of sugar." Studies of an ethanol leaf extract, GS4, in diabetic rat and rabbit models have reported regeneration of islets of Langerhans, decreases in blood glucose, and increases of serum insulin (Shanmugasundaram et al 1990). Postulated theories for mechanism of action include an increase in glucose uptake and utilization, increase in insulin release through cell permeability, increase in β -cell number, and stimulation of β -cell function (Shane-McWhorter 2001,

Persaud 1999). Trials in groups of patients with type 1 diabetes (n =64) and T2DM (n = 47) showed improved glycemic control with chronic adjunctive use of GS4 extract compared with those who received conventional treatment alone (Shanmugasundaram et al 1990, Baskaran et al 1990).

In another study, the antioxidative potential of *Momordica charantia*, *Azadiracthta indica*, *Allium sativum* and *Ocimum sanctum* was assessed in streptozotocin induced diabetic rats. Lipid peroxide levels were also measured in normal, diabetic and treated animals. Malonaldehyde (MDA) levels were significantly higher and antioxidant activity was found to be low in diabetic groups as compared with the control groups, and significant alteration in both the MDA levels and antioxidant activity was observed when above herbal hypoglycaemic agents were given to diabetic rats. On the basis of the results the researchers concluded that *M. charantia*, *A. Indica*, *A. sativum* and *O. sanctum* are not only useful in controlling lipid peroxide levels but are also helpful in further strengthening the antioxidant potential (Mahdi et al 2003).

Fruits and Vegetables

Intake of fruits and vegetables have been associated with a reduced risk of non communicable diseases. A prospective study by Joshipura et al (1999) showed that consumption of 6 servings daily of fruits and vegetables was associated with a 30% reduction in the risk of ischemic stroke among men and women. The study also controlled lifestyle confounders, and found out that green leafy and cruciferous vegetables and citrus fruits and juice, in particular, were protective in nature.

La Vecchia et al (1998) reported a high intake of fruits and vegetables associated with a decreased prevalence of heart attacks and angina pectoris. Klerk et al (2000) reported that increasing the consumption of fruits and vegetables could reduce the incidence of cancer and cardiovascular deaths.

Fruit and vegetables have been shown to decrease LDL cholesterol concentrations in humans. In Dietary Approaches to Stop Hypertension (DASH) trial, a diet high in fruits and vegetables was associated with a

reduction in LDL cholesterol compared to a control diet. However the association did not reach standard levels of statistical significance (Obarzanek 2001). In the Indian Diet Heart study, fruit and vegetable consumption decreased LDL-cholesterol concentrations by approximately 7% (Singh et al 1992).

Recently, in the US National Heart, Lung and Blood Institute Family Heart Study, the consumption of fruits and vegetables was inversely related to LDL-cholesterol concentrations in men and women (Djousse et al 2004).

A recent report of 1710 men, aged 41-57 years who were followed for 40 years, demonstrated that intake of fruit and vegetables was inversely associated with an age related rise in blood pressure over the course of study (Miura et al 2004).

Singh (1993) conducted a RCT examining the effects of supplementing the guava fruit in the diet of 72 participants. They found a significant decrease in mean systolic and diastolic pressures (7.5/ 8.5 mm Hg net decrease respectively) among participants of the guava supplemented diets.

Antioxidants are substances that inactivate reactive oxygen species and therefore significantly delay or prevent oxidative damage. Fruits, including berries, and vegetables are rich sources of antioxidants such as vitamin E, vitamin C, polyphenols, flavonoids and carotenoids.

Vinson et al in the year 2001 found that the combination of citrus extract and vitamin C produced a synergistic antioxidant effect in an in vitro lipoprotein oxidation model. They conducted a double blind placebo controlled study with 26 normal and hypercholesterolemic subjects. The citrus extract and vitamin C, but not vitamin C or vitamin E alone, significantly lowered triglycerides. The combination of citrus extract and vitamin C increased the lag time of lipoprotein oxidation, compared with vitamin C alone or a placebo; and was significantly better antioxidant than vitamin E.

Cambridge Heart Antioxidant Study (CHAOS), results demonstrated that daily Vitamin E (400 mg or 800 mg alpha-tocopherol) decreased the risk (relative risk 0.53) of subsequent nonfatal myocardial infarction in cardiac patients (Stephens 1996). In a cohort study by Feskens et al (1995) vitamin C was inversely related to the incidence of diabetes and impaired glucose tolerance

Singhal and colleagues (2001) conducted a RCT on 175 patients, out of which the 1st group was given 400 units a day of vitamin E, 2nd group of patients received 1000 mg of vitamin C, 3rd group was given 25,000 IU daily of vitamin A and the 4th group received 400 grams of fresh fruit daily for 30 days. They found that lipid peroxide decreased significantly in all the treatment groups. The group receiving fruits had significantly decreased cholesterol levels and LDL cholesterol, and increase in HDL cholesterol levels. They concluded that all the antioxidant vitamins and fruit decrease the degree of lipid peroxidation in CHD patients. However fresh fruit came out to be best choice as it also favourably modified the lipid profile.

Khaw et al in year 2001 found out from EPIC Norfolk prospective study that plasma ascorbic acid concentration was inversely related to mortality from all causes, and from cardiovascular disease, and ischaemic heart disease in men and women. Risk of mortality in the top ascorbic acid quintile was about half the risk in the lowest quintile ($p < 0.0001$). The relation with mortality was continuous through the whole distribution of ascorbic acid concentrations. A 20 $\mu\text{mol/L}$ rise in plasma ascorbic acid concentration, was equivalent to about 50 g per day increase in fruit and vegetable intake and was associated with about a 20% reduction in risk of all cause mortality, independent of age, systolic blood pressure blood cholesterol, cigarette smoking habit, diabetes and supplement use. The interpretation from the study was that small increase in fruit and vegetable of about one serving daily had encouraging prospects for prevention of cardiovascular disease.

Flavonoids are large group of polyphenolic antioxidants that occur naturally in vegetables and fruits (Vinson 2001). The most abundant flavonoids in the diet

are flavanols (catechins plus proanthocyanidins), anthocyanins and their oxidation products (Scalbert and Williamson 2000).

The Zutphen Elderly Study in year 1993 showed the association of flavonoid intake and lower rate of CHD. The study revealed that when the flavonoid intake was less than 19 mg/day, the CHD mortality rate was 18.5/1000 persons per year which decreased significantly to 7.8/1000 persons per year, when the flavonoid intake was increased to more than 30 mg/day (Hertog 1993).

The seven-country study in year 1995 also strengthens the association of flavonoid intake and lower rate of CHD. The results of this study suggested that people with very low intakes of flavonoids had higher risks of coronary diseases (Hertog 1995).

Garden Cress Seeds (*Lepidium sativum*)

Garden cress seeds (GCS) have been considered for their anti cancer, anti hypertensive, anti asthmatic, hypoglycemic, fracture healing properties etc. In a study on animal models it was seen that GCS at a dose of 10 mg/kg/h reduced blood glucose levels both in normal and diabetic rats. At the same time as a potent increase of glycosuria was observed both in normal and diabetic rats. Thus it can be concluded that the aqueous GCS extract can cause a potent inhibition of renal glucose reabsorption which in turn reduced blood sugar (Eddouks et al 2005). This renal effect can be said as one of the mechanisms explaining the observed hypoglycaemic activity of GCS in normal and diabetic rats without affecting basal plasma insulin concentrations. The effect of *L. sativum* seeds was studied on in vitro rate of starch hydrolysis for testing their potential to slow down the hydrolysis of starch to glucose in diabetic patients. GCS were found to reduce starch hydrolysis by 41%. When tested on 11 NIDDM and 14 normal subjects, the seeds were found to significantly lower glucose response to meal in both normal and diabetics. Further diabetics showed higher reductions than healthy subjects. In the long term treatment of diabetics with 15 g/day of *L. sativum*, 9 out of 11 subjects

showed reduction in levels of blood glucose from 10.2 mM/l to 8.3 mM/l at the end of the study (Patole 1998).

The antihypertensive and diuretic effects of the aqueous extract of *L.sativum* were studied both in normotensive and spontaneously hypertensive rats. Daily aqueous extract led to reduction in the systolic blood pressure significantly from 7th day to the end of treatment in SHR rats (Maghrani et al 2005).

The chemo protective effects have been seen through action on detoxification of toxins with the supplementation of 5% GCS juice in rats (Kassie et al 2002).

GCS are known to be an excellent source of dietary iron and hence several studies have been carried out to supplement GCS as a source to improve the hemoglobin status. On supplementation with a laddoo made with GCS along with other ingredients for 60 days among school children showed marked increase in Hb levels. In another study carried out in the department among anemic women, significant rise in Hb status was noted (0.99g/dl) with supplementation of chikki made with GCS and niger seeds at the level of 60g/day (Sharma & Garg 2002). The anti asthmatic activity of GCS powder has been demonstrated on subjects with asthma through a improvement in pulmonary function tests and clinical symptoms as well as severity of the symptoms with daily consumption of 3g GCS powder (Paranjape and Mehta 2006).

In a study by Iyer et al (2009) on T2DM subjects, a nonsignificant reduction of 4.76% in GHb values and maintenance of lipid levels was noted with supplementation of GCS khakhra (at a level of 3g GCS/day) for a period of 28 days. It was observed that 25% of the diabetic subjects attained normal metabolic control and lipid levels post supplementation.

Embilica officinalis

Amla (*Embilica officinalis*) is an important source of Vitamin C, minerals and amino acids. As a very important source of vitamin C, this is one of the major

ingredients of the famous tonic Chavanaprasam and can also help to improve intelligence and memory power.

A study by Rao et al (2005) on streptozotocin induced diabetic rats showed that amla supplementation reduced oxidative stress and also improved adiponectin levels.

Aldose reductase (AR) is involved in the development of secondary complications of diabetes including cataract. Ascorbic acid and tannoids present in amla were found to be responsible for the inhibition of AR. The inhibition of AR by *E. officinalis* tannoids is 100 times higher than its aqueous extract and comparable to or better than quercetin (Suryanarayana et al 2004).

Shah and Iyer (2003) investigated the effect of ascorbic acid rich fruits amla and guava in hyperlipidemias. There was no significant difference found with guava supplementation however a significant lowering in TC, LDL and Non HDL levels was observed in amla group. In another study by Iyer et al (2009), 60 days of supplementation with amla brought about a significant reduction in lipid levels in Type 2 diabetics. Encouraging results were seen in subjects with higher initial FBS levels.

TRIPHALA, an ayurvedic formulation, is an equiproportional mixture of fruits of three medicinal herbs, amalaki (*Emblica officinalis*), haritaki (*Terminalia chebula*) and bibhitaki (*Terminalia bellerica*) (Kulkarni et al 1995). According to the traditional Indian medicinal system (Ayurveda), triphala strengthens the different tissues of the body, prevents ageing, and promotes health and immunity. It corrects constipation, cleanses and tonifies the gastrointestinal tract and also detoxifies the whole body, and improves digestion and assimilation. It exhibits anti-viral, anti-bacterial, anti-fungal and anti-allergic properties (Singh 2003). Triphala and its constituents act as cardio-tonic, control blood pressure, improve blood circulation and reduce cholesterol levels. Triphala is also a free-radical scavenger (Naik et al 2006).

Soyabean

Soybean foods represent an excellent source of high quality protein, are low in saturated fat, and are cholesterol free (Messina 1999). Soybeans have a low glycemic index (Jenkins et al 1981). A soybean diet may be a good option in T2DM individuals due to its effect on hypertension, hypercholesterolemia, atherosclerosis and obesity, which are very common diseases in diabetic patients (Mateos-Aparicio et al 2008).

Soybeans are rich in phytates, soluble fiber, and tannins, all of which correlate inversely with carbohydrate digestion and glycemic response (Liener 1994). It is generally accepted that a high fibre diet, particularly soluble fibre, is useful to control plasma glucose concentration in diabetics. In subjects with glucose intolerance, soy-fiber supplementation improved glucose tolerance and insulin response (Lo 1986).

A metaanalysis on soybean revealed that the substitution in the diet of animal protein for soybean protein, reduces the concentration of total cholesterol, low-density lipoprotein cholesterol and triglycerides (Anderson et al 1995).

Substituting animal protein for soybean or other vegetable protein may also decrease renal hyperfiltration, proteinuria, and renal acid load and therefore reduces the risk of renal disease in T2DM (Jenkins et al 2003). **In a study in Korean T2DM soybean-derived pinitol significantly decreased mean fasting plasma glucose, insulin, fructosamine, HbA_{1c}, HOMA-IR, total cholesterol, LDL-cholesterol, LDL/HDL-cholesterol ratio, and systolic and diastolic blood pressure and increased HDL-cholesterol (Kim et al 2005).**

Thus, a number of indigenous products have shown hypoglycemic and hypolipidemic effects. Efforts are on to find out newer products and to test their efficacy in the management of diabetes mellitus. One of the newer products is barley grass.

BARLEY GRASS

Barley grass consists of the young green leaves of the barley plant. Barley plants can grow under a wide range of soil and climatic conditions. Barley grass is at its nutritional peak before the plant begins to produce flowers and seeds. Harvesting takes place approximately 2 weeks after seeding. At this stage of development, the young grass contains vitamins and minerals similar to those of dark green vegetables. Barley grass is available commercially in dried and powdered form prepared from the whole leaves or juice obtained by milling the leaves (www.drugs.com).

History

The science of life, Ayurveda, which evolved in ancient India, was designed not only to treat diseases, but also emphasized the ways to prevent and manage long term chronic health problems. The ancient Indian physicians were able to stabilize diabetes effectively, type-II diabetes in particular, by advocating weight loss, dietary formulations and exercises like in the case of modern medicine. In the case of diet, barley (यव, yava – *Hordeum vulgare* Linn.), one of the oldest cultivated grains found prime importance as a substitute for other foodgrains. More than 2800 years ago, the Indian physician Charaka mentioned that 'use of parched barley grains and its flour (Sattoo) prevents the development of diabetes' according to the verse (Ch.Chi.6.48) from Charaka Samhita:

‘भृष्टान् यवान् भक्षयतः प्रयोगाच्छुष्कांश्च सक्तून् भवन्ति मेहाः’

Use of barley in diabetes as described in Charaka Samhita

‘सषष्टिकां स्यात्तृणधान्यमन्नं यवप्रधानस्तु भवेत् प्रमेही.

यवस्य भक्ष्यान् विविधांस्तथाध्यात् कफप्रमेही मधुसंप्रयुक्तान्’

The verse (Ch.Chi.6.21) mentions that ‘the diet of diabetic patients should consist predominantly of barley, wherein various food items should be prepared along with different wild varieties of rice. In the primary stages of

diabetes development, a person should take honey also along with various food items prepared with barley'.

Moran observed that the ancient Greeks (AD 45–117) were the first to advocate diet and lifestyle management for individuals with diabetes. Barley is considered to be the first cereal grain cultivated by humans. Ancient Asian and Middle Eastern cultures reportedly included young wheat and barley grass plants in their diets. In the early part of the 20th century, the roles of cereal grains and vitamins in nutrition were investigated. For example, chickens fed a 10% mixture of cereal grass responded well in growth, appeared to have increased resistance to degenerative diseases, and increased winter egg production. Further studies concerning “grass juice factor,” a water-soluble extract of grass juice, found several beneficial growth and health effects from its supplementation in animal diets. A dehydrated preparation of cereal grass called cerophyl was approved as an “accepted food” by the Council of Foods of the American Medical Association in 1939 (Tiwari 2008, www.drugs.com).

Chemistry

A wide spectrum of vitamins, minerals, amino acids, and enzymes and other phytochemicals have been isolated from barley grass. It is particularly rich in beta-carotene, calcium, iron, and vitamin C, and contains abundant chlorophyll. Other vitamins, electrolytes (eg, potassium, phosphorus, magnesium), and minerals isolated from the plant in substantial quantities include vitamins B₁, B₂, B₆, B₁₂, pantothenic acid, and folic acid. Also of note are enzymes, particularly the antioxidant enzyme superoxide dismutase, and nitrogen reductase.

Green barley essence is said to provide a high quantity and good balance of minerals. It has almost 25 times the K of wheat, 37 times the Ca, more than twice the Mg, 5 times the iron. It also contains significant amounts of Mn and Zn. It has an extremely high percentage of alkalinity. Spinach, the most popular alkaline food has an alkalinity of 39.6, whereas the alkalinity of green barley essence is as high as 66.4. Protein comprises about 45% by weight of

the ingredients of green barley essence in comparison to only 10% in wheat flour. Extracts from the green leaves of barley were found to contain large amounts of essential fatty acids like linoleic acid and linolenic acid and also essential amino acids such as valine, leucine, isoleucine, phenylalanine, threonine and methionine. Green barley essence contains numerous enzymes like cytochrome oxidase, peroxidase, catalase, fatty acid oxidase, transhydrogenase, nitrogen oxyreductase and aspartate aminotransferase, superoxide dismutase (Hagiwara 1986).

Biologists identified a substance called P4D1 in barley grass. This substance not only had strong anti-inflammatory action but was shown to actually repair the DNA in the cells of the body. This aided in the prevention of carcinogenesis, aging, and cell death. It was reported that P4D1 suppresses or cures pancreatitis, stomatitis, inflammation of the oral cavity, and dermatitis, and also lacerations of the stomach and duodenum.

Besides chlorophyll and a myriad of vitamins, minerals and enzymes, barley grass is said to have 30 times as much vitamin B1 as in milk, 3.3 times as much vitamin C, 6.5 times as much carotene as in spinach, 11 times the amount of calcium in cow's milk, nearly five times the iron content of spinach, nearly seven times the vitamin C in oranges, four times the vitamin B1 in whole wheat flour, 80 micrograms of vitamin B12 per 100 grams of dried barley plant juice. Dried barley grass juice was found to contain per 100 grams: 775 Na, 8,800 K, 1,108 Ca, 224.7 Mg, 15.8 Fe, 1.36 Cu, 534 P, 7.33 Zn (www.theolife.com).

Young green parts of barley plants, as a potential source of nutritionally valuable substances, were analysed for the contents of vitamin C, total polyphenols, phenolic compounds, amino acids, and saccharides, and for the activity of catalase (Paulířková et al 2007). The contents of vitamin C, total polyphenols, and ferulic acid decreased with the age of barley plants. The influence of the variety has not been proved unequivocally. The contents of vitamin C between 0.107–6.357 g/kg dry matter (DM), of total polyphenols between 17.167–35.559 g/kg DM, and of ferulic acid between 0– 5.916 g/kg

DM were found. Catalase activity amounted to 4.5–29.7 TSU. The monosaccharide profile showed high contents of glucose (15.40–88.40 g/kg DM) and fructose (37.60–81.40 g/kg DM) which decreased with the plant growth. The contents of saccharose and galactose were low, ranging between 0–7.70 g/kg DM and 3.70–5.30 g/kg DM, respectively. The relations between their contents and the growth phase were insignificant. The total amino acid content decreased with the plant age. High contents of aspartic (15.232–28.682 g/kg DM) and glutamic acids (16.694–35.526 g/kg DM), as well as minimal contents of sulphur amino acids, especially methionine (2.586–5.03 g per kg DM), could be noted. The highest catalase activity was found in the early growth phase (18.5–35.1 TSU). The yield of juice pressed out from frozen green matter amounted to 68%. The pressed out juice was preserved by fluid drying, freeze drying, and freezing. In respect to folates and total polyphenols contents and the antioxidant activity, freezing was the most suitable procedure for preserving. The results also indicated that the contents of nutritional substances were strongly dependent on the growth phase; the barley variety and the growth site appeared to be less important.

The phenolic profile of barley (*Hordeum vulgare* L.) leaves, seeds, awns, and stems, collected from two different locations in Portugal, was determined by a high-performance liquid chromatography/diode array detector (HPLC/DAD). A total of 28 compounds were identified and quantified, which included 4 phenolic acids, 6 C-glycosylflavones, and 18 O-glycosyl-C-glycosyl flavones, with some of them acylated. The greatest diversity of compounds was found in barley leaves (26 flavonoids and 2 phenolic acid derivatives), which also exhibited the highest concentration of phenolics. Isoorientin-7-O-glucoside (lutonarin) was the major compound in leaves. The authors thus concluded that barley leaves may constitute an important dietary source of protective compounds (Ferrerres et al 2009).

Barley Grass Uses and Pharmacology

Many claims have been made regarding the health benefits of barley grass supplements. Suggested benefits include prevention and cure of cancer, treatment of HIV infection, cholesterol lowering, detoxification of pollutants,

protection against solar and other forms of radiation, and boosting energy and immunity. Barley grass has antiinflammatory, deodourizing, germicidal, invigorating properties. It promotes cell growth and prevents deposition of cholesterol on arterial walls

Green barley essence supposedly promotes the best functioning of the body rather than targeting a specific condition or symptom. Ailments where green barley essence has been found to be beneficial include obesity, asthma, eczema and other skin problems, anemia, fasting, reduced potency, constipation, lumbago, gastritis, diabetes, high blood pressure, low blood pressure, heart disease, nephrosis, hepatitis, cancer, liver diseases, leukemia, atopic dermatitis, pancreatitis, peptic ulcer, pimples, skin roughening, hair loss, constipation, hyperacidity, inflammation, circulatory insufficiency, irritability, allergies, tooth problems, near-sightedness, alcohol problems, flu and colds, rheumatism, arthritis, Alzheimer's disease, backaches, edema, osteoporosis, sleep disorders, burns, migraines, multiple sclerosis, depression, menopausal complaints, menstrual problems, leg cramps, Parkinson's disease, warts, lack of hydrochloric acid (anacidity), neurosis and symptoms of premature ageing (Hagiwara 1986). However, objective evidence supporting many of these claims is lacking.

Clinical experiments with 25 dermatologic patients tested found that those who took green barley essence recovered earlier than those who did not. Improvement of blood flow, bowel movement, appetite and recovery from fatigue were also observed (Hagiwara 1986).

Diabetics are at a higher risk of developing coronary artery disease and peripheral atherosclerosis than the general population. Patients with T2DM often have elevated levels of TG and small, dense LDL (Sd-LDL) along with lower levels of HDL cholesterol. The particles of Sd-LDL ($d = 1.040\text{--}1.054$ g/ml) are more susceptible to oxidation than larger, buoyant LDL (B-LDL) because both their entry into and retention within the artery walls are greater than those of larger lipoprotein particles. Hyperglycemia is commonly associated with increased oxidative changes in LDL. Metabolic changes

caused by hyperglycemia include increased polyol pathway flux, elevated oxygen free radical formation, and advanced glycosylation. These factors appear to accelerate red blood cell hemolysis and plasma LDL oxidation (Yu et al 2002, Krauss 2004).

Natural plant flavonoids, saponarin/lutonarin = 4.5/1, isolated from young green barley leaves were examined for their antioxidant activity using cod liver oil, ω -3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid), phospholipids (lecithin I and II), and blood plasma. The saponarin/lutonarin mixture inhibited malonaldehyde formation from cod liver oil, eicosapentaenoic acid, docosahexaenoic acid, lecithin I, lecithin II and blood plasma by $85.88 \pm 0.12\%$, 45.60 ± 1.08 , $69.24 \pm 0.24\%$, 43.08 ± 0.72 , $69.16 \pm 2.92\%$ and $62.20 \pm 0.11\%$, respectively, at a level of 8 μ mol. The antioxidant activities obtained from the saponarin/lutonarin mixture were comparable to those obtained from α -tocopherol and butylated hydroxy toluene (BHT) in all lipids tested (Benedet et al 2007).

Reactive oxygen species have been shown to play an important part in mediating the production of proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α). The ability of barley leaf extract to scavenge free radicals is thought to derive from the presence of polyphenolic compounds. This phenolic moiety of the structure can donate hydrogen atoms to deleterious oxy radicals and form the less-reactive phenoxyl radicals in the process (Yu et al 2002). Green barley extracts, in particular a purified extract containing micromolecular substances less than 1 kDa, have shown in vitro inhibitory actions on TNF- α from peripheral blood and synovial fluid of patients with rheumatoid arthritis (Cremer 1998).

Yu et al (2002) evaluated the effects of supplementation of young barley leaf extract (BL) and/or antioxidative vitamins C and E on different low-density lipoprotein (LDL) subfractions susceptibility to oxidation and free radical scavenging activities in patients with T2DM. For the study thirty-six type 2 diabetic patients were enrolled. The subjects received one of the following supplements daily for 4 weeks: 15 g BL, 200 mg vitamin C and 200 mg

vitamin E (CE), or BL plus CE (BL + CE). Following supplementation participants in all the groups had significantly decreased levels of plasma TC and LDL-C. The vitamin E contents in the LDL subfractions were increased significantly following supplementation with each antioxidant treatment. Lag times of B-LDL and Sd- LDL increased significantly at week 4 as compared to week 0 in all the three groups. The lucigenin-chemiluminescence and luminol-chemiluminescence levels in blood were significantly reduced after 4 weeks of BL, CE or BL + CE supplementation. This indicates that BL acts as an oxygen radical scavenger. Its ability to scavenge free radicals may be derived from the polyphenolic structure of BL.

The antioxidative and hypolipidemic effects of barley leaf essence (BL) were investigated in a rabbit model of atherosclerosis (Yu et al 2002). Twenty-four New Zealand White male rabbits were assigned randomly into four dietary groups. The normal group was fed regular rabbit chow and the control group was fed a chow containing 0.5% cholesterol and 10% corn oil. The BL group and the probucol group were fed the same diet as the control group plus 1% (w /w) BL or 1% (w/w) probucol, respectively. After consumption of the experimental diets for 12 weeks, the plasma levels of total cholesterol, triacylglycerol and LDL were decreased in the BL group and the probucol group compared to the control group. The lucigenin-CL and luminol-CL levels in whole blood were higher in the control group than in the normal group and lower in the BL group and the probucol group than in the control group. However, these differences were not significant. In the BL group and probucol group, post-experimental T50 (the time required to achieve 50% RBC hemolysis) and lag phase of LDL oxidation were significantly higher than in the control group. Ninety percent of the intimal surface of the thoracic aorta was covered with atherosclerotic lesions in the control group, but only 60% of the surface was covered in the BL group. The authors concluded that this 30% inhibition of hyperlipidemic atherosclerosis by BL was associated with a decrease in plasma lipids and an increase in antioxidative abilities. These results suggest that the antioxidant and hypolipidemic effects of BL could be useful in the prevention of cardiovascular disease in which atherosclerosis is important.

In another study forty hyperlipidemic patients, smokers and non-smokers, were studied. Subjects received 15 g young barley leaf extract (BL) or 60 g adlay daily for four weeks. The plasma total and LDL-cholesterol (LDL-C) levels were reduced following treatment with either BL or adlay. Further, the lag phase of LDL oxidation increased after either supplementation. However, it seemed that BL had stronger antioxidative effect on the prevention of LDL oxidation than adlay. The results also indicated that the antioxidative effect was less pronounced in smokers than in non-smokers (Yu et al 2004).

Another study evaluated whether supplementation of patients with T2DM with an olive oil-enriched diet and young barley leaf essence for 4 weeks affected the susceptibility of different low-density lipoprotein (LDL) subfractions to oxidation and free radical activity. Thirty type 2 diabetic patients were randomly assigned to 3 groups. The first group of subjects (controls) received placebo only. The second group of subjects received 15 g of barley leaf essence. The third group received an olive oil-enriched diet plus 15 g of barley leaf essence. There were no changes in fatty acid composition of the LDL particles in either the barley leaf essence group or the control group. The olive oil-enriched diet induced fatty acid composition changes, increasing oleic acid and decreasing linoleic acid significantly. The vitamin E content and lag times of LDL subfractions of both test groups increased significantly compared to the control group. The addition of olive oil to the diet increased further the vitamin E content and lag time, and decreased the ΔA_{234} levels of B-LDL and Sd-LDL. The blood lucigenin-CL and luminol-CL levels were significantly reduced in both test groups compared with the control group. Thus, supplementation with barley leaf essence may help to scavenge oxygen free radicals and inhibit LDL oxidation (Yu and Tsai 2003).

Cholesterol-lowering effects have been attributed to the hexacosyl alcohol and β -sitosterol fractions of barley leaf extract. β -sitosterol is thought to act by inhibiting the intestinal absorption of cholesterol and accelerating its catabolism to bile acid. The mechanism of action of hexacosyl alcohol remains unclear.

Ohtake et al (1985) studied the hypocholesterolemic effects of green juice from young barley leaves on hypercholesterolemia in rats fed on a high cholesterol diet (HCD). The n-hexane extract from a water insoluble fraction of green juice showed hypocholesterolemic activity. Two substances responsible for the hypocholesterolemic effects were isolated from the n-hexane extract and purified by silica gel chromatography. One of them was β -sitosterol, and the other n-hexacosyl alcohol. In the rats fed on HCD added with n-hexacosyl alcohol at a concentration of 1%, the plasma cholesterol level was hardly lowered on day 3 but markedly on day 9. In a similar experiment, β -sitosterol markedly lowered the plasma cholesterol level of rats on both day 3 and day 9. Through these experiments, the authors concluded that barley leaves contained hypocholesterolemic substances, and that two compounds such as β -sitosterol and n-hexacosyl alcohol were responsible for the hypocholesterolemic activity.

Tsai et al (2005) investigated the effect of young barley leaf essence (BL) on serum lipids. Seventy-two Syrian hamsters were randomly divided into 6 dietary groups fed one of the following diets for 6 weeks : -tocopherol (150 mg/kg diet), with 1%, 3% or 5% BL, or a blank (control) in a high-fat (14%) high-cholesterol (0.2%) diet, or a low-fat diet (rat chow). Results demonstrated that ingestion of 3% or 5% BL significantly reduced the levels of serum triacylglycerol, total cholesterol and low-density lipoprotein-cholesterol (LDL-C), and enhanced the HDL-C/LDL-C ratio.

Antiulcer activity of green juice from young barley leaves and of fractions from the green juice was examined in another study. Fractions containing water soluble proteins and water soluble organic compounds showed significant antiulcer activity in the stress, acetic acid and aspirin induced stomach ulcer at an oral dose of 500 mg/kg. A fraction containing water insoluble substances also showed antiulcer activity in the stress and acetic acid induced ulcer. It was observed that those fractions affected neither the secretion of acid and pepsin from the stomach nor the absorption of aspirin from the gastrointestinal tract. Findings of the study suggested that the antiulcer action of the fractions

may be due to the protection of the stomach mucosa from injury by attacking factors (Ohtake et al 1985).

Thus various studies have highlighted the following:

1. Barley grass is a treasure house of various nutrients and bioactive compounds.
2. Barley grass has antioxidative properties.
3. Barley grass has shown hypolipidemic properties.

Overall knowledge gaps identified from the review of literature are:

1. A number of risk factors have been identified for diabetes mellitus. However, risk factor profile of type 2 diabetics who visit pathology labs is not available.
2. Prevalence data of MAU in T2DM subjects visiting pathological labs is scanty.
3. Tracking of industrial T2DM subjects for dyslipidemia and blood pressure measurements have not been investigated so far.
4. Food product development in the Indian context and sensory evaluation of products with barley grass powder have not been attempted so far.
5. Indepth intervention trials with barley grass powder in the management of T2DM have not been studied so far.

Thus the present study made an attempt to address the above issues.