1.1 BACKGROUND

Metabolic syndrome (MS), comprising a spectrum of chronic disease risk factors that include abdominal obesity, dyslipidemia, hypertension, and elevated fasting plasma glucose (Reaven 1991). Over the past two decades, a striking increase in the number of people with the metabolic syndrome worldwide has taken place. This increase is associated with the global epidemic of obesity and diabetes (Robert et al 2001). Different terminologies used for metabolic syndrome are as follows:

- Beer-Belly syndrome
- Atherothrombogenic syndrome
- Deadly quarter
- Dysmetabolic syndrome
- Insulin resistance syndrome
- Syndrome X

1.1.1 Origin & Concept of Metabolic Syndrome

The concept of the metabolic syndrome has existed for at least 80 years (Cameron AJ et al 2004). This constellation of metabolic disturbances was first described in the 1920s by Kylin, a Swedish physician, as the clustering of hypertension, hyperglycaemia, and gout. Later, in 1947, Vague drew attention to
upper body adiposity as the obesity phenotype that was commonly associated with metabolic abnormalities associated with type 2 diabetes and cardiovascular disease.

The clinical importance of the syndrome was highlighted some 40 years later by Reaven who described the existence of a cluster of metabolic abnormalities with insulin resistance as the central pathophysiological features and labelled it syndrome X. In 1988, Reaven proposed the concept of syndrome X.

### 1.1.2 Defining Metabolic Syndrome

While the concept of the metabolic syndrome was accepted, in an attempt to achieve some agreement on definitions and provide a tool for clinicians and researchers, a number of organizations formulated definitions. These were concordance in what are essential components of metabolic syndrome, glucose tolerance, obesity hypertension dislipidemia, but all differed in the details.

The first attempt at a global definition of metabolic syndrome was proposed by the World Health Organization (WHO) consultation group in 1988 as insulin resistance, in addition to 2 other risk factors, being requisites for diagnosis. Recognizing that the WHO definition might be too complex to apply in many settings and as it is lies heavily on insulin resistance, The European group for the study of insulin resistance in 1999 developed a modified version of the WHO definitions which would be easier to use as it relied on fasting insulin.

Subsequently, two years later, National Cholesterol Education Program (NCEP-ATP III) in 2001 and International Diabetes Federation (IDF) in 2005 proposed another definition designed to have clinical utility; this definition did not
include a specific measure of insulin sensitivity. While diagnosis using ATP III criteria was based on the presence of any 3 out of 5 risk factors, IDF considers abdominal obesity as a mandatory component of metabolic syndrome.

More recently, in an effort to standardize the criteria for metabolic syndrome, a joint interim statement was made by a collaborative team consisting of the IDF Task Force on Epidemiology and Prevention, National Heart, Lung and Blood Institute (NHLBI), American Heart Association (AHA), World Heart Federation and the International Association for the Study of Obesity. It was proposed that abdominal obesity should no longer be a prerequisite feature of metabolic syndrome, and that diagnosis should be based entirely on the presence of any 3 of the 5 risk factors (Alberti KG, Zimmet P, Shaw J, 2006).

Again NCEP-ATP III definition (2001) was revised in 2005 and is based on any three risk factors. Similarly, the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) base their definition on the presence of three risk factors.

**NCEP ATP III (2001) criteria for metabolic syndrome**

The purpose of ATP III was to identify people at higher long-term risk for cardiovascular diseases (CVDs) who deserved clinical lifestyle intervention to reduce risk. Presence of three of the following five factors is required for diagnosis of metabolic syndrome.

- Central obesity: Abdominal waist circumference: Men >102 cm, women >88 cm
• Fasting plasma glucose >100 mg/dl or diagnosed type 2 diabetes mellitus (T2DM)

• Fasting plasma triglyceride >150 mg/dl or on medication

• Fasting plasma HDL cholesterol: Men <40 mg/dl, women <50 mg/dl or medication

• Blood pressure ≥130/85 mmHg or medication.

It is apparent that the WHO definition was better suited as a research tool whereas the NCEP: ATP III definition was more useful for clinical practice. Clinicians prefer simple tools with which to assess patients and improve their management and it is generally agreed that the NCEP: ATP-III definition is simpler for practice and it is popular because of its simplicity as its components are easily and routinely measured in most clinical settings. It requires only a fasting assessment of blood glucose, whereas the WHO definition can requires an oral glucose tolerance tests. The ATP III criteria are more practical and may be a better predictor of coronary heart disease (CHD) risk in any population. Unlike the WHO criteria, screening for microalbuminuria is not required for ATP III criteria.

Therefore we have used NCEP: ATP III definition to diagnose the patients of metabolic syndrome in this study. All the above mentioned definitions and criteria which are given by different organization to define metabolic syndrome are comprehensively described in review section (Table 2.1.1).
1.1.3 Epidemiology of Metabolic Syndrome

Global Burden

A global transition in the disease pattern has been observed, where the relative impact of infectious diseases is decreasing while chronic diseases like cardiovascular disease (CVD) and diabetes are increasingly dominating the disease pattern (Johnsen et al 2007). Epidemiologists in India and international agencies such as the world health organization (WHO) have been sounding an alarm on the rapidly growing burden of CVD for the past 15 years. Metabolic Syndrome prevalence has increased significantly over the last years, reaching pandemic proportions worldwide (Ford, Giles, & Mokdad 2004).

It is estimated that 20-25 % of the world adult population suffer from metabolic syndrome disorders (Mishra et al 2010). Prevalence of this syndrome is increasing dramatically throughout the world, not only in adult or older populations but also in children and young people running in parallel with the worldwide epidemic of obesity and diabetes (Milagros 2007). Findings from NHANES III suggest that 24% of American men and 23% of American women, or about 47 million people, have metabolic syndrome.

As with other chronic diseases, the prevalence of metabolic syndrome is increasing with current prevalence estimates in the Asia-Pacific region between 10% and 30% (WHO 2000). The metabolic syndrome by any of the definitions so far examined is very common in adults in many parts of the world, typically being found from one in six to one in three adults (sometime more), rising with age and being higher in men than women.
Burden of metabolic syndrome in India

It is estimated that CVD will be the largest cause of disability and death in India, with 2.6 million Indians predicted to die due to CVD by 2020 (Goenka et al 2000, Reddy et al 2006). Nearly 30% of Indians have metabolic syndrome disorder (NIN 2010). The prevalence of metabolic syndrome is increasing exponentially in India, both in the urban and rural areas. It has escalated in different parts of India to figures now ranging from 11% to 41% (Misra A et al 2008). Given the enduring outbreak of overweight and obesity, it is expected that the prevalence of the MS will continue to grow. Another study by Prasad et al (2008) in India, reported the prevalence of metabolic syndrome is 33.5% overall, 24.9% in males and 42.3% in female. The Sentinel surveillance project in Indian Industrial population illustrated 27% prevalence (ATP III criteria) during 2001-03 (Misra et al 2010). These data highlight the urgent need for control of upstream causes of obesity (excessive caloric intake, poor dietary habits and physical inactivity) to control the rapidly increasing epidemic of diabetes and coronary heart disease in India.

1.1.4 Metabolic Syndrome and Cardiovascular Disease

Metabolic syndrome is a complex web of metabolic risk factors that are linked with a 2-fold risk of CVD (Sattar N et al 2003), 5-fold risk of diabetes (McNeil 2005) and fivefold increase in the mortality over a 5-10 year period (Greenstone 2008). There is strong evidence to suggest that Individuals with Metabolic syndrome have a 30%-40% likelihood of developing diabetes/CVD within 20 years; depending on the number of components they have (Enas EA 2007). According to the National Cholesterol Education Program (NCEP) panel, metabolic syndrome will soon have a
greater impact on premature coronary artery disease than tobacco (NCEP ATP III 2001). Metabolic syndrome is a multiplex risk factor for atherosclerotic cardiovascular disease (ASCVD). The risk of ASCVD accompanying the metabolic syndrome is approximately doubled compared with an absence of the syndrome.

The Metabolic syndrome appears to promote the development of ASCVD at multiple levels. Elevations of apo B containing lipoproteins initiate atherogenesis and drive lesion development. Atherosclerotic plaque development is accelerated by low levels of HDL-C, by elevated glucose levels and by inflammatory cytokines (S M Graundy 2007). The main reason why metabolic syndrome is attracting scientific and commercial interest is that the factors defining the syndrome are all factors associated with increased morbidity and mortality in general and from CVD in particular.

1.1.5 Factors involved in the development of Metabolic Syndrome

The exact mechanisms of the complex pathways of metabolic syndrome are not clear yet, but it is known to be a complex interaction between genetic, metabolic and environmental factors (Feldeisen et al 2007). The most important risk factors are diet, genetics, aging, sedentary behavior or low physical activity, disrupted sleep, mood disorders/psychotropic medication use, and excessive alcohol use (Hollenberg 2002).

➢ Sedentary lifestyle (Low physical activity)

Physical inactivity is a predictor of CVD events and related mortality. Many components of metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central); reduced HDL cholesterol;
and a trend toward increased triglycerides, blood pressure, and glucose in the genetically susceptible.

➢ Genetic factors

There is a considerable inter individual variation in insulin sensitivity amongst healthy individuals, even when body weight and the level of physical activity are taken into consideration. Some authors consider that approximately 25% of the ‘normal’ population has insulin resistance (Reaven 1999). Genetic factors are likely to be involved since variations in insulin sensitivity represent a familial trait (Sakul et al 1997).

➢ Dietary factors

a whole array of dietary factors, such as high intakes of saturated fatty acids and low intakes of o3 fatty acids (Connor 2000) amounts of simple carbohydrates and or fructose (Hollenbeck 1993) are reported to contribute to the development of components of metabolic syndrome. (Mennen et al 2000, Pereira et al 2002a).

1.1.6 Prevention and Management of the Metabolic Syndrome

Given the central role played by insulin resistance in the pathogenesis of the syndrome, all strategies which improve insulin sensitivity are thought to be effective in preventing or improving the metabolic syndrome. Combining a heart healthy diet pattern and regular physical activity with even a Small amount of weight loss (7-10%) in overweight person can reverse the metabolic syndrome. The Primary approach is to reduce the major risk factors for cardiovascular disease: stop smoking and reduce LDL cholesterol, blood pressure and glucose levels to the recommended levels by:
Introduction

- Weight loss to achieve a desirable body weight (BMI less than 25 kg/m2).

- Increased physical activity, with a goal of at least 30 minutes of moderate-intensity activity on most days of the week.

- Healthy eating habits that include reduced intake of salt, saturated fat e.g. butter, ghee, coconut, coconut oil and coconut milk, palm oil, fatty meats, Trans fats e.g. vanaspati (Dalda), partially hydrogenated oils used in snacks and dietary cholesterol e.g. egg yolks, meat, dairy.

1.1.7 Dietary Strategies (Current therapeutic options)

The National Cholesterol Education Program’s Adult Treatment Panel III (ATP III) (2001) has developed guidelines for reducing the risk of CVD which strongly urge lifestyle modification, including dietary changes, as the foundation and initial intervention for persons at risk for CVD. An important component of the lifestyle modification is a ‘heart-healthy’ diet, which specifically includes a recommendation for consumption of at least 5-10 g viscous soluble fibre (VSF) per day. In addition to reducing saturated fat and cholesterol intake, and increasing cis-unsaturated fat intake, the importance of other dietary approaches, such as increasing the intake of viscous soluble fibers has become increasingly recognized.

Role of Dietary Fiber

Current evidence suggests that dietary fiber that is rich in whole and unrefined grains is protective and plays important roles in preventing or delaying the onset of chronic diseases and disorders such as coronary heart disease, (Leu S et al 2000, Truswell 2002) diabetes mellitus, (Meyer et al 2000) cancer and colon dysfunction.
Dietary fiber can be classified as either soluble or insoluble in water. Cellulose, lignin, some pectins, and some hemicelluloses are insoluble fibers. Vegetables and cereal grains are especially rich in insoluble fiber, with the highest amounts in wheat and corn. Insoluble fiber is responsible for increased stool bulk and helps to regulate bowel movements. The natural gel-forming fibers, such as β-glucans, gums, mucilages (e.g. psyllium), pectins, and some hemicelluloses are soluble. Foods rich in soluble fiber are dried beans, oats, barley, and some fruits and vegetables. The mean total daily fiber intake amongst adults in most industrialized countries is well below 25 g, the minimal amount recommended by various health organizations. Out of total dietary fiber intake, approximately 20% should be soluble and 80% is insoluble dietary fiber.

Soluble Fiber (β-glucans)

β-Glucan is a viscous soluble fiber found in cereals, in particular oats and barley, as well as in yeast, bacteria, algae, and mushrooms. β-glucans are non-starch polysaccharides composed of glucose molecules in long linear glucose polymers with mixed β-(1→4) and β-(1→3) links with an approximate distribution of 70% to 30%.
This specific chemical structure is responsible for physical properties, such as viscosity and solubility, as well as the potential to influence cholesterol metabolism. Numerous studies demonstrated that diets high in soluble fiber grains (oats, barley) lower blood cholesterol more than diets high in more insoluble grains (wheat, rice) (Behall et al 1997, Leinonen et al 2000, Bruce B et al 2000, Bridges SR 1992). A meta-analysis by Brown et al (1999) showed that daily intake of 2–10 grams of soluble fiber significantly lowered serum total cholesterol and LDL-cholesterol concentrations.

**How Beta-Glucans Work**

Several of the principal benefits of soluble fiber in metabolic syndrome patients are indisputably due to its effect on carbohydrate absorption. Viscous fibers such as psyllium, β-glucans, and pectin may form a gel in the small intestine, which acts to delay nutrient absorption, slowing the delivery of glucose into the bloodstream and reducing the need for insulin. These fibers’ ability to lower postprandial glycemia and insulinemia, as well as cholesterol, has been established in numerous studies, but long-term effects are less well known. Bacteria ferment β-glucans in the intestinal tract, producing short-chain fatty acids. These may stimulate insulin release from the pancreas and alter glycogen breakdown by the liver and therefore play a role in glucose metabolism and protect against insulin resistance.
Barley (As a Source of Glucan)

*Barley* (Hordeum vulgare) a member of the grass family, is a major cereal grain grown in temperate climates globally. It is primarily a cereal grain popularly known as jau in India. It is the fourth most important cereal crop after rice, wheat and maize.

A very high fiber content, vitamins and minerals, antioxidants, heart health and diabetes protection are just some of the barley nutrition benefits that make it one of the best whole grain choices. Although barley may not be as popular as other whole grains like oats, wheat, barley is called the “King of Cereals” for some impressive health benefits. To our knowledge, barley contains huge amount of dietary fiber (soluble (β-glucan) and insoluble) is a affluent source of vitamins & mineral especially B vitamins and trace minerals. Other components in barley have been coupled with many health benefits such as tocotrienol, lignan, phytoestrogen, phenolic compounds, and phytic acid.

Recently, the US Food and Drug Administration (FDA 2001) allows the health claim statement that, depending on the β-glucan content, consumption of soluble fibre from barley in a diet may reduce the risk of CVD. The high viscosity of β-glucan may be particularly effective at reducing postprandial glycemia and several trials using oat or barley products reported significant reductions in glycemic response (Holm J et al1992, Wood PJ et al1994, Hallfrisch J et al 1995). Among participants in the National Health and Nutrition Examination Survey (NHANES) I Follow-up Study, each 5 g/d increase in viscous soluble fiber intake diminished the risk of CVD by 6% and coronary heart disease by 8%. The magnitude of the cholesterol-lowering
Introduction

effect in the relevant studies was variable. When only the higher-quality studies using barley grain products (no extracts) were taken into account (Anonymous 2005, Behall 2004a, Behall 2004b, Rondanelli 2011, Shimizu et al 2008, Sundberg et al 2008) the reduction in total cholesterol levels ranged from -0.06 to -0.50 mmol/L (-1.1% to -7.5%) while the reduction in LDL-cholesterol levels ranged from 0 to -0.32 mmol/L (0% to -8.5%).

1.2 Rationale of the Study

With the elevated risk not only of diabetes but also of cardiovascular disease from the metabolic syndrome, there is urgent need for strategies to prevent the emerging global epidemic. The metabolic syndrome is a master of disguise since it can present in various ways according to the different components that constitute the syndrome. Metabolic syndrome has become an important public health problem that demands urgent therapeutic attention and interventional approaches.

Preventing and treating this syndrome is an area of public health urgency from the perspective of improving the morbidity and mortality statistics as well as in reducing its economic burden. The essential emphasis in the management of metabolic syndrome is to mitigate modifiable risk factors such as obesity, physical inactivity and an inappropriate atherogenic diet through lifestyle changes.

Why Uses Barley?

Within recent years, the US (FDA), (2001) has endorsed the relation between an increase in soluble fiber and a decrease in serum total cholesterol by ratifying health claims for oats and for psyllium fiber. The active component in oats has been
identified as the linear mixed-link (1→3)(1→4) β-D-glucan (β-glucan), which reduces serum total cholesterol by 5–10% (5) and which in oats is present at close to 4% (by wt). Barley contains 5–10% (by wt) β-glucan and so may be expected to have similar cholesterol-lowering effects. The health claim was amended to allow inclusion of barley and barley products. Compared to oats, barley has been utilized as the beta-glucan source in few studies. Work conducted in a laboratory indicates that consumption of a diet rich in barley results in as great or even greater reduction in plasma cholesterol and other blood lipids. (Behall KM 2002 & 2004, Hallfrisch J et al. 2003). Data from these studies are currently being used as support for an application to the FDA for a health claim for barley similar to that for oats. In studies comparing the response of plasma cholesterol and triglycerides to diets rich in oats or barley, barley appeared to be more effective in lowering plasma cholesterol than oats, perhaps because of its higher β-glucan content.

In a review of the effect of fiber-rich carbohydrates on features of the Metabolic Syndrome, Davy and Melby (2003) report that consumption of 20-35 g/day of total dietary fiber and at least 3 g/day of soluble fiber, as recommended by the American Dietetic Association, results in a reduction in risk factors for cardiovascular disease and diabetes. The recommended intake for total fiber for adults 50 years and younger is set at 38 grams for men and 25 grams for women, while for men and women over 50 it is 30 and 21 grams per day, respectively, due to decreased food consumption.

It is essential to determine ways to increase intake of total fiber and, especially, soluble fibers. Increasing the intake of whole grain products such as barley
would increase both total and soluble dietary fiber in the diet and most likely would result in decreasing the risk factors for disease even in men and women already overweight. Most research on soluble fiber has focused on oats. Barley, another excellent soluble fiber source, has received little attention. Thus, research is needed to assess the health effects of human consumption of barley on risk factors associated with cardiovascular diseases.

**In view of above facts, this study was carried out with the following objectives:**

**1.3 Objectives of the Study**

**General Objective**

To investigate the effects of barley consumption on cardiovascular risk factors among patients with metabolic syndrome.

**Specific Objectives**

- To assess the baseline characteristics and disease profile of the study subjects.
- To assess the lifestyle (behavioral) determinants at baseline and during the trial.
- To assess the differential pattern of dietary intake at baseline and throughout the intervention.
- To determine the effect of intervention on blood pressure, body composition, blood lipid profile and glucose metabolism as well as on the features of metabolic syndrome.
Hypothesis

Intervention using Barley will have no effect on Anthropometric measurements, body composition, blood pressure, blood glucose and fasting lipid profile among patients with metabolic syndrome.