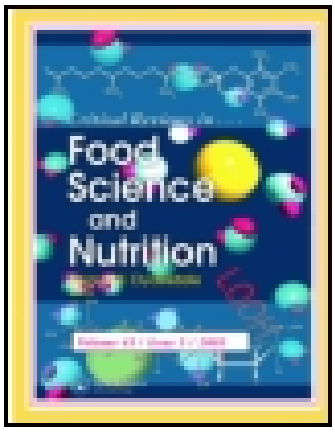

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Interplay between Proteins and Metabolic Syndrome- A Review

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Title: Interplay between Proteins and Metabolic Syndrome- A Review

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Critical Reviews in Food Science and Nutrition

ABSTRACT

Metabolic syndrome is characterized by hypertension; hyperglycaemia; hypertriglyceridaemia; reduced high-density lipoprotein cholesterol levels and abdominal obesity. Abundant data suggest that, compared with other people, patients meeting these diagnostic criteria have a greater risk of having substantial clinical consequences, the two most prominent of which are the development of diabetes mellitus and coronary heart disease. The metabolic syndrome is a health issue of epidemic proportions. Its prevalence in the worldwide continues to increase, hand in hand with that of obesity. Protein, on the other hand, is the foundation of cell-building, especially in muscle tissue. The body needs protein to build not only muscle cells, but the cells of major organs, skin and red blood cells. For people with metabolic syndrome, one of the other functions of protein is to slow down the absorption of carbohydrates. When proteins are consumed with carbohydrates, it takes longer for the digestive system to break down that meal. This means that the sugar

created from those carbohydrates is released at a slower rate, preventing spikes in both blood sugar and insulin. As the understanding of the metabolic syndrome evolves, it is likely that more comprehensive therapeutic options will become available.

Keywords: Metabolic Syndrome, protein, diabetes mellitus, cardiovascular diseases

INTRODUCTION

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 (Johnson, 2007). Epidemiologists in India and international agencies such as the World Health Organization (WHO) have been sounding an alarm on the rapidly rising burden of CVD for the past 15 years. It is estimated that by 2020, CVD will be the largest cause of disability and death in India, with 2.6 million Indians predicted to die due to CVD (Goenka et al., 2009).

Metabolic Syndrome (MS) is a complex web of metabolic factors that are associated with a 2-fold risk of CVD and a 5-fold risk of diabetes. Individuals with MS have a 30ï 40% probability of developing diabetes and/or CVD within 20 years, depending on the number of components present (Enas et al., 2007).

The most operational definition of MS was proposed by World Health Organization (1998) with hyperglycemia and/ or insulin resistance as a central feature, associated with two or more related metabolic abnormalities *i.e.* elevated blood pressure, dyslipidemia, central obesity or microalbuminuria. The National Cholesterol Education Programme (NCEP) definition requires three or more of the following features *i.e.* abdominal obesity, elevated triglyceride level, reduced HDL-C level, elevated blood pressure or elevated fasting blood glucose (Grundy, 2007).

CONSTITUENT RISK FACTORS OF METABOLIC SYNDROME

Metabolic syndrome arises from insulin resistance accompanying abnormal adipose deposition and function (Olufadi and Byrne, 2008). It is a risk factor for diabetes, coronary heart disease, fatty liver, and several cancers as well. The clinical manifestations of this syndrome may

include hyperglycemia, hypertension, hypertriglyceridemia, abdominal obesity and reduced high-density lipoprotein cholesterol (HDL-C).

According to National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions

- Fasting glucose Ó100 mg/dL (or receiving drug therapy for hyperglycemia)
- Blood pressure Ó130/85 mm Hg (or receiving drug therapy for hypertension)
- HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
- Waist circumference Ó102 cm (40 in) in men or Ó88 cm (35 in) in women; if Asian American, Ó90 cm (35 in) in men or Ó80 cm (32 in) in women
- Triglycerides Ó150 mg/dL (or receiving drug therapy for hypertriglyceridemia)

Data suggest that patients meeting these diagnostic criteria have a greater risk of significant clinical consequences, most importantly the development of diabetes mellitus and of coronary heart disease (Hanley et al., 2005). Studies have shown that metabolic syndrome doubles the risk of coronary artery disease and may also increase the risk of stroke, fatty liver disease, and cancer (Giovannucci, 2007).

Risk factors for metabolic syndrome are insulin resistance and abdominal obesity; other associated conditions can be ageing, physical inactivity and hormonal imbalance (Park et al., 2003). Multiple metabolic pathways have also been suggested to link insulin resistance and compensatory hyperinsulinemia to the other metabolic risk factors. It is recognized that some people who are not obese by traditional measures however are insulin resistant and have

abnormal levels of other metabolic risk factors. Although insulin-resistant individuals need not be clinically obese, they commonly have an abnormal body fat distribution that is characterized by predominant upper body fat. Excess upper body fat can accumulate either subcutaneously or intraperitoneally (visceral fat). Many researchers claim that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment (Brochu et al., 2000; Nyholm et al., 2004) others find that excess subcutaneous abdominal fat also carries a significant association with insulin resistance (Kelley et al., 2000; Sites et al., 2000; Nielsen et al., 2004). Regardless of the relative contributions of abdominal subcutaneous fat and visceral fat to insulin resistance, a pattern of abdominal obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower-body obesity. Upper-body obesity is caused by an unusually high release of nonesterified fatty acids from adipose tissue, contributing to accumulation of lipid in sites other than adipose tissue. Unusual lipid accumulation in liver and muscle seemingly predisposes to insulin resistance and dyslipidemia (Petersen and Shulman, 2002).

Adipocytes produce a variety of biologically active molecules, known as adipocytokines or adipokines, including TNF-Ŭ, plasminogen activator inhibitorï 1 (PAI-1), leptin, resistin and adiponectin (Unger, 2003). Non-regulated production of these adipocytokines participates in the pathogenesis of obesity-associated metabolic syndrome. Increased production of TNF-Ŭ and PAI-1 from accumulated fat lead to the development of insulin resistance and thrombosis respectively, in obesity (Uysal et al., 1997). In contrast, adiponectin exerts anti-atherogenic and insulin-sensitizing effects and hence a decrease in plasma adiponectin is causative for insulin

resistance and atherosclerosis in obesity. However, the mechanisms by which fat accumulation leads to such dysregulation of adipocytokines have not been elucidated (Berg et al., 2001).

Oxidative stress plays crucial roles in the pathogenesis of various diseases. In diabetes, oxidative stress decreases glucose uptake in muscle and fat and decreases insulin secretion from pancreatic ϐ cells. Increased oxidative stress, by directly affecting vascular wall cells, also underlies the pathophysiology of hypertension and atherosclerosis (Furukawa et al., 2004).

More recently, metabolic syndrome has been noted to be associated with a state of chronic, low-grade inflammation. It is speculated by some researchers that inflammation of this type underlies or exacerbates the syndrome. For example, inflammatory cytokines reportedly induce insulin resistance in both muscle and adipose tissue. Interestingly, insulin-resistant people generally manifest evidence of low-grade inflammation, even without an increase of total body fat (Hanley et al., 2004).

Critical Reviews in Food Science and Nutrition

ROLE OF PROTEINS IN ALLEVIATING THE SYMPTOMS OF METABOLIC SYNDROME

It has been noted that an emerging Asian Indian phenotype has high body fat with relatively less BMI, less lean body mass and marked abdominal obesity. It is likely that amino acid imbalance may be a major contributing factor. Traditionally, this has been discussed solely in the context of a protein stability to provide specific patterns of amino acids to satisfy the demands for synthesis of protein as measured by animal growth or, in humans, nitrogen balance. Complementary proteins providing all essential amino acids required for protein synthesis may assist in alleviating the symptoms of MS, particularly in this phenotype. As understanding of

protein's actions expands beyond its role in maintaining body protein mass, the concept of protein quality must expand to incorporate these newly emerging actions of protein into the protein quality concept. The nutritional management of MS is best served by counselling change in a socio-cultural context and step wise fashion by negotiation rather than prescription with particular preference to protective Indian foods (Donald et al., 2008). New research reveals increasingly complex roles for protein and amino acids in regulation of body composition and bone health, gastrointestinal function and bacterial flora, glucose homeostasis, cell signalling, and satiety.

The evidence available upto date suggests that quality of protein is important not only at the minimum Recommended Dietary Allowance level but also at higher intakes (Millward et al., 2008).The dietary intake of amino acids is relevant since essential amino acids stimulate skeletal muscle protein synthesis to a much greater extent than non-essential amino acids (Tipton et al., 1999). Well nourished Indians showed a trend toward improved muscle function with higher lysine intakes. There are several lines of reasoning to suggest that lysine intake may influence muscle function (Kurpad et al., 2002). High-protein, low-carbohydrate diets have also been investigated for treatment of type 2 diabetes with positive effects on glycemic regulation, including postprandial glucose and insulin responses, reducing fasting blood glucose and the percentage of glycated hemoglobin. Specific effects of increasing protein compared with reducing carbohydrates have not been extensively investigated. The higher protein and reduced carbohydrates appears to enhance weight loss with greater loss of body fat and reduced loss of lean body mass. Additional research is needed to determine specific types of protein for optimum health of individuals who differ in age, physical activity, and metabolic phenotypes.

Diets with total protein intake of 1.5 g/kg/d and carbohydrate intake 150 g/d are effective for treatment of type 2 diabetes, obesity and the Metabolic Syndrome. These diets improve body composition and enhance glycemic control. During weight loss, protein-rich diets reduce loss of lean tissue and increase loss of body fat. It has been proposed that keys to understanding the relationship between dietary protein and carbohydrates are the relationships between the branched-chain amino acid leucine and insulin and glucose metabolism. Leucine is known to interact with the insulin signaling pathway to stimulate downstream signal control of protein synthesis, resulting in maintenance of muscle protein during periods of restricted energy intake. Leucine also appears to modulate insulin signalling and glucose use by skeletal muscle. These mechanisms produce protein sparing and provide a stable glucose environment with low insulin responses during energy-restricted periods. Whereas total protein is important in providing substrates for gluconeogenesis, leucine appears to regulate oxidative use of glucose by skeletal muscle through stimulation of glucose recycling via the glucosealanine cycle. (Layman and Walker 2006).

Manny Noakes Senior Research Dietitian, CSIRO Human Nutrition (Clinical Research Unit) concluded the effects of high protein diet. Health benefits provided by moderately high protein diets and conventional high carbohydrate weight loss diets are: LDL cholesterol lowered on average 5%, Plasma triglycerides lowered on average 9%, insulin lowered on average 19% and glucose lowered on average 4%. Whereas, the advantages of moderately high protein high red meat diets are: Greater weight, fat and midriff loss on high protein diet in those women with elevated TG, Greater lowering of plasma triglycerides, Haemoglobin levels improved more on

high protein high red meat diet and B_{12} status improved on high protein high red meat diet (Noakes and Clifton 2005).

Ninety per cent of world population is dependent on animal foods for high quality protein (Singh, 2008). The traditional vegetarian Indian meals usually take care of including foods from different sources in order to improve their protein quality. The concern for optimum protein quality to prevent metabolic abnormalities holds significance for a large lacto vegetarian population of India which depends on plant foods for obtaining essential amino acids. Optimum protein quality from meals along with physically active lifestyle may help the people to have right proportion of fat mass and lean mass which may have protective role against MS. With the growing epidemic of obesity and the MS, reduction in the consumption of refined carbohydrates and sugar, replaced by either minimally processed whole grain products and healthy sources of fats and protein, should become a major public health priority, together with regular physical activity and weight maintenance.

The risk of developing the MS increases strikingly above a BMI of ≈25 (WHO 1998). Park et al., (2003) reported a prevalence of MS in 4.8, 22.8 and 60.2% of normal-weight (BMI: 18.5ï 24.9), overweight (25.0ï 29.9), and obese (≥ 30) men in the US population. Prevalence rates were similar in US women. A combination of increased access to food and decreased demands with respect to physical activity has led to risk of MS.

MS is affecting a quarter to a third of the adults, and its prevalence is rising, in parallel with increasing obesity and population ageing. The prevalence of MS in affluent Indians residing in urban metropolitan cities in India is higher (29%) than that reported from studies on Indians residing in US (21%). The clinical relevance of MS is that it identifies people who are at

increased long term risk of cardiovascular diseases and diabetes mellitus, thus providing an opportunity for preventive lifestyle interventions (Misra and Misra, 2003). It is also higher than that reported from most of rural and urban populations in India (Ramchandran et al., 2003). According to the three definitions, the age-adjusted prevalence of MS for adults 25 to 64 years old was 3.2, 4.9, and 3.9% in men and 7.2, 11.5, and 10.9% in women, respectively. Prevalence of MS in Americans aged 30 to 79 years was approximately 25% in white men and 21% in white women; 29% in Mexican American men and 33% in Mexican American women; and 44% in Native American men and 57% in Native American women. MS prevalence increases significantly with age in women, but not in men, as reported by Meigs et al., (2003).

Two studies from India reported significantly different prevalence for men (36% vs 8%) and for women (47% vs 18%) (Gupta et al., 2003).This discrepancy may be because the study that found substantially higher prevalences defined obesity by modified ATP III criteria (waist circumference =90 cm in men and =85 cm in women) that may have been more suitable for the generally thinner population of India (Ramchandran et al., 2003). Prevalence is far lower in some European countries (ie, France, Finland) than in the United States. These variations are undoubtedly due to differences in diet, age structure and environmental variables, such as daily activity levels. Genetic factors may explain as much as 50% of the variability in metabolic syndrome traits (Mills et al., 2004). Age plays an important role. An adult aged 60 to 69 years has a 44% risk of having the metabolic syndrome compared with a 7% risk in those aged 20 to 29 years (Ford et al., 2002). Genetics probably contributes, in part, to the marked differences seen in various ethnic populations in the United States (Meigs et al., 2003).

The metabolic syndrome (MS) is a multiplex risk factor for atherosclerotic cardiovascular disease (ASCVD). The risk of ASCVD accompanying the MS is approximately doubled compared with an absence of the syndrome. The MS appears to promote the development of ASCVD at multiple levels. Atherosclerotic plaque development is accelerated by low levels of HDL-C, by elevated glucose levels and by inflammatory cytokines. Elevations of apoB containing lipoproteins initiate atherogenesis and drive lesion development (Grundy et al., 2008).

Much of the interest in the metabolic syndrome stems from its close association with a variety of clinical conditions, most important, type 2 diabetes and CVD. A study of 4423 non-diabetic individuals who were followed for 5 years showed that those with metabolic syndrome at baseline were at a 9-to 34-fold increased risk of developing diabetes (Klein et al., 2002). The degree of risk correlated with the number of metabolic abnormalities. In a 4-year longitudinal study of 890 non-diabetic Pima Indians, those with the metabolic syndrome were almost 3 times more likely to develop diabetes (Hanson et al., 2002). The West of Scotland Coronary Prevention Study (WOSCOPS) showed that the metabolic syndrome increased risk of diabetes by nearly 24-fold among 5974 non-diabetic persons at 5-year follow-up (Sattar et al., 2003).

In 1200 middle-aged Finnish men, cardiovascular mortality was almost 4 times higher in those with the metabolic syndrome diagnosed using the ATP III criteria and almost 3 times higher using the WHO criteria at the end of the 11-year study (Lakka et al., 2002). A recent analysis of data from the Scandinavian Simvastatin Survival Study (4S) and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/ TexCAPS), involving a total of 11,000 persons, demonstrated that the metabolic syndrome increased risk for major coronary events (*ie*,

fatal and nonfatal myocardial infarction [MI], unstable angina, or sudden cardiac death) by about 1.5-fold (Girman et al., 2004).

A one-year, multicenter, controlled trial involving obese subjects who were randomly assigned to either a low-carbohydrate, high-protein, high-fat diet or a low-calorie, high-carbohydrate, low-fat (ñconventionalò) diet was conducted. After three months and six months, subjects on the low-carbohydrate diet had lost more weight as compared to the subjects on the conventional diet. After 12 months, the difference was not significant. In terms of cholesterol, increases in high-density lipoprotein cholesterol concentrations and decreases in triglyceride concentrations were greater among subjects on the low-carbohydrate diet than among those on the conventional diet throughout most of the study. Both diets significantly decreased diastolic blood pressure and the insulin response to an oral glucose load (Samaha and Iqbal, 2003).

In another study, Farnsworth et al., (2003) included either a high-protein diet of meat, poultry, and dairy foods (HP diet: 27% of energy as protein, 44% as carbohydrate, and 29% as fat) or a standard-protein diet low in those foods (SP diet: 16% of energy as protein, 57% as carbohydrate, and 27% as fat) during 12 week of energy restriction (6ï 6.3 MJ/d) and 4 week of energy balance (≈8.2MJ/d). Fifty-seven overweight volunteers with fasting insulin concentrations> 12 mU/L completed the study. Results revealed that weight loss (7.9 ± 0.5 kg) and total fat loss (6.9 ± 0.4 kg) did not differ between diet groups. In women, total lean mass was significantly (P = 0.02) better preserved with the HP diet (-0.1 ± 0.3 kg) than with the SP diet (-1.5 ± 0.3 kg). The reduction in serum triacylglycerol concentrations was significantly (P< 0.05) greater in the HP diet group (23%) than in the SP diet group (10%). Those fed the HP diet had significantly (P< 0.03) less glycemic response at weeks 0 and 16 than did those fed the SP diet.

Critical Reviews in Food Science and Nutrition

After weight loss, the glycemic response decreased significantly ($P< 0.05$) more in the HP diet group. Markers of bone turnover, calcium excretion and systolic blood pressure were unchanged. It can be concluded that replacing carbohydrates with protein from meat, poultry and dairy foods has beneficial metabolic effects and no adverse effects on markers of bone turnover or calcium excretion.

Beneficial effects of high protein diets may be an increased satiety, increased thermogenesis, sparing of muscle protein loss and enhanced glycemic control (Stamler et al., 2004).

It was studied that high-protein diets low in fat may represent an appealing diet plan but promote a more healthful weight loss. Healthy adults ($n= 20$) were randomly assigned to two low-fat diets, one was high protein (<30% energy) and other was high carbohydrate (60% energy). The intakes were strictly controlled during the six week trial. Body composition and metabolic indices were assessed before and after the trial. It was found that low-fat, energy-restricted diets of varying protein content (15 or 30% energy) promoted healthful weight loss, but diet satisfaction was greater in those consuming the high-protein diet (Johnston et al., 2004).

The effect of a high-soy-protein diet on weight loss without losing muscle mass in pre-obese and obese subjects was studied by Deibert et al., (2004). The change of body composition, weight, metabolic and hormonal parameters were determined induced by different intervention protocols. Three different interventions containing lifestyle education (LE-G), or a substitutional diet containing a high-soy-protein low-fat diet with (SD/PA-G) or without (SD-G) a guided physical activity program were designed. A total of 83 subjects completed 6 months study. BMI dropped significantly in all groups (LE-G: - 2.2 ± 1.43 kg/m^2; SD-G: - 3.1 ± 1.29 kg/m^2; SD/PA-

Critical Reviews in Food Science and Nutrition

G: - 3.0 ± 1.29 kg/m^2). Subjects in the SD-G and in the SD/PA-G lost more weight during the 6-months study (- 8.9 ± 3.9; - 8.9 ± 3.9 kg) than did those in the LE-G (- 6.2 ± 4.2 kg), and had a greater decrease in fat mass (- 8.8 ± 4.27; - 9.4 ± 4.54 kg) than those in the LE-G (- 6.6 ± 4.59 kg). In contrast, no significant intra individual or between-group changes in the fat-free mass were seen. In all groups, metabolic parameters showed an improvement in glycemic control and lipid profile of the subjects. The study concluded that a high-soy-protein and low-fat diet can improve the body composition in overweight and obese people, losing fat but preserving their muscle mass.

A strong inverse association between physical activity and MS, an association that is much steeper in unfit individuals was demonstrated by Paul et al., (2004). Thus, prevention of metabolic disease may be most effective in the subset of unfit inactive people. Frank (2005) found a significant relationship between increased protein intake and lower risk of hypertension and coronary heart disease. Protein quality describes characteristics of a protein in relation to its ability to achieve defined metabolic actions.

It is well established that under most conditions, protein is more satiating than the isoenergetic ingestion of carbohydrates or fat (Yancy et al., 2004). Both soy-nut and soy-protein had beneficial effects on serum concentrations of total cholesterol, LDL cholesterol, triacylglycerol, and apoB-100. Such results have also been seen among subjects with different types of diseases (Hoie et al., 2005). Beneficial effects of soy consumption on blood lipids were the most consistently reported findings (Hermansen et al., 2005). This suggests that a modest increase in protein, at the expense of the other macronutrients, may promote satiety and facilitate weight loss through reduced energy consumption (Tannous et al., 2006).

Critical Reviews in Food Science and Nutrition

Layman et al., (2005) examined the interaction of 2 diets (high protein, reduced carbohydrates vs. low protein, high carbohydrates) with exercise on body composition in women (n=48, ╒46 y old, BMI=33kg/m^2) during weight loss. The study was a 4-month weight loss trial using a 2×2 block design (Diet×Exercise). Diets were equal in total energy (7.1 MJ/d) and lipids (╒30% energy intake) but differed in protein content and the ratio of carbohydrate: protein at 1.6 g/(kg/d) and ᾽ 1.5 (PRO group) vs. 0.8 g/(kg/d) and ˛ 3.5 (CHO group), respectively. Exercise comparisons were lifestyle activity (control) vs. a supervised exercise program (EX: 5 d/wk walking and 2 d/wk resistance training). Subjects in the PRO and PRO + EX groups lost more total weight and fat mass and tended to lose less lean mass (P = 0.10) than the CHO and CHO ± EX groups. Exercise increased loss of body fat and preserved lean mass. This study demonstrated that a diet with higher protein and reduced carbohydrates combined with exercise additively improved body composition. The combined effects of diet and exercise were additive for improving body composition.

The effects of dietary protein intake on energy restriction (ER)-induced changes in body mass and body composition was assessed by Mahon et al., (2007). 54 postmenopausal women, age 58 ± 2 y, body mass index 29.6 ± 0.8 kg/m^2, were assigned to one of four groups. For 9 weeks, three ER groups ate a 1000 kcal/d lacto-ovo vegetarian basal diet plus 250 kcal/d of either beef (BEEF, n = 14), chicken (CHICKEN, n = 15), or carbohydrate/fat foods (CARB (lacto-ovo), n = 14), while a control group (CON, n = 11) consumed their habitual diets. For all ER subjects combined, body mass (- 6.7 ± 2.4 kg, 9 %), fat mass (- 4.6 ± 1.9 kg, 13 %), and fat-free mass (- 2.1 ± 1.1 kg, 5 %) decreased. It concluded that overweight postmenopausal women can achieve significant weight loss and comparable short-term improvements in body composition and lipid-

Critical Reviews in Food Science and Nutrition

lipoprotein profile by consuming either a moderate-protein (25% of energy intake) poultry- or beef-containing diet or a lacto-ovo vegetarian protein (17% of energy intake) diet. The study measured the clinical markers of metabolic and cardiovascular diseases.

In another study, Lord et al., (2007) examined whether the predominant source of protein consumed (animal or vegetable) by older women was associated with muscle mass index (MMI). Thirty-eight healthy, normal weight sedentary women, aged between 57-75 years and taking no medication that could influence metabolism were studied. Significant correlations were observed between MMI and body mass index, fat-free mass, muscle protein content, total protein intake, animal protein intake, fat mass and visceral fat and daily energy expenditure. The results suggested that protein intake, especially from animal sources, may be associated with a better preservation of MMI. However, a stepwise regression analysis showed animal protein intake to be the only independent predictor of MMI.

Similarly, Campbell (2007) investigated the role of low-fat, hypo and isocaloric diets differing in protein: carbohydrate ratios combined with exercise on MS risk factors. Fifty-four obese women with MS risk factors completed a 12-week intervention that consisted of three, 60-minute, weekly aerobic and resistance training sessions, as well as random assignment to one of three diets: low protein (LP; 1g protein: 4g carbohydrate), intermediate protein (IP; 1:2) or high protein (HP; 1:1). Diet composition played no significant role in improving body weight, insulin sensitivity, lipid profile, blood pressure or fitness. The IP diet reduced body fat percentage and waist: hip ratio, while increasing lean mass percentage significantly than the other diets.

Various strategies have been proposed to prevent the development of metabolic syndrome. These include increased physical activity such as walking 30 minutes every day

(Lakka and Laaksonen, 2007) and a healthy, reduced calorie diet (Feldeisen and Tucker, 2007). There are many studies that support the value of a healthy lifestyle as above. However, one study stated that these measures are effective in only a minority of people (Katzmaryk et al., 2003).

A 2007 study of 2,375 male subjects over 20 years suggested that daily intake of a pint of milk or equivalent dairy products more than halved the risk of metabolic syndrome (Elwood et al., 2007). The most obvious method of prevention is undoubtedly to reduce the amount of carbohydrates, specifically fast digesting starches and sugars.

Another study was done to examine the effects of 3:1 and 1:1 carbohydrate to protein ratios, hypocaloric diets with and without exercise, and risk factors associated with the metabolic syndrome in overweight and obese Canadian women. The study concluded that a high-protein diet was superior to a low-fat, high-carbohydrate diet either alone or when combined with an aerobic/resistance-training program in promoting weight loss and nitrogen balance, while similarly improving body composition and risk factors for the metabolic syndrome in overweight and obese Canadian women (Meckling and Sherfey, 2007).

Treyzon et al., (2008) determined the effects of a protein-enriched meal replacement (MR) on weight loss and lean body mass (LBM) retention by comparison to an isocaloric carbohydrate-enriched MR within customized diet plans utilizing MR to achieve high protein or standard protein intakes. The meal plan was designed to achieve individualized protein intakes of either 2.2 g protein/kg of LBM per day [high protein diet (HP)] or 1.1 g protein/kg LBM/day standard protein diet (SP).Weight loss trial was conducted in 100 obese men and women comparing two isocaloric meal plans utilizing a standard MR to which supplementary protein or carbohydrate powder was added. Body weight, body composition, and lipid profiles were

Critical Reviews in Food Science and Nutrition

measured at baseline and 12 weeks. There were no differences in weight loss at 12 weeks (-4.19 ± 0.5 kg for HP group and -3.72 ± 0.7 kg for SP group, $p > 0.1$). Subjects in the HP group lost significantly more fat weight than the SP group (HP = -1.65 ± 0.63 kg; SP = -0.64 ± 0.79 kg, P = 0.05). The study concluded that higher protein MR within a higher protein diet resulted in similar overall weight loss as the standard protein MR plan over 12 weeks. However, there was significantly more fat loss in the HP group but no significant difference in lean body mass.

A moderate increase in dietary protein in association with physical activity and an energy-controlled diet may improve the regulation of body weight by 1) favouring retention or accretion of fat-free mass at the expense of fat mass at a similar physical activity level, 2) reducing the energy efficiency with respect to the body mass regained and 3) increasing satiety (Jones et al., 2008). Dietary protein is more satiating than carbohydrate or fat and has been shown to reduce food intake after controlled liquid preloads and meals and diets. Higher protein dietary patterns that are low in saturated fat may be considered as a legitimate option for weight management (Noakes, 2008).

Gordon et al., (2008) studied the effects of dietary protein on the composition of weight loss in post-menopausal women. Two 20-week hypocaloric diets (one maintaining dietary protein intake at 30% of total energy intake (1.2-1.5 g/kg/d *i.e.* "high protein diet", and the other maintaining dietary protein intake at 15% of total energy (0.5-0.7 g/kg/d *i.e.*" low protein diet" were fed to 24 post menopausal, obese women with mean age and BMI of 58 yrs and 33.0 kg/ m^2, respectively. The "high protein diet" group lost 8.4 ± 4.5 kg and the "low protein diet" group lost 11.4 ± 3.8 kg of body weight. The mean percentage of total mass lost as lean mass was 17.3

Critical Reviews in Food Science and Nutrition

± 27.8% and 37.5 ± 14.6%, respectively. It was concluded that maintaining adequate protein intake may reduce lean mass loss associated with voluntary weight loss in older women.

An elevation of protein intake affects both short and long term mechanisms. First, an increased protein intake increases satiety despite similar or lower energy intake. Second, thermogenesis is increased. Third, energy efficiency is lower during overfeeding. Fourth, fat free mass is preserved. Dietary protein-induced satiety may be due to amino acid composition, anorexigenic hormone concentrations, and energy expenditure (Hochstenbach-Waelen et al., 2009).

The excess calorie intake along with lack of sufficient physical activity in already high risk populations acts like a double whammy. James (2008) found a stronger association between regular physical activity and lower prevalence or incidence of MS. Interventional studies are limited but suggest that regular exercise reduces the incidence of metabolic syndrome. The amount and intensity of physical activity required to prevent or reverse MS has yet to be definitely determined. Evidence suggests that regular, moderate-intensity physical activity may be preventive of MS and that activity of greater intensity may carry greater benefit. Greater cardio respiratory fitness has demonstrated an even stronger negative association with MS. Strength training is recommended as an adjunct to regular aerobic exercise but is not the primary form of activity to prevent or manage MS.

A study was conducted to investigate the effects of a protein-rich diet in comparison with a conventional protein diet on weight loss, weight maintenance, and body composition in subjects with the metabolic syndrome. It was found that individuals with the metabolic syndrome achieved significant weight loss while preserving fat-free mass when treated with an energy-

restricted, high-protein diet that included nutrient-dense meal replacements, as compared with the results for conventional protein intake. An intervention with a protein-enriched diet may have advantages for the management of the metabolic syndrome (Mors et al., 2010).

In the United States (US), the prevalence of the MS in the adult population was estimated to be more than 25% by Nestel et al., (2007). Similarly, the prevalence of MS in 7 European countries was approximately 23%. It was estimated that 20%ï 25% of South Asians have developed MS and many more may be prone to it (Eapen et al., 2009). The main reason why MS 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 (Johnson, 2007).

Asian Indians are a high risk population with respect to diabetes and CVD, and the numbers are consistently on the rise (Enas et al., 2007). The prevalence of MS in Asian Indians varies according to the region, the extent of urbanization, lifestyle patterns, and socioeconomic/cultural factors. Recent data show that about one third of the urban population in Indiaôs major cities have MS (Misra and Khurana, 2009). The NCEP definition is more flexible as it can diagnose MS even in the absence of glucose intolerance, which in itself is a predisposition to dysmetabolic dyslipidemia, an obesity phenotype and proinflammatory status. The prevalence of MS by modified NCEP ATP III criteria showed gender-specific differences. Marked heterogeneity in the prevalence of MS according to gender has been illustrated. The prevalence of MS in males was two times higher as compared to females, whereas in other studies in India, MS prevalence in women was 1.5ï 2 times higher than in males. A higher

Critical Reviews in Food Science and Nutrition

prevalence in men might be related to their higher rates of overweight BMI, impaired blood glucose levels, high TG, and low levels of HDL-C (Sawant et al., 2011).

The prevalence of MS of 26.9% in males and 18.4% in females in southern India was found which is in concordance with the previous study (Chow et al., 2008). The prevalence of MS in the study population was 19.52%, which corroborates with Deepa et al., (2007). CURES 34 study showing prevalence of 18.3%. The prevalence of MS did not change with respect to age difference, 20ï 40 and 41ï 60 age groups showed similar prevalence of MS, and a marginal decrease was seen in >60 age group.

It has been studied that quality protein intake, and distribution of that protein, could play an important role with lean mass (LM), bone mineral density (BMD) and bone mineral content (BMC). Research has demonstrated that muscle protein synthesis is maximally stimulated at approximately 10 g of essential amino acids (EAA)/meal. This study sought to determine the relationship between the amount of quality protein consumed and the amount of times the approximately 10 g EAA threshold was reached at a meal, with respect to LM, BMD and BMC. It was found that quality protein consumed in a 24-hour period and the amount of times reaching the EAA threshold per day was positively associated with LM, BMD and BMC, and had an inverse relationship with body fat percentage (Loenneke et al., 2010).

Dougkas et al., (2011) observed the impact of dietary components on body-weight and food intake regulation. The large data available from both epidemiological and intervention studies provide evidence of a negative but modest association between milk and dairy product consumption and BMI and other measures of adiposity, with indications that higher intakes result in increased weight loss and lean tissue maintenance during energy restriction. The

purported physiological and molecular mechanisms underlying the impact of dairy constituents on adiposity are incompletely understood but may include effects on lipolysis, lipogeneis and fatty acid absorption. Furthermore, accumulating evidence indicates an impact of dairy constituents, in particular whey protein derivatives, on appetite regulation and food intake.

Dietary interventions can be more efficacious than medications for reducing the incidence of metabolic syndrome (Potenza and Mechanick, 2009). With this knowledge, a clinical nutritional protocol can be instituted to target some of the major associated areas of dysfunction occurring in cases of metabolic syndrome. Furthermore, diets high in protein can increase satiety, decrease food intake, and may promote body weight maintenance after weight loss (Plantenga et al., 2009). The effect of protein on these metabolic targets could promote weight loss and, therefore, benefit patients with metabolic syndrome. A study conducted to determine the prevalence of metabolic syndrome in Turkish elderly revealed that MS is highly prevalent in elderly people particularly among women. 61.7% of the total sample was found to have metabolic syndrome (Akbulut et al., 2011). Sarcopenia measured as appendicular skeletal mass (ASM), and central obesity measured as visceral fat area (VFA) may act synergistically to influence metabolic syndrome. However, several previous studies reported that metabolic risk is higher in non-sarcopenic obesity groups than in sarcopenic obesity groups because of the close relationship between muscle mass and body fat. Muscle-to-fat ratio was significantly associated with waist circumference, blood pressure, lipid profiles and glucose levels (TaeNyun et al., 2011).

Metabolic Syndrome: Risk Assessment

ASCVD

Many studies (Isomaa et al., 2001; Lakka et al., 2002; Sattar et al., 2003; Girman et al., 2004; Malik et al., 2004) have found that many middle-aged people with the metabolic syndrome are at higher absolute risk for ASCVD in the near future. Moreover, because of the high relative risk for ASCVD, long-term (lifetime) risk for ASCVD is increased even when 10-year risk is not considered to be high, e.g., in young adults who develop the syndrome. An exacerbating factor raising lifetime risk for ASCVD is an increased susceptibility for developing premature type 2 diabetes mellitus in future.

All individuals having the metabolic syndrome deserve long-term management and follow-up in the clinical setting, to reduce lifetime risk for ASCVD. The primary aim is to reduce the underlying risk factors. Such individuals need to be categorized according to *absolute* 10-year risk (NCEP, 2002). For metabolic syndrome patients without ASCVD or diabetes, Framingham risk scoring should be performed to estimate 10-year risk for coronary heart disease (CHD) (NCEP, 2002). This assessment triages patients into 3 risk categories based on 10-year risk for CHD:*high risk* (10-year risk >20%), *moderately high risk* (10-year risk 10% to 20%), or *lower to moderate risk* (10-year risk <10%). Individuals with any clinical form of ASCVD or with diabetes belong in the *high-risk* category (NCEP, 2002).

Thus, detecting metabolic syndrome is only one part of overall risk assessment for cardiovascular disease. Although patients with the metabolic syndrome are at higher lifetime risk, in the absence of diabetes they do not necessarily have a high 10-year risk. Estimating 10-year risk entails key risk factors beyond those of the syndrome, i.e., age, sex, smoking, and total cholesterol. Moreover, risk factors of the metabolic syndrome are not graded for severity as are the risk factors contained in Framingham scoring. Framingham investigators find little or no

increase in predictive power for CHD by adding abdominal obesity, triglycerides, or fasting glucose to their 10-year risk algorithm (Grundy et al., 2004; Wilson, 2004). It has not been rigorously tested in multivariable models, whether adding other factorsð apoB, small LDL, CRP, and insulin levelsð will enhance shorter-term prediction of ASCVD or not.

Type 2 Diabetes Mellitus

When metabolic syndrome factors exist in together with diabetes, it poses higher risk for the development of cardiovascular diseases (Alexander et al., 2003). Compared with other metabolic risk factors, Impaired Fasting Glucose (IFG) (fasting glucose 100 to 125 mg/dL) carries the highest predictive power for diabetes (Liao et al., 2004). A closely related measure is Impaired Glucose Tolerance (IGT), defined as a 2-hour plasma glucose Ó140 mg/dL and <200 mg/dL observed during a standard oral glucose tolerance test (OGTT). The American Dietetic Association has introduced the term ñprediabetesò to apply to individuals with either IFG or IGT (Genuth et al., 2003). IGT in fact exceeds IFG in frequency; IGT uncovers more individuals at increased risk for diabetes than IGF. In part to reduce the need for OGTT in routine practice, the ADA recently reduced the threshold for IFG to 100 mg/dL, from its previous 110 mg/dL (Genuth et al., 2003). OGTT nonetheless remains an option in normoglycemic individuals who appear to be at elevated risk for developing diabetes. Some individuals who already have type 2 diabetes mellitus will be identified by performing OGTT in people with IFG. Intensive lifestyle management of individuals with IFG (or IGT) will delay conversion to type 2 diabetes mellitus (Knowler et al., 2002) and hence controlling metabolic syndrome.

Thirteen studies with outcome data for reversal of MS involving 3907 participants were included in the meta-analysis. Insufficient trials reported cardiovascular events/mortality or

Critical Reviews in Food Science and Nutrition

incidence of type 2 diabetes to conduct a meta-analysis for these outcomes. Interventions alone or in combination included lifestyle (diet and/or exercise) and pharmacological therapy. Using random-effect models, both lifestyle (odds ratio, OR 3.81; 95% confidence interval, CI 2.47ï 5.88) and pharmacological interventions (OR 1.59; 95% CI 1.04ï 2.45) were statistically superior compared with control for reversing MS. Using mixed treatment comparison methods, the probability that lifestyle interventions were the most clinically effective was 87%. Evidence suggests that both lifestyle and pharmacological interventions can reverse MS. However, there is a lack of data on whether these benefits are sustained and translate into longer term prevention of diabetes and/or cardiovascular disease (Dunkley et al., 2012).

Management of Underlying Risk Factors

Genetic predisposition, although is a major factor in metabolic syndrome, rarely does it become clinically manifested in the absence of some degree of obesity and physical inactivity. Hence, therapies to alleviate these underlying risk factors constitute first-line intervention. Intensive cessation efforts are required if smoking; another risk factor for ASCVD is present. The underlying risk factors are modified to prevent or delay onset of ASCVD; and if type 2 diabetes mellitus is not already present, it becomes necessary to prevent it as well.

Abdominal Obesity

In individuals with abdominal obesity and metabolic syndrome, weight reduction deserves first priority (Klein et al., 2004). Weight reduction and maintenance of a lower weight are best achieved by a combination of reduced caloric intake and increased physical activity and

the use of lifestyle changes. First target of weight loss is to achieve a decrease of about 7 to 10% from baseline total body weight during a period of 6 to 12 months. For this, a reduction of 500-1000 calories per day is recommended. Physical activity helps to enhance caloric deficit. Recommended amount of weight, when achieved, will reduce the severity of most or all of the metabolic risk factors. It is important to maintain a lower weight and this requires long-term follow-up and monitoring.

Weight-loss drugs, available in the market, possess limited utility in the management of obesity. Bariatric surgery is being used increasingly in the United States for severe obesity. It may benefit the individuals at high risk for the complications of obesity. Weight-loss surgery is however not without risk. Patients must be selected with a team of healthcare professionals who are qualified to make appropriate clinical judgments about the pros and cons.

Physical Inactivity

Weight reduction is assisted by increasing physical activity, it also has beneficial effects on metabolic risk factors; and importantly, it reduces overall ASCVD risk (Franklin et al., 2004). Recommendations for the public call for Ó30 minutes of moderate-intensity exercise, such as brisk walking, on most, and preferably all days of the week (Grundy et al., 2004; Thompson et al., 2003); even more exercise adds more benefit. Thus, going beyond current recommendations will be particularly beneficial for people with the metabolic syndrome. Weight loss or weight-loss maintenance will be promoted by doing sixty minutes or more of continuous or intermittent aerobic activity, preferably every day. Preference is given to 60 minutes of moderate-intensity brisk walking to be supplemented by other physical activities (Grundy et al., 2004). The latter include multiple short (10- to 15-minute) bouts of activity (walking breaks at

work, gardening, or household work), using simple exercise equipment (eg, treadmills), jogging, swimming, biking, golfing, team sports, and engaging in resistance training (Pollock et al., 2000); avoiding common sedentary activities in leisure time (television watching and computer games) is also advised. To achieve adherence to an activity program, self-monitoring of physical activity is required.

AHA guidelines (Thompson et al., 2003) call for clinical assessment of risk for future ASCVD events before initiating a new exercise regimen. This includes a detailed history of physical activity. For high-risk patients (eg, those with recent acute coronary syndromes or recent revascularization), physical activity should be carried out under medical supervision. It is recommended that exercise should be tested before vigorous exercise sessions in selected patients with cardiovascular disease and other patients with symptoms or those at high risk (Thompson et al., 2003). It is not necessary, however, that all individuals beginning an exercise program of moderate intensity that is moderately progressive undergo an exercise stress test, although this issue remains controversial till date.

Critical Reviews in Food Science and Nutrition

Atherogenic and Diabetogenic Diets

In addition to weight control and reduction of total calories, the diet should be low in saturated fats, *trans* fats, cholesterol, sodium, and simple sugars (NCEP, 2002; Krauss et al., 2000). In addition, there should be ample intakes of fruits, vegetables, and whole grains; fish intake should be encouraged with recognition of concerns about the mercury content of some fish (Chobanian et al., 2003). Dyslipidemia of the metabolic syndrome can be exacerbated by very high carbohydrate intakes. ATP III (NCEP, 2002) recommended that for individuals entering cholesterol management the diet should contain 25% to 35% of calories as total fat. It is

difficult to sustain the low intakes of saturated fat required to maintain a low LDL-C, if the fat content exceeds 35%. On the other hand, if the fat content falls below 25%, triglycerides can rise and HDL-C levels can decline (Garg et al., 1994); thus, very-low-fat diets may exacerbate atherogenic dyslipidemia. Some investigators favour fat intakes in the range of 30% to 35% to avoid any worsening of atherogenic dyslipidemia in patients with the metabolic syndrome; others, however, are concerned about possible weight gain resulting from long-term ingestion of higher fat intakes and thus prefer intakes in of 25% to 30% range.

It has long been an interest in the question of whether changing the macronutrient content of the diet can promote weight reduction. More recently, interest has grown in the possibility that high-protein, low-carbohydrate diets will enhance weight reduction (Foster et al., 2003). For many years, a low-fat diet was advocated because the high caloric density of fat could increase the likelihood of obesity. The reason seems to be that fat and protein offer satiety that is absent with carbohydrates. Whether this effect of fat and protein on satiety makes the diet more effective for producing weight loss is a disputable hypothesis. Moreover, research documenting that high-fat/high-protein/low-calorie diets can achieve long-term maintenance of a lower body weight is lacking. No more weight reduction is shown in severely obese patients after 1 year of consumption of low carbohydrate diet compared to those eating a conventional weight-loss diet (Stern 2004). High-fat diets not only tend to be higher in saturated fat but they often are deficient in fruits, vegetables, and whole grainsð all of which are important components in currently recommended diets. High-protein diets of any sort are not well tolerated by individuals with chronic renal disease who have markedly reduced glomerular filtration rate; excess protein enhances phosphorus load, which can cause acidosis and worsen insulin resistance (Mitch and

Maroni, 1998; Mitch 2005). Finally, preoccupation with macronutrient composition to promote weight loss fails to identify the key factors affecting body weight. A combination of caloric restriction, physical activity, and motivation is required for effective weight loss; effective lifelong maintenance of weight loss essentially requires a balance between caloric intake and physical activity. Diets high in protein and low in carbohydrates are effective for treatment of type 2 diabetes, obesity and the MS. These diets improve body composition and enhance glycemic control (Dhir et al., 2013). During weight loss, protein-rich diets reduce loss of lean tissue and increase loss of body fat.

New research reveals increasingly complex role for protein and amino acids in regulation of body composition and bone health, gastrointestinal function and bacterial flora, glucose homeostasis, cell signalling, and satiety. Richard et al., (2013) observed that consuming Mediterranean Diet even in the absence of weight loss significantly reduces inflammation. However, the degree of waist circumference reduction with the weight loss magnifies the impact of the Mediterranean Diet on other markers of inflammation associated with MS.

Management of Metabolic Risk Factors

Attention must be given to the metabolic risk factors beyond lifestyle therapies directed toward underlying risk factors. If ASCVD or diabetes is present, or if the 10-year risk as determined by Framingham risk factors is relatively high, then drug therapies for risk factors may be required as defined by current guidelines (NCEP, 2002; Chobanian et al., 2003; Genuth et al., 2003).

Atherogenic Dyslipidemia

This condition consists of abnormal levels of triglycerides and apoB, small LDL particles, and low HDL-C. As long as LDL-C remains above goal level, LDL-C is the primary target of therapy even in the metabolic syndrome. Other risk factors are secondary. The LDL-C goals depend on estimates of absolute risk. Non-HDL-C becomes the next target of treatment after the LDL-C goal is reached in patients with atherogenic dyslipidemia in whom serum triglyceride levels are Ó200 mg/dL. A related and potential secondary target is an elevated total apoB (Grundy 2002); this measure denotes the number of atherogenic lipoproteins in circulation (Sniderman, 2004; Yusuf et al., 2004; Lamarche et al., 1997; Carr and Brunzell, 2004; Brunzell, 2005). Some researchers hold that total apoB is superior to non-HDL-C as a target of lipid-lowering therapy (Brunzell, 2005; Sniderman, 2004; Sattar et al., 2004). ATP III however identified non-HDL-C rather than total apoB as a secondary target (after LDL-C) because accurate measurement of non-HDL-C is more readily available in clinical practice. Goals for non-HDL-C parallel those for LDL-C except that the former are 30 mg/dL higher than the latter.

Triglyceride-lowering drugs should be considered to prevent the development of acute pancreatitis when triglycerides are Ó500 mg/dL (NCEP, 2002). To achieve non-HDL-C goals at triglycerides <500 mg/dL, triglyceride-lowering drugs may be useful in combination with LDL-lowering therapy. Beyond lowering of non-HDL-C, a tertiary aim in patients with atherogenic dyslipidemia is to raise HDL-C when it is reduced. HDL-C should be raised to the extent possible after attaining goals for LDL-C and non-HDL-C, however no specific goal of therapy is recommended for low HDL-C.

Two therapeutic options are available if non-HDL-C remains elevated after the LDL-C goal is reached. First, intensification of LDL lowering often also reduces non-HDL-C. For

example, statins lower both LDL-C and non-HDL-C by a similar percentage; moreover, statins reduce risk for ASCVD events in patients with the metabolic syndrome (Ballantyne et al., 2001). Second, a triglyceride-lowering drug can be added to LDL-lowering therapy. Both fibrates and nicotinic acid reduce non-HDL-C and reportedly decrease risk for ASCVD in patients with the metabolic syndrome/type 2 diabetes mellitus (Rubins, 2000; Rubins et al., 2002; Canner et al., 2005). Hence, combining a fibrate or nicotinic acid with LDL-C-lowering treatment becomes an option (Grundy et al., 2005; Bays et al., 2003). Both fibrates and nicotinic acid raise HDL-C as well as reduce triglycerides and small LDL particles. Fenofibrate seems preferable to gemfibrozil because risk for severe myopathy appears to be lower for fenofibrate in combination with statins, if a statin is being used for LDL-C lowering (Jones and Davidson, 2005). Patients with IFG, IGT, or diabetes who are treated with nicotinic acid deserve careful monitoring for worsening of hyperglycemia and other related metabolic disorders (Grundy et al., 2002). Lower doses of nicotinic acid lessen this risk. Whether adding a fibrate or nicotinic acid to statin therapy will reduce cardiovascular events more than a statin alone has not been evaluated adequately in randomized clinical trials; consequently the use of this combination probably should be limited largely to high-risk individuals who stand to gain the most from it. Higher doses of the statin generally should be avoided to minimize risks for myopathy or hepatic effects, if a fibrate or nicotinic acid is used with a statin.

Atherosclerosis, the underlying cause of atherosclerotic cardiovascular disease (ACVD) develops due not only to a single cardiovascular risk factor but to a variety of complex factors. The concept of the multiple cardio-metabolic risk factor clustering syndrome has been proposed as a highly atherogenic state independent of hypercholesterolemia and smoking. Body fat

distribution especially visceral fat accumulation is a major correlate of a cluster of diabetogenic, atherogenic, prothrombotic and proinflammatory metabolic abnormalities referred to as the MS, with dysfunctional adipocytes and dysregulated production of adipocytokines (hypoadiponectinemia). Medical research has focused on visceral adiposity as an important component of the syndrome in Japanese subjects with a mild degree of adiposity compared with Western subjects. For the prevention of ACVD at least in Japan, it might be practical to stratify subjects with multiple risk factors for atherosclerotic cardiovascular disease based on visceral fat accumulation. Visceral fat reduction through health promotion programme using risk factor-oriented approaches may be effective in reducing ACVD events as well as producing improvement in risks and hypoadiponectinemia. The study discussed visceral adiposity as a key player in the syndrome. Visceral fat reduction with life-style modification is a potentially useful strategy in the prevention of ACVD in patients with the MS (Kishida et al., 2012).

Elevated Blood Pressure

The goal for antihypertensive therapy is a blood pressure of <140/90 mm Hg, when overt hypertension is present without diabetes or chronic kidney disease (Chobanian et al., 2003). In the presence of diabetes or chronic kidney disease, the blood pressure goal is <130/80 mm Hg (Chobanian et al., 2003). Lifestyle changes deserve increased emphasis in people with the metabolic syndrome; the goals here are to reduce blood pressure as much as possible even in the absence of overt hypertension and to obtain other metabolic benefits of lifestyle change. Mild elevations of blood pressure often can be effectively controlled with lifestyle therapies like increased physical activity, alcohol moderation, weight control, sodium reduction and increased consumption of low-fat dairy products and fresh fruits and vegetables, in accord with the Dietary

Approaches to Stop Hypertension (DASH) diet (Chobanian et al., 2003). Antihypertensive drugs usually are necessary to prevent long-term adverse effects, eg, myocardial infarction, stroke, and chronic kidney disease, if hypertension cannot be adequately controlled by lifestyle therapies (Chobanian et al., 2003). The benefits of therapy extend to patients with type 2 diabetes mellitus whose blood pressure is above goal level, and presumably to hypertensive patients with the metabolic syndrome. Some investigators support angiotensin-converting enzyme (ACE) inhibitors as first-line therapy for hypertension in the metabolic syndrome, especially when either type 2 diabetes mellitus or chronic renal disease is present (Barnett et al., 2004). Indeed, inhibition of the renin-angiotensin system with ACE inhibitors or angiotensin receptor blockers (ARBs) may lower risk for diabetes itself (Scheen, 2004). ARBs may be used in those who cannot tolerate ACE inhibitors or as an alternative to ACE inhibitors in people who have left ventricular dysfunction (Ball and White, 2003). Use of diuretics in patients with IFG or IGT may increase the likelihood of progression to type 2 diabetes mellitus, although diuretics do in fact lower the risk for cardiovascular events (Chobanian et al., 2003). It is believed by most investigators in the hypertension field that the potential benefit of low-dose diuretics in combination antihypertensive therapy outweighs their risk.

Critical Reviews in Food Science and Nutrition

Elevated Fasting Glucose

In the diagnosis of metabolic syndrome, elevated fasting glucose (Ó100 mg/dL) includes both IFG and type 2 diabetes mellitus. Weight reduction, increased physical activity or both will delay (or prevent) the onset of type 2 diabetes mellitus in metabolic syndrome patients with IFG (or IGT if assessed) (Knowler et al., 2002; Tuomilehto et al., 2001). In addition, metformin (Knowler et al., 2002), thiazolidinediones (Buchanan et al., 2002; Knowler et al., 2005) and

acarbose (Chiasson et al., 2002) will lower risk for type 2 diabetes mellitus in people with IFG or IGT. Except for a preliminary trial with acarbose (Chiasson et al., 2003), no clinical trial evidence is yet available to document that oral hypoglycemic agents will lessen risk for cardiovascular events. Moreover, neither of these drugs are recommended in this statement solely for the purpose of preventing diabetes because their long-term safety and cost effectiveness have not been documented as yet.

Clinical trials confirm a reduction in cardiovascular risk from treatment of dyslipidemia (Ballantyne et al., 2001; Rubins, 2000; Rubins et al., 2002; Goldberg et al., 1998; Haffner et al., 1999; Collins et al., 2005) and hypertension (Chobanian et al., 2003). Glycemic control to a hemoglobinA_{1c} of <7% reduces microvascular complications and may decrease risk for macrovascular disease.

Prothrombotic State

People suffering from metabolic syndrome typically manifest elevations of fibrinogen, plasminogen activator inhibitor-1, and other coagulation factors. For primary prevention, the only available long-term approach to counter their contribution to arterial thrombosis is low-dose aspirin or other antiplatelet agents. These agents, especially aspirin, are recommended in patients with established ASCVD provided they are not contraindicated. Their efficacy in individuals with type 2 diabetes mellitus without ASCVD has not been established conclusively through clinical trials, although they are widely recommended in such individuals. Aspirin prophylaxis is an attractive therapeutic option to lower vascular events in metabolic syndrome patients who are at moderately high risk for ASCVD (Pearson et al., 2002).

Proinflammatory State

Measurement of CRP is the simplest way to identify a proinflammatory state in clinical practice. People with the metabolic syndrome frequently have a proinflammatory state as shown by elevated cytokines (eg, tumor necrosis factor-Ŭ and interleukin-6) and acute-phase reactants (eg, CRP, fibrinogen) (Ridker et al., 2003; Ridker et al., 2004). CRP levels >3 mg/L can be taken to define proinflammatory state in a person without other detectable causes (Pearson et al., 2003). The finding of an elevated level of CRP supports the need for lifestyle changes. The latter, particularly weight reduction, will reduce CRP levels and hence will mitigate the underlying inflammatory. No drugs that act exclusively through this mechanism are available for reducing cardiovascular risk. However, several drugs used to treat other metabolic risk factors have been reported to reduce CRP levels (eg, statins, ACE inhibitors, nicotinic acid, fibrates, thiazolidinediones) (Jialal et al., 2001; Schieffer et al., 2004; Nesto, 2004). At present, these drugs cannot be recommended specifically to reduce a proinflammatory state.

Critical Reviews in Food Science and Nutrition

Conclusion

This review recognizes many issues related to the metabolic syndrome that require further research for clarification. Primary need is for improved strategies to achieve and sustain long-term weight reduction and increased physical activity. Moreover, a lack of understanding of the genetic and metabolic contributions to the causation of the syndrome stands in the way of developing new therapeutic approaches. At present, significant improvement is needed in tools to

assess short-term risk for ASCVD and diabetes in patients with the metabolic syndrome. Although statins and other LDL-lowering drugs effectively reduce the risk for ASCVD, adequate therapies for remaining dyslipidemias either are not available or have not yet been proved to reduce risk in combination with LDL-lowering drugs. Clinical trials to date have not been carried out to confirm ASCVD risk reduction from decreasing insulin resistance per se, however, insulin resistance is an attractive target for prevention of ASCVD. The emerging relationship between a proinflammatory state and the development of both ASCVD and diabetes deserves much additional investigation. Finally, the cost-effectiveness and long term safety of various drugs, both alone and in combination therapies, requires more extensive research.

Amino acids and dietary proteins are important modulators of glucose metabolism and insulin sensitivity. Although high intake of dietary proteins has positive effects on energy homeostasis by possibly increasing energy expenditure and inducing satiety, it has detrimental effects on glucose homeostasis by increasing Gluconeogenesis and promoting insulin resistance. Varying the quality rather than the quantity of proteins has been shown to modulate insulin resistance, hence helping in alleviating the symptoms of metabolic syndrome.

Metabolic syndrome can be clinically manifested in a variety of ways. A definite number of metabolic changes thus occur in people with clinical evidence of the syndrome. Identification of these changes should provide a broader picture of the metabolic status of an affected individual. Many of these factors cannot be readily identified in routine clinical practice. Nevertheless, several factors appear to overlap with alternative measures of the same underlying or metabolic risk factor. For example, there are several ways to estimate body fat distribution. Similarly, multiple tests for insulin resistance have been proposed; each examines a different

aspect of the insulin-resistance phenomenon. The International Diabetic Federation report lists many of these factors as important targets for research even when they are not used for routine clinical diagnosis. Metabolic, epidemiological and genetic studies directed to a broad profile of parameters related to the metabolic syndrome should provide new insights into the responsible pathways.

Critical Reviews in Food Science and Nutrition

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