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The Metabolic Syndrome: Where Are We and Where Do We Go?

The Metabolic Syndrome, also known as Syndrome X, refers to a constellation of atherosclerotic risk factors, including insulin resistance, hyperinsulinemia, dyslipidemia, essential hypertension, and abdominal obesity. We review four major published studies involving animals and humans that may be linked together in a unified hypothesis and justify a comprehensive approach in the treatment of this ever-increasing syndrome.

Key Words: atherosclerotic risk factors, insulin resistance, hyperinsulinemia, dyslipidemia, essential hypertension, abdominal obesity

The combination of metabolic disturbances known as the metabolic syndrome has been described since the 1920s. Reaven first described it succinctly in 1988 as Syndrome X; it combined insulin resistance, dyslipidemia, and hypertension. In 1989, Kaplan renamed it "The Deadly Quartet" and added abdominal obesity to the list of disturbances. In 1992, Haffner again renamed it the "Insulin Resistance Syndrome."[1,2]

A recent experimental animal study by Roberts et al.[3] aimed to determine whether the abnormalities seen in the metabolic syndrome were reversible through dietary approaches. The first step was to demonstrate that diet could lead to the metabolic abnormalities. The researchers raised a group of rats on a high-fat (primarily saturated fat), high-refined carbohydrate (sucrose) diet (HFS), similar to the typical U.S. diet. After 2 years they observed that the rats had developed obesity, hypertension, hyperinsulinemia, and hypertriglyceridemia.[4] Interestingly, the group of rats consuming a low-fat, high-complex carbohydrate diet (LFCC) did not develop these factors despite the long study duration. Investigators then randomly assigned rats to either the LFCC diet or the HFS diet for 20 months. The LFCC diet was 59.8% energy as carbohydrate and 28% energy as protein, whereas the HFS diet was 40% energy as carbohydrate and 20.7% energy as protein. After 20 months, the researchers switched a group of HFS rats to the LFCC diet (HFS/LFCC) for 2 months. Body weight and energy intake were measured weekly during the study. At the end of the 22-month period, they measured skeletal muscle glucose transport, plasma insulin, systolic blood pressure, and plasma lipids.

Researchers found insulin-stimulated glucose transport significantly reduced in the HFS group. Insulin resistance can be defined as needing >200 units of insulin daily to control hyperglycemia and prevent ketosis and can occur with excessive tissue uptake of fatty acids leading to inhibition of insulin activity at the cellular level. Obesity is the most common cause of insulin resistance and is due to a decrease in insulin receptor number and failure to activate tyrosine kinase at the postreceptor level.[5] Plasma insulin, blood pressure, plasma triglycerides, low-density lipoprotein cholesterol (LDL-C), the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), total cholesterol, and body weight were all significantly elevated in the HFS group when compared with the LFCC group. The HFS/LFCC rats had normalization of glucose transport, blood pressure, plasma insulin, and VLDL-C, and a decrease in obesity. The authors proposed that the metabolic abnormalities seen in the metabolic syndrome are not an aging phenomenon because the animals in the LFCC group did not develop these abnormalities. It was concluded that diet therapy could potentially reverse insulin resistance and hyperinsulinemia despite prolonged carbohydrate metabolism impairment. The authors also concluded that obesity could be at least partially reversed by dietary modification to include a low-fat, low-refined carbohydrate diet without caloric restrictions.[3]

Three series of interconnected clinical observations have provided evidence that metabolic syndrome can also be reversed in human beings. The first involves a clinical observation of the incidence of the metabolic syndrome in the U.S. population. In 2001, the National Cholesterol Education Program produced an updated version of their clinical guidelines, known as ATP III.

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Each set of guidelines published advances in cholesterol management: ATP I addressed patients with coronary heart disease and elevated or borderline LDL-C, ATP II set a new, lower standard LDL-C level for patients with coronary heart disease, and ATP III aimed to address primary prevention in a group of patients with multiple risk factors. ATP III also created the most recent definition of the metabolic syndrome.[6] This definition was applied to the Third National Health and Nutrition Examination Survey (NHANES III), from 1988 to 1994, in an attempt to determine the prevalence of the metabolic syndrome in the United States. Patients were considered to have the metabolic syndrome if they exhibited three or more of the following criteria:

- Abdominal obesity: waist circumference >102 cm in men and >88 cm in women,
- Hypertriglyceridemia: ≥150 mg/dL,
- Low HDL-C: <40 mg/dL in men and <50 mg/dL in women,
- High blood pressure: ≥130/85 mm Hg,
- High fasting glucose: ≥110 mg/dL.

The analysis found that 22% of U.S. adults have the metabolic syndrome as defined by these parameters.[7] Despite the standard belief that this disease is more common in men,[8] NHANES III found similar prevalence among men and women, 24.0% and 23.4%, respectively. The metabolic syndrome was more prevalent among Mexican Americans (31.9%) and less so among whites (23.8%) and African Americans (21.6%).

In an elegant analysis of all data published on exercise and the metabolic syndrome, Shahid et al.[9] noted that an exercise program could positively affect many of the abnormalities found. They created an "ideal program" that was preferably aerobic at 40 to 65% of VO2max (maximal oxygen consumption during exercise) for 20 to 45 minutes per session, three to four times weekly. Review of different studies demonstrated that:

- A single glycogen-depleting bout of exercise led to increased insulin sensitivity in the exercised muscle for up to 48 hours,
- There was a negative correlation between systolic blood pressure and physical fitness,
- Physical training led to a decrease in plasma triglyceride levels,
- Regular physical exercise resulted in lower levels of plasminogen activator inhibitor (a measure of clotting tendency) and improved fibrinolytic activity,
- The addition of exercise to a weight loss program causes a disproportionate loss of intra-abdominal fat.

Finally, a study by Tuomilehto et al.[10] examined the effect of lifestyle modifications, including dietary and physical activity, on the development of type 2 diabetes. The authors randomly assigned 522 middle-aged, overweight subjects with impaired glucose tolerance to either an intervention or a control group. The intervention group underwent multiple personalized counseling sessions aimed at increasing physical activity and fiber intake and reducing weight, and total and saturated fat intake. Dietary advice was tailored using 3-day food records obtained at 4-month intervals. At baseline and annually, the control group was given oral and written information about dietary and physical activity modification. No individualized information was given to the control group members. Within the first year, the intervention group lost significantly more weight than the control group: 4.2 ± 5.1 kg versus 0.8 ± 3.7 kg ($P < 0.001$), respectively. The incidence of diabetes in the intervention group was 54% lower among women and 63% lower among men—a 58% decline in the cumulative incidence of diabetes. Patients in the intervention group who did not achieve lifestyle modifications had a 35% incidence of diabetes.

The findings from these published studies are important because there is still no standard of care for treating the metabolic syndrome. Based on the above review, it is likely a program combining weight loss with physical activity will achieve the best results. Dietary modifications would include a low-fat and high-fiber diet, and physical activity would combine aerobic activity with resistance training. The "ideal program" would be similar to that proposed by Shahid et al.,[9] although any increase in activity would be beneficial. In our own experience, the combination of dietary modifications with physical activity has created the most significant changes in weight and comorbidities. If a common link can be found between all of the metabolic abnormalities, an integrated solution can be achieved for management of this ever-increasing healthcare epidemic.

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Elderly Women Need Dietary Protein to Maintain Bone Mass

Excess dietary protein is considered a risk factor for osteoporosis owing to the potential for renal acid load. Researchers who conducted a recent prospective study of older adults reported that animal protein had a protective role for bone, especially in elderly women, whereas plant protein was negatively associated with bone mineral density. An interaction between protein and calcium suggested protein alone was not the important factor. Other studies confirm the beneficial effect of increasing dietary protein intake in older women to reduce bone mineral density loss and risk of fracture, suggesting that emphasis should be placed on promoting adequate protein intake in elderly women.

Key Words: animal protein, plant protein, net acid production, bone mineral density, osteoporosis

Scientists have long known that excess dietary protein raises net acid excretion, thereby causing a rise in urinary calcium excretion, and leading to bone loss.[1,2] Whereas it has been difficult to define the amount of dietary protein that qualifies as "excess," the common perception is that the typical North American diet, high in animal protein, is sufficient to evoke changes in calcium metabolism and result in bone loss and subsequent osteoporotic fractures.[3,4] Recent studies have challenged this popular view of dietary protein, however, particularly for elderly women. A review of the recent studies on how protein intake affects bone mineral density (BMD) or hip fracture incidence in elderly women shows near consensus that increasing protein intake is not harmful but beneficial to bone health (in the range of usual intake) of the women studied.

Of the six prospective studies relating dietary protein to bone health (measured as BMD or fracture incidence) in older American women, only Feskanich et al.[5] found a significant increase in fracture risk, and this risk was seen only for protein intakes greater than 95 g/day, which corresponds with intakes of less than 10% of protein intake for U.S. women 50 years and older.[6] (Table 1) The other five studies involving subjects with mean protein intakes between 68 and 79 grams/day, found that the higher protein intakes were associated with reduced fracture risk,[7] higher BMD,[8] or reduced BMD loss.[9–11] Mean calcium intakes did not reach the Adequate Intake level of 1200 mg[12] in any study. The calcium-to-protein ratio of subjects in studies showing a protective effect of protein was higher than in the study showing an adverse effect, suggesting that the calcium-to-protein ratio may be important when considering protein effects on bone.[13]

The debate concerning protein and its effect on bone has also raised the issue of the type of protein; animal protein is thought to provide more potential renal acid load than plant-based protein. Likewise, Sellmeyer et al.[8] found that a greater ratio of plant-based to animal protein was beneficial in reducing BMD loss and hip fracture risk in elderly women. As shown in Table 1, however, most of the recent studies of elderly women found no benefit of plant-based protein over animal protein,[10] or an advantage of animal protein over plant-based protein.[7,9,11] One study has suggested that consumption of plant-based protein may cause loss of bone because there was a negative association between vegetable protein and BMD in elderly female subjects, but not in male subjects.[11] In this study, Promislow et al. examined protein intake and BMD in 1526 men and women aged 55 to 92 years who were participants in the Rancho Bernardo cohort.[11] This group of subjects has been studied by these authors since the early 1970s. Between

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