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In this Issue:
The Metabolic Syndrome, Insulin Resistance and Cardiovascular Disease

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The Metabolic Syndrome, Insulin Resistance and Cardiovascular Disease

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Whether you are a primary care specialist or a sub-specialist, you are probably seeing more patients with diabetes as well as patients with metabolic syndrome (also known as “pre-diabetics”). There are several potential reasons for the “pandemic,” but most experts agree that the majority of patients possess the combination of improper behavior — over-eating and under-exercising — with genetic or ethnic tendencies. Subsequently, the development of obesity with other metabolic problems begins to occur concomitantly.

For most of the 20th century, cardiovascular disease (CVD) was identified as the major cause of morbidity and mortality in the developed world. During this period there was considerable effort to understand the underlying biology of the disease and to identify the contributing risk factors. As risk factors were identified, it became apparent that more than one was often present in the same individual. Toward the end of the century, the clustering of CVD risk factors was first described — most notably the simultaneous presence of obesity, type II diabetes, hyperlipidemia and hypertension. Although insulin resistance (i.e., resistance to insulin-stimulated glucose uptake) as a feature of type II diabetes was first described many years earlier, hyperinsulinemia was also found to be a key feature of type II diabetes, as well as hyperlipidemia, obesity and hypertension.

This risk-factor clustering, and its association with insulin resistance, led investigators to propose the existence of a unique pathophysiological condition, called the “metabolic” or “insulin resistance” syndrome. This concept was unified and extended with the landmark publication of Gerald Reaven in 1988 (1). Reaven postulated that insulin resistance and its compensatory hyperinsulinemia predisposed patients to hypertension, hyperlipidemia and diabetes, and was thus the underlying cause of much CVD.

As defined principally by the World Health Organization (2) and the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III) (3), the metabolic syndrome has been identified as the presence of three or more of these risk factors:

- Elevated triglycerides of greater than 150.
- Diminished HDL with gender specificity (women less than 50, and men less than 40). An ideal HDL is greater than 60 and actually will negate one of the other risk factors used in calculating a Framingham cardiovascular 10-year risk score of having a future event.
- Increased waist circumference. Also gender specific, with greater than 40 inches (102 cm) in men and greater than 35 inches (88 cm) in women. A simple tape measure can be used by the nursing staff as part of the vital signs taken at each visit. With the patient in a relaxed state, measure the largest circumference between the umbilicus and the top of the ilium. The greater the amount of visceral adiposity, the greater the risk of the development of metabolic syndrome. The visceral adipocytes are glandular in nature and produce adipokynes, angiotensinogen, insulin resistance factors along with procoagulants (14).

- Elevated blood pressure: systolic blood pressure of greater than 130 mmHg and a diastolic blood pressure of greater than 85 mmHg.
- Elevated fasting serum glucose of greater than 100 mg%.

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The ADA and the European Association for the Study of Diabetes issued a controversial joint statement in September 2005 stating that the metabolic syndrome may be a group of disorders that have disparate pathologies. The syndrome, they contend, appears to confer no greater risk of CVD risk as a whole than does the sum total of its parts and can mislead patients in believing that they have a “disease” rather than a cluster of cardiovascular risk factors which should be treated individually (4). The primary basis for this recommendation has been based on data from the National Cholesterol Education Program, Adult Treatment Program III. The Framingham risk score has actually been shown to be superior to the clinical criteria for metabolic syndrome for predicting CVD events (3).

As the mechanisms underlying the metabolic syndrome continue to be debated, most physicians agree these patients are at increased risk for the subsequent development of vascular disease. Therefore, smoking cessation, reduction of LDL cholesterol, adequate blood pressure control and improvement of hyperglycemia are of the utmost importance for the prevention of vascular disease, whether or not the patient has the clinical criteria for metabolic syndrome.

These tasks can often be accomplished by weight reduction through dietary discretion, regular exercise of 120-150 minutes per week or 2000 calories of energy expenditure/week, and the introduction of medications when appropriate based on risks and benefits. Healthy eating habits should not only include calorie counting but also limitations of carbohydrates, saturated fats, trans-fats and cholesterol.

There has also been an association between markers of inflammation and insulin resistance (5), as well as inflammation and obesity (7, 8, 9), leading some investigators to conclude that inflammation is integrally related to the components of the metabolic syndrome (10).

One of the many markers identified is C-reactive protein (CRP), which has been studied in great detail. It has been found to be an independent CVD risk factor (11, 12) and an independent marker of insulin resistance (13); CRP is also strongly associated with adipose-derived cytokines — including interleukin-6 and tumor necrosis factor (14) — and is more likely to be elevated in obese insulin-resistant, but not obese insulin-sensitive, subjects (6).

Several other molecules/markers have also been found to be closely related to the components of the metabolic syndrome. For example, thiazolidendiones (pioglitazone,rosiglitazone), biguanides (metformin), and more recently glucagon-like protein (GLP-1) inhibitors (exenatide).

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risk of thrombosis. With the development of unstable plaques which frequently ulcerate, this can prove to be a deadly combination.

PAI-1, produced by the visceral adipocyte, acts as a tissue plasminogen activator (TPA) inhibitor, which converts plasminogen to plasmin, leading to the degradation of fibrin on the vascular wall. It can be reduced by weight loss, exercise and thiazolidendiones (TZDs). The TZDs (pioglitazone, rosiglitazone) may have additional pleiotrophic vascular effects in addition to their known PPAR-

activation not only displays beneficial effects on glucose homeostasis but also on lipid metabolism, endothelial function and vessel wall inflammation. In small retrospective studies, these medications have shown to decrease carotid intimal media thickness and microalbuminuria, both markers of endothelial dysfunction in diabetics and non-diabetic hypertensives. Also, there is evidence that TZDs may also decrease post stent restenosis rates following coronary stent placement in diabetics (17). More evidence in the form of large double-blinded prospective studies are necessary and currently underway. In the PROActive study — the first prospective double blind study involving a TZD — pioglitazone failed to reach clinically significant primary outcomes prevention but did reveal a decrease in secondary endpoints. The primary secondary endpoints of life threatening events showed that pioglitazone significantly reduced the risk of myocardioc infarction, cerebrovascular events and death by 16 percent (p<0.027) (18).

Is diabetes a glucose issue or is it the etiology of why we have an elevated glucose problem? That question needs to be further elucidated. Does insulin resistance (as the underlying problem in most of these patients) and the co-existence of hypertension, hyperlipidemia and hyperglycemia predicate the inevitable development or aggressive progression of CVD? Since the metabolic syndrome does not include all known CVD risk factors, it should convey risk independently of other conventional risk factors (e.g., LDL, age, smoking and family history); however, the proportion of the global CVD risk captured by the syndrome is unknown. It would be invaluable to know, from a list of all known CVD risk factors, the hierarchy of combinations with the highest predictive value. Then, a true comparison between the metabolic syndrome or perhaps some new combination would tell us what is the best CVD predictive model. J. Ross Tanner, D.O. currently practices in Anchorage, Alaska with Diabetic Consultants of Alaska. He is board certified in Internal Medicine and Clinical Lipidology.

REFERENCE

17. American College of Cardiology 53rd Annual Scientific Session. Preventive Effects of Rosiglitazone on Restenosis After Coronary Stent Implantation in Patients With Type 2 Diabetes Mellitus. Abstract 1062-46 March 6, 2004
Physician conferences and grand rounds

**May 02**
Tuesday 8:30 a.m.  Pediatric Grand Rounds  
PAMC West Auditorium

**May 03**
Wednesday 8 a.m.  Breast Cancer Conference  
PAMC East Auditorium

**May 04**
Thursday 8 a.m.  Cancer Conference  
Alaska Regional Hospital

**May 09**
Tuesday 9:30 a.m.  Pediatric Grand Rounds  
Children’s Hospital at Providence

**May 10**
Wednesday 7:30 a.m.  Chest Case Conference  
PAMC East Auditorium

**May 11**
Thursday 8 a.m.  Cancer Conference  
Alaska Regional Hospital

**May 16**
Tuesday 12 p.m.  Family Practice Rounds  
PAMC West Auditorium

**May 16**
Tuesday 8:30 a.m.  Pediatric Grand Rounds  
Alaska Regional Hospital

**May 17**
Wednesday 8 a.m.  Breast Cancer Conference  
PAMC East Auditorium

**May 18**
Thursday 8 a.m.  Cancer Conference  
Alaska Regional Hospital

**May 23**
Tuesday 8:30 a.m.  Pediatric Grand Rounds  
Alaska Native Med Center

**May 24**
Wednesday 7:30 a.m.  Chest Case Conference  
PAMC East Auditorium

**May 25**
Thursday 8 a.m.  Cancer Conference  
Alaska Regional Hospital

**June 01**
Thursday 8 a.m.  Cancer Conference  
PAMC East Auditorium

**June 02**
Tuesday 8:30 a.m.  Pediatric Grand Rounds  
Alaska Regional Hospital

**June 07**
Wednesday 8 a.m.  Breast Cancer Conference  
PAMC East Auditorium

**June 08**
Thursday 8 a.m.  Cancer Conference  
PAMC East Auditorium

**June 13**
Tuesday 8:30 a.m.  Pediatric Grand Rounds  
PAMC West Auditorium

**June 14**
Wednesday 7:30 a.m.  Chest Case Conference  
PAMC East Auditorium

**June 15**
Thursday 8 a.m.  Cancer Conference  
PAMC Willow Room

**June 21**
Wednesday 8 a.m.  Breast Cancer Conference  
PAMC Willow Room

**June 22**
Thursday 8 a.m.  Cancer Conference  
PAMC Willow Room

**June 29**
Thursday 8 a.m.  Cancer Conference  
PAMC East Auditorium

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**Welcoming New Physicians**

Superior health care starts with highly skilled specialists who bring essential knowledge and proven experience to the table. That’s why we’re proud to welcome the following new physicians:

- **Katharine Lamperti, MD**  
  Anesthesia  
  Providence Anchorage Anesthesia Group  
  3300 Providence Drive #207  
  561-0005

- **Steven Liu, MD**  
  Oncology  
  Katmai Oncology Group  
  561-0321

- **Robert Moreland, MD**  
  Dermatology  
  Alaska Center for Dermatology  
  646-8500

- **Philip Mabry, DDS**  
  Dentist  
  Boniface Dental Center  
  337-9448

- **Thomas Wanat, DMD**  
  Dentist  
  3340 Providence Dr. #560  
  562-6549

- **Marc Slonimski, MD**  
  Pain Management  
  Advanced Pain Center of Alaska  
  278-2741

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**Continuing Medical Education Calendar**

**May 5, 2006**

**HIV / AIDS: 2006 Update**

The conference will review recent advances in understanding the biology of HIV infection, recognizing common clinical manifestations, current antiretroviral guidelines, new antiretroviral medications, post exposure prophylaxis, and management of concurrent Hepatitis B and HIV infection. The course is designed for all physicians who treat patients with HIV infection. Physicians are encouraged to bring cases for discussion.

**May 12 & 13, 2006**

**Human Sexuality: New Directions and Dilemmas**

This conference will present a selection of the dilemmas which patients present to their physicians and behavioral health professionals in clinical practice. The course is designed to be helpful to all physicians and behavioral health professionals who see both adult and pediatric patients in a clinical consultative setting. The conference is presented jointly with the Alaska Chapter of the American Psychological Association. Participants wanting AK-PA credit will need to pay a separate $40 fee to AK-PA for continuing education credit from AK-PA.

**June 22-24, 2006**

**American College of Physicians Conference: Travel Medicine**

We all travel, and we all worry about traveling. Our shrinking world presents wonderful opportunities for enlarging horizons. At the same time we face unprecedented dangers in the acquisition and transmission of exotic and not-so-exotic diseases. This course is designed to update physicians and other practitioners who advise patients on travel issues. Happy travels, and we'll see you in Anchorage in June!