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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-diabetes”). 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 adipocytokines, 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%. If greater than 126 mg%, the diagnosis of diabetes can be established.

There are currently no medications approved for the specific treatment of the metabolic syndrome as a constellation of disorders. But there are FDA-approved medications to treat each component of



this syndrome, with the exception of impaired fasting glucose. Many physicians have used anti-hyperglycemic medications “off-label” to treat impaired fasting glucose or impaired glucose tolerance. For example, thiazolidendiones (pioglitazone, rosiglitazone), biguanides (metformin), and more recently glucagon-like protein (GLP-1) inhibitors (exenatide).

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 associated with insulin resistance, metabolic syndrome risk factors and the risk of CVD. These include increased levels of plasminogen activator inhibitor (PAI-1) (15), fibrinogen (16), factor VII activation and thus an increase in prothrombin, as well as increased platelet aggregation. These factors and others can contribute to the increased



in vascular tissue and indirectly via effects on other tissues. 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 principal secondary endpoints of life threatening events showed that pioglitazone significantly reduced the risk of myocardial 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.

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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_ agonism for the treatment of insulin resistance/hyperglycemia. Peroxisome proliferator-activated receptors (PPARs) are transcription factors that influence vascular function by altering gene expression

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Providence Alaska Learning Institute

Continuing Medical Education Calendar

May 5, 2006 Friday 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 Friday/Saturday 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 Thursday-Saturday 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!

June 29, 2006 Thursday Neonatology Lecture NICU

Two one-hour lectures; topic and speaker to be announced.

August 4-5, 2006 Friday/Saturday TBA

Sept 7 & 8, 2006 Thursday/Friday 23rd Annual Denali Oncology Group, Hoonah, Alaska

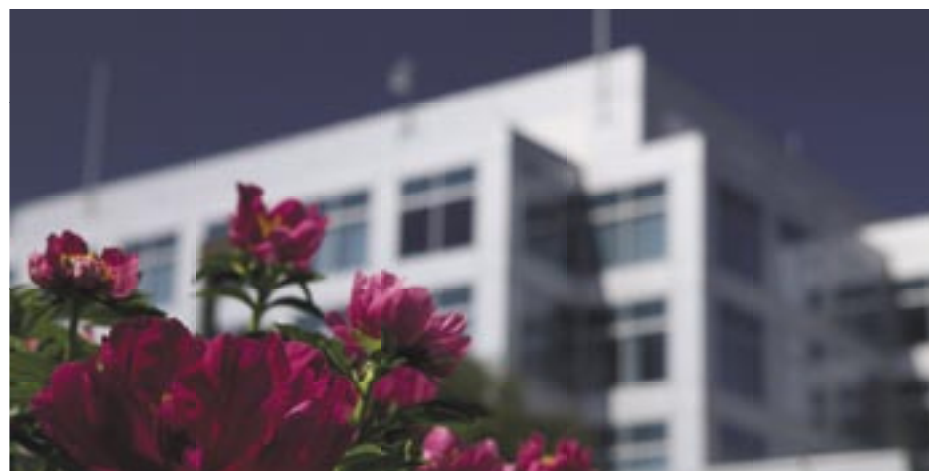
Oct 6 & 7, 2006 Thursday/Friday Coagulation Conference

Oct 19, 2006 Thursday Neonatology Lecture NICU

Two one-hour lectures; topic and speaker to be announced.

Nov 3 & 4, 2006 Friday/Saturday TBA

Dec 1 & 2, 2006 Friday/Saturday TBA



Please contact Providence Alaska Learning Institute (907-261-3011) to be placed on the mailing list for a workshop brochure or flyer announcing CME lectures. All seminars will be held in the lower level auditorium(s) at Providence Alaska Medical Center unless otherwise indicated. You can now access Providence Physician CME information on the Providence web site. Go to www.providence.org/alaska and click on "For Physicians."

This is a preliminary announcement. Dates, times and topics are subject to change. This list does not represent all seminars that may be offered. Courses that offer CME Category I Credit meet the criteria of the State of Alaska Board of Nursing as acceptable continuing education for nursing relicensure in the State of Alaska. Providence Alaska Learning Institute reserves the right to establish minimum and maximum attendance and, if necessary, to change, move or cancel a course without notice.

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 8:30 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
Jun 01	Thursday 8 a.m.	Cancer Conference	PAMC East Auditorium
Jun 06	Tuesday 8:30 a.m.	Pediatric Grand Rounds	Alaska Regional Hospital
Jun 07	Wednesday 8 a.m.	Breast Cancer Conference	PAMC East Auditorium
Jun 08	Thursday 8 a.m.	Cancer Conference	PAMC East Auditorium
Jun 13	Tuesday 8:30 a.m.	Pediatric Grand Rounds	PAMC West Auditorium
Jun 14	Wednesday 7:30 a.m.	Chest Case Conference	PAMC East Auditorium
Jun 15	Thursday 8 a.m.	Cancer Conference	PAMC Willow Room
Jun 21	Wednesday 8 a.m.	Breast Cancer Conference	PAMC Willow Room
Jun 22	Thursday 8 a.m.	Cancer Conference	PAMC Willow Room
Jun 29	Thursday 8 a.m.	Cancer Conference	PAMC East Auditorium

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



Phillip Mabry, DDS
Dentist
Boniface Dental Center
337-9448



Steven Liu, MD
Oncology
Katmai Oncology Group
562-0321



Thomas Wanat, DMD
Dentist
3340 Providence Dr. #560
562-6648



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



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