Inflammation, Atherosclerosis, and Aspects of Insulin Action

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C-reactive protein

At the American Diabetes Association Postgraduate Course held in New York on 5 February 2005, Alan Chait (Seattle, WA) discussed C-reactive protein (CRP). Although it may not be as predictive of cardiovascular disease (CVD) as cholesterol, hypertension, and cigarette use (1), CRP appears to be the strongest “novel” risk factor thus far identified, showing greater predictive power than homocysteine, interleukin (IL)-6 (2), and other inflammatory markers, such as serum amyloid A (SAA), circulating levels of which parallel CRP, and intracellular adhesion molecule (ICAM)-1. CRP adds prognostic information at all levels of risk based on Framingham score (3).

Chait noted that several studies have shown that persons with diabetes without prior myocardial infarction have increased CVD risk, either to the same degree as persons without diabetes but with prior evidence of CVD (4,5) or to a somewhat lower level (6). An important potential linkage between diabetes and atherosclerosis may involve inflammatory factors. CRP is increased by diabetes, as well as by obesity, estrogen, cigarette smoking, chronic infections such as gingivitis, and chronic inflammatory diseases such as rheumatoid arthritis, while being decreased by statins (7), fibrates, niacin, aspirin (8), α-tocopherol (in high dose), thiazolidinediones (TZDs) (9), alcohol, and lifestyle factors such as exercise and weight loss (10), with weight loss also decreasing IL-6 levels (11). CRP increases if one simply counts the number of positive metabolic syndrome markers, dyslipidemia, upper-body obesity, hypertension, and hyperglycemia (12). Furthermore, CRP is a member of the pentraxin family, which consists of five noncovalently associated peptides surrounding a central core, binding bacterial and fungal polysaccharides. CRP acts as a member of the innate immune system, activating the classical pathway of complement fixation and inducing phagocytosis. SAA, another acute-phase protein, is induced by IL-6, IL-1, and tumor necrosis factor (TNF)-α and is synthesized by the liver. SAA is an apolipoprotein associated primarily with HDL, inducing matrix-degrading enzymes and acting as a chemoattractant for monocytes, as well as mediating lipid delivery to peripheral cells and removal of cholesterol from damaged tissues. The COOH-terminus of SAA leads to its retention in areas of inflammation, playing a role in the innate immune system as well. Thus, inflammatory stimuli, by eliciting a macrophage response, promote release of cytokines, which in turn promote hepatic synthesis of inflammatory factors such as CRP and SAA. Chait noted that insulin has what may be considered an anti-inflammatory effect in inhibiting the hepatic response to cytokine stimulation. Although insulin resistance is associated with increased CRP levels, insulin secretion does not itself increase CRP (15). CRP levels in nondiabetic persons increase with worsening glycemia and particularly with postload glycemia (16). Insulin resistance is associated with a number of inflammatory markers in addition to CRP, such as secretory phospholipase A2, e-selectin, and ICAM-1 (17). In the context of insulin resistance, obese persons have improvement in insulin sensitivity and in CRP with weight loss, while obese persons with normal insulin sensitivity, whose CRP level is lower, do not show further decrease following weight loss, suggesting improvement in insulin sensitivity rather than weight loss to mediate the reduction in CRP (18).

The adipocyte is another important component of inflammation. Adipose tissue secretes inflammatory cytokines such as TNF-α and IL-6, and CRP levels increase with increasing weight. A new concept is that obesity leads to macrophage infiltration of adipose tissues, perhaps because of the action of factors produced by adipocytes themselves, with macrophages rather than adipocytes producing some of the typically measured inflammatory cytokines (19). In this view, macrophages may produce factors such as TNF-α, causing insulin resistance, while both macrophages and adipocytes produce factors that increase hepatic CRP synthesis, such as IL-6.

Atherosclerosis is accelerated both directly by effects of cytokines on endothelial cells and indirectly by cytokine effects on the liver, causing increased production of CRP and related factors (20). CRP induces endothelial cell adhesion molecules and increases endothelial cell monocyte chemoattractant protein-1 (21), inhibits nitric oxide synthesis (22), increases plasminogen activator inhibitor (PAI)-1 expression (23), and leads to endothelial dysfunction (24), with atherosclerosis-prone mice overexpressing CRP showing evidence of increased atherosclerosis (25). Similarly, there is evidence that SAA may be a mediator of atherosclerosis. HDL particles containing SAA rather than apolipoprotein (apo)A1 show adherence...
to vascular proteoglycans via the tethering region of SAA, suggesting the existence of “inflammatory HDL.” (26).

Chait reviewed current recommendations that CRP is of greatest use in CVD risk assessment of persons with intermediate CVD risk (10–20%/10 years), appearing not to be useful either in low-risk persons or in those at high risk, who would already be given aggressive therapy (27). He noted that CRP levels are not very stable, changing with infection and other intercurrent stresses, so that serial CRP measurement has been suggested not to be useful in monitoring therapy. Two recent studies have challenged this paradigm concept; the REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) study showed CRP to be independent of LDL cholesterol in predicting progression of atherosclerosis (28), and the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) study demonstrated that CVD events in persons at high risk were associated with both higher LDL and higher CRP levels, whereas LDL cholesterol levels <70 mg/dl were associated with better outcome in those persons with lower CRP levels (29). Thus, there is now evidence suggesting that one might follow CRP levels to optimize treatment of high-risk persons.

Coronary artery calcification

Ronald Goldberg (Miami, FL) reviewed the use of the coronary artery calcium (CAC) score (30), a novel risk factor, which although very different from CRP, may also allow one to increase the precision with which therapy is offered. Coronary plaque evolution is associated with calcification, a phenomenon exploited in measuring CAC. CAC may be measured either with spiral computed tomography or with the more accurate electron beam tomography. The prevalence of CAC increases with age and is greater in males (31), with normative data available from more than 10,000 persons (32). CAC is associated with CVD independent of age, blood pressure, diabetes, cigarette smoking, and lipids both in cross-sectional (33,34) and prospective studies (35), suggesting, Goldberg stated, that “you are as old as your arteries.” Indeed, CAC predicts risk more accurately than traditional risk factors (36). CAC correlates with the Framingham risk score and even more strongly with family history, obesity, and sedentary lifestyle (37). Insulin resistance was associated with increased CAC score in the Framingham Offspring Study, with a greater effect of glycemic abnormality (38). This correlation is somewhat debated, however, with there being some evidence of a stronger correlation with visceral fat levels (39). Both diabetes and metabolic syndrome are associated with increasing CAC levels, with evidence of greater effect of diabetes than metabolic syndrome in men but a greater effect of metabolic syndrome than diabetes in women (40). As with CRP, the number of metabolic abnormalities present has been associated with higher CAC score (41).

In persons with type 2 diabetes, age, male sex, diabetes duration, waist-to-hip ratio, blood pressure, and statin therapy are associated with CAC (42), with Goldberg wondering whether CAC can be used in monitoring therapies. In type 1 diabetes, CAC is associated with diabetes duration, HbA1c (A1C), BMI, and insulin dose (43), with baseline CAC correlating with the CAC score at 2-year follow-up, suggesting a relationship to initial plaque level (44). There is some evidence that interventions influence CAC, with statins appearing to decrease progression (45) and with an association of physical activity with reduction in CAC. Goldberg suggested that CAC measurement is less costly than stress testing, which only gives risk information in the presence of obstructive CAD, and concluded that the CAC score predicts risk more accurately than and independent of standard risk factors, as well as adding to the risk assessment.

Dyslipidemia and insulin resistance

Assessing LDL size and density in the metabolic syndrome, John D. Brunzell (Seattle, WA) noted the association of metabolic syndrome with type 2 diabetes and with familial combined hyperlipidemia (FH), both of which contribute to premature coronary disease. The metabolic syndrome is associated with maldistribution of body fat, increased free fatty acids (FFAs), and insulin resistance, leading to type 2 diabetes, hypertension, dyslipidemia, and hypercoagulability. There is a high correlation between insulin sensitivity and intra-abdominal fat (47). The effect of insulin resistance may be mediated by increased portal FFAs, by hepatic or muscle fat, by decreased adiponectin, or by other factors. The National Cholesterol Education Program criteria (48) have been used to show the high prevalence of metabolic syndrome in the population, with evidence that metabolic syndrome rather than hyperglycemia per se is associated with CVD (13).

The dyslipidemia of the metabolic syndrome is associated with increased triglycerides, decreased HDL3 cholesterol, and increased small dense LDL particles, in the presence of normal LDL cholesterol. The liver makes triglyceride-rich VLDL particles, each containing one apoB molecule, with subsequent processing by lipoprotein lipase to remnant lipoprotein particles containing less triglyceride and further processing by hepatic lipase to LDL and then to small dense LDL particles. Thus, hepatic lipase plays a major role in the development of diabetic dyslipidemia. In addition, triglyceride-rich VLDL interacts with LDL to exchange triglycerides for cholesterol ester via cholesterol ester transfer protein (CETP) to produce atherogenic small LDL. CETP also mediates an interaction of VLDL with HDL3 to produce less antiatherogenic HDL3. Insulin-resistant persons from a normal population, and similarly (but to a greater extent) persons with type 2 diabetes, have increased VLDL cholesterol, a shift in LDL cholesterol to more dense (hence smaller and more numerous) particles, and a decrease in HDL cholesterol.

FH is caused, Brunzell stated, by an interaction between genes for insulin resistance/metabolic syndrome and a lipid disturbance such as increased apoB production. In these families there is variability in lipoprotein phenotype, and lipid levels vary over time in individuals, with apoB always elevated although differently distributed between VLDL and LDL. ApoB measurement may then be particularly helpful in the assessment of FH (49). FH is a particularly atherogenic dyslipidemia, with risk of myocardial infarction twice that in spouse control subjects and in persons with familial hypertriglyceridemia (50). Seven-year follow-up of the Quebec cardiovascular study showed that LDL size and apoB are independent risk factors, with persons having large LDL manifesting a doubling of in risk with increased apoB, while those with small LDL have a sixfold increase in risk with high apoB (51).

Small LDL particles are more atherogenic, permeating the arterial wall, bind-
ing proteoglycans, and showing greater susceptibility to oxidation. Assessment of these particles can be performed directly with gradient gel electrophoresis or ultracentrifugation or indirectly by measuring apoB and simply with calculation of the non-HDL cholesterol. Therapy to decrease small LDL particle levels in HF can involve weight loss or administration of nicotinic acid, with or without a statin. In persons with diabetes, statins and TZDs are effective, with some evidence of benefit of nicotinic acid as well (52). Recent studies described by Brunzell compared effects of rosiglitazone and pioglitazone, showing similar effects on A1C, subcutaneous fat, insulin resistance, FFAs, adiponectin, and hepatic fat, but some differences in lipid effects, with pioglitazone but not rosiglitazone decreasing triglycerides and rosiglitazone, leading to a greater increase in LDL cholesterol, although both increased LDL size and buoyancy and increased HDL, with rosiglitazone having a greater effect in increasing HDL. Brunzell noted that TZDs decrease CRP and hepatic steatosis, with “the crucial thing” the question of whether they reduce CVD events. Outcome studies are in progress. He suggested particular benefit of niacin, with doses of <3 g daily increasing HDL by approximately one-quarter and decreasing triglycerides by one-third, and with modest effect in reducing LDL levels (53,54).

Ernest Schaefer (Boston MA) discussed lipoprotein(a), diabetic dyslipidemia, and coronary heart disease. Lipoprotein(a) was found to be associated with CHD risk over 40 years ago (55). Niacin was shown to reduce lipoprotein(a) in 1989 (56), and the apo(a) gene was cloned and sequenced in 1991, with recognition of its similarity to plasminogen (57). Apo(a) is attached to apoB100 by a disulfide bond (58) and contains a variable number of kringle protein repeat sequences, so termed because of the their shape resembling that of a type of Danish pastry. The lower–molecular weight isoforms are less rapidly cleared and associated with higher lipoprotein(a) levels (59,60). The apo(a) secretion rate is approximately one-third that of apoB100, but apo(a) has twice the residence time of apoB100 in circulation, suggesting that apo(a) attaches to an apoB100 in VLDL and may then associate with another apoB100 particle in circulation before being cleared. Lipoprotein(a) levels are highly heritable, and there is also lipoprotein(a) elevation in patients with renal disease and in African Americans. Increased lipoprotein(a) is strongly associated with premature CVD and is present in 19% of families with premature coronary heart disease but 10% of control families (61). In the Lipid Research Clinics trial, mean lipoprotein(a) levels were 23.7 in persons with CVD vs. 19.5 mg/dl in control subjects, with persons in the upper 40% of lipoprotein(a) having a doubling in CVD event rates (62,63). Similarly, in the Framingham study, there was 2.4- and 1.7-fold increase in CVD risk in women and men, respectively, with increased lipoprotein(a) levels (64), and meta-analysis of 18 studies shows a 1.7-fold increase in risk for persons in the highest tertile of lipoprotein(a) with adjustment for age, blood pressure, diabetes, cigarette use, and LDL and HDL cholesterol (65). Treatment approaches that lower lipoprotein(a) include niacin, leading to 20–30% reductions, and estrogen plus progesterone, reducing levels 15–25%. Interestingly, in the HERS (Heart and Estrogen-Progestin Replacement Study) there was evidence of reduction in CVD with hormone replacement therapy in women with increased lipoprotein(a) (66). Atorvastatin 40 mg daily decreases lipoprotein(a) cholesterol by 16%, although actually increasing the total lipoprotein(a) level (67).

Adipokines and inflammation in insulin resistance

P. Antonio Tataranni (Paris, France) discussed the roles of adipokines and of inflammatory factors in the metabolic syndrome, addressing pathophysiological linkages, including obesity, insulin resistance, glucotoxicity, lipotoxicity, and cell nutrient overload (68). High-dose salicylates have long been recognized to improve diabetes, and there is increasingly the concept that diabetes is a disease of the innate immune system (69). Macrophages stimulated by injury or infection secrete cytokines such as IL-6, IL-1, and TNF-α, leading to hepatic production of acute-phase reactants including fibronogen, SAA, CRP, lipoprotein(a), and PAI-1, with there also being a feedback system whereby cytokines act in the central nervous system to decrease the hepatic effects. Chronic hyperstimulation by overnutrition may, however, lead to a state of chronic macrophage activation, chronic increase in cytokines, with central obesity, insulin resistance, defective insulin secretion, and overproduction by the liver of the hepatic products of cytokine activation.

Tarantino asked how this hypothesized mechanism of the metabolic syndrome might come about, with overnutrition increasing cytokines, and what molecular mechanisms exist linking cytokines to insulin resistance and decreased insulin secretion. He described a series of studies of Pima Indians related to the question of whether inflammation is caused by diabetes or is rather a causal factor, noting that on average the body temperature of this population is ~1° higher and that there is a negative correlation of body temperature with insulin sensitivity. A number of markers of inflammation are associated with insulin resistance and risk of type 2 diabetes in Pimas. One of the first such discovered was CRP (70). The leukocyte count (white blood cell count [WBC]) correlates with body fat, insulin sensitivity, and fasting insulin, but not with the acute insulin response to intravenous glucose. Adjusted for age, sex, and percent body fat, the WBC is associated with cumulative incidence of diabetes (71). Longitudinal analysis shows that the baseline WBC is associated with the decrease over time in insulin sensitivity but not with the change in acute insulin secretion. CRP and ICAM (72), as well as ALT, which is indicative of steatohepatitis (73), are further inflammatory markers in the Pimas. Similar studies have been reported in other populations. In the ARIC (Atherosclerosis Risk in Communities) study, insulin sensitivity correlated with WBC, fibrinogen, sialic acid, and orosomucoid, as well as with low serum albumin (74). In the WHI (Women’s Health Initiative) study, WBC (75), CRP, and IL-6 (76) correlated with risk of type 2 diabetes. An association of CRP with development of diabetes was also reported in an elderly population, although this population failed to show increased risk with WBC, albumin, fibrinogen, platelet count, or factor VIIc (77).

These and many other studies suggest that obesity indeed is associated with subclinical inflammation and with insulin resistance. Tarantino discussed the many cytokines originating in adipose tissue (adipokines). Adipocytes produce com-
plement factor B; the serine protease adipsin; acylation-stimulating protein, a paracrine signal increasing adipocyte triglyceride synthesis; TNF-α; IL-6, -8, and -10; monocyte chemoattractant protein-1; PAI-1; lipoprotein lipase; CETP; ACE; the prostacyclin prostaglandin E2; vascular endothelial growth factor; hormones such as leptin, resistin, adiponectin, and angiotensinogen; and the enzymes 17-hydroxysteroid dehydrogenase and 11-β-hydroxysteroid dehydrogenase. Adiponectin is a specific white adipose tissue-derived protein, with anti-inflammatory/antiatherogenic properties such as decreasing the expression of adhesion molecules, decreasing monocyte adhesion to endothelial cells, decreasing uptake of oxidized LDL, decreasing foam cell formation, and decreasing proliferation and migration of vascular smooth muscle cells. Adiponectin increases insulin sensitivity, increases smooth muscle glucose uptake and FFA oxidation, decreases hepatic glucose production, and decreases intracellular triglycerides. Adiponectin exists in low- and high-molecular weight forms, with the latter having a biological effect. Despite being expressed exclusively by adipocytes, its levels are lower in obese individuals. At any level of adiposity, however, persons with higher levels of adiponectin have greater insulin sensitivity (77). Low adiponectin is a characteristic of persons having increased risk of diabetes, with multivariate analysis showing it to explain the effect of CRP, IL-6, TNF-α, secretory phospholipase A2, e-selectin, ICAM-1, and VCAM-1 (78–82).

Tarantino suggested that adiponectin “is a key piece of the puzzle,” potentially offering a link between overnutrition and insulin resistance, further implying that cytokines are side players rather than direct mediators. He turned to the question of a molecular link between activation of the innate immune system and impairment of insulin action and insulin secretion, discussing studies showing that the inhibitor of NF-κB (IκB)-β is inactivated by adipokines and bacterial lipopolysaccharides but activated by insulin. Breakage of the nuclear factor-κB (NF-κB/IκB dimer leads to release of NF-κB, leading to inflammatory effects via actions in the cytoplasm and cell nucleus. Mice heterozygous for an inactivating mutation of IκB have decreased insulin response (83). High-fat diet– and obesity-related insulin resistance are improved by inhibition of NF-κB by salicylates or by genetic deletion. Interestingly, activation or inhibition of muscle NF-κB in mice does not change their phenotype, while activation in either liver or fat produces systemic insulin resistance. Specific inhibitors of NF-κB are being developed as pharmacological approaches to breaking the chain of events that leads from overnutrition to insulin resistance and decreased insulin secretion, although there is as yet no evidence of a relationship between inflammation and insulin secretory dysfunction, and the precise molecular mechanism linking inflammation to impairment of insulin action remains uncertain.

There is no consensus as to the existence of a “unique defect at the molecular level” in the metabolic syndrome, with Tarantino pointing out that it may be simply “an epidemiological construct,” with increased waist circumference and dyslipidemia the major constituents. Visceral and subcutaneous fat differ in lipolytic response to catecholamines, with visceral fat having increased adrenergic receptors, lower insulin sensitivity, and altered adipokines. Obesity with excess visceral fat is associated with reduced adiponectin, whereas obese persons with normal visceral fat have normal adiponectin levels, and low adiponectin and high visceral fat are independently associated with low HDL cholesterol (84). In the HPFS (Health Professionals Follow-up Study), low adiponectin predicted elevated 6-year risk of myocardial infarction, controlling for age, exercise, cigarettes, CRP, BMI, A1C, blood pressure, alcohol, and diabetes, with the relationship between adiponectin and HDL cholesterol explaining part of the association (85). A crucial question, based on these considerations, is whether greater understanding of the interrelationship between adiponectin and inflammation will lead to better understanding and treatment of the metabolic syndrome.

**New concepts of the insulin (and related) receptors**

At a meeting of the Metropolitan Diabetes Society, New York, New York, 5 April 2005, Pierre Demeys (Genotofte, Denmark) discussed aspects of insulin action based on current understanding of the expanding physiological role of insulin and the insulin receptor. Insulin is composed of an A- and B-chain and belongs to a family of 10 peptides present in the human genome, IGF-1 and -2, and the seven relaxin-related peptides. The latter group of hormones have a G-coupled receptor system that is completely different from the tyrosine kinase receptors for insulin and IGF-1 and -2. Insulin-like molecules are found throughout the vertebrate and invertebrate kingdoms, with Bombyxin an insulin-related neurosecretory peptide present in invertebrates such as the silkmoth, Bombyx mori.

There are a total of 19 different human tyrosine kinase receptors identified at present, all of which have the property of manifesting biologic activity upon the interaction of two activated receptors, although only the insulin receptor, IGF-1R, and insulin receptor–related receptor existing in the nonactivated state are identified as dimers. The insulin receptor has A and B isoforms; the former plays a role in embryogenesis and oncogenesis. The insulin receptor A and B isoforms and IGF-1R exist on a variety of cells, with there also being hybrid receptors with dimers of two of the three peptides. Mice not expressing the insulin receptor develop severe hyperglycemia with ketoadosis, while those lacking the IGF-1R have severe growth retardation (86). An important question, which can be addressed by analysis of the molecular configuration of insulin and IGF-1, is why IGF-1 does not bind strongly to the insulin receptor.

Demeyts addressed the relationship between insulin action and aging. Death results from an increase in systemic molecular disorder, which to this point has appeared to be inevitable. Conceptually, this process may be regulated by two sets of genes, those controlling DNA repair and antioxidant defenses, and deleterious genes promoting DNA damage and oxidant stress; from an evolutionary perspective, the latter must have had benefit in early life to be commonly present, despite their propensity to cause harm in older age.

The insulin receptor is also an ancient molecule, with related receptors found in coelenterates, insects, gastropods, and prochordates (87). An invertebrate insulin receptor that has been the subject of a great deal of interest is that of the nematode Caenorhabditis elegans, which has been widely used in biological, biochemical, and genetic studies. C. elegans is ~1.5 mm in length, with 20,000 genes
found on six chromosomes. In this species, the insulin–IGF-1 system regulates longevity, as manifested by two forms, the short-lived adult reproductive form and the long-lived dauer form. Under environmental conditions of food scarcity, low insulin-like signaling causes development of the latter larval form, with cessation of feeding and development of a thick surrounding cuticle (88).

*C. elegans* has 38 insulin-like peptides and expresses a peptide, daf-16 (89), analogous to the insulin-responsive vertebrate peptide fox (forkhead transcription factor) 01. The *C. elegans* insulin-like ligands are secreted by specific gustatory and olfactory neurons, suggesting a feedback process between the reproductive and sensory systems in this species, perhaps explaining aspects of insulin signaling in vertebrates.

Demeys speculated that insulin signaling in vertebrates may be related to antimicrobial and antioxidant factors. Studies in rodents suggest that reduced IGF signaling is associated with delayed aging (90). In humans, long life is associated with greater insulin sensitivity (91). Other functions of the insulin system in humans include its actions in the brain (92), with evidence of learning- and memory-related roles and of impairment of these functions in Alzheimer’s disease (93), as well as a new set of possible anti-inflammatory and antiatherosclerotic roles (94).

Domenico Accili (New York, NY) discussed new concepts based on studies in mice of the actions of insulin and IGF-1 and of the pathogenesis of human diabetes. Classical sites of insulin action are in skeletal muscle, liver, and the adipocyte. New understanding of additional insulin effects addresses the roles of insulin receptors in the brain, in adipocytes acting as endocrine cells, and in β-cells. While diabetes was previously thought to be a disease of insulin resistance resulting in increased substrate flux, hepatic glucose production, and secondary β-cell failure, with hyperglycemia as a form of compensatory mechanism, current understanding suggests that a number of adipocyte products such as FFAs and TNF-α are mediators of decreased insulin action, but with insulin resistance in muscle and fat not being sufficient to cause the development of diabetes. Mice lacking the insulin receptor can be “rescued” by restoring it in the liver, brain, and β-cell, with the liver responding to both direct insulin effects and indirect actions via vagal signals originating in the arcuate nucleus of the hypothalamus. β-Cell dysfunction leads to islet hypertrophy and hyperplasia, ultimately with decreased islet coherence and relative decrease in β-cell and increase in α-cell mass, with the islet effect of insulin being to increase islet mass.

Thus, the understanding of insulin’s actions will be increasingly important in a variety of pathophysiological states, including diabetes, atherosclerosis, aging, and brain function.

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