PPARs in Diabetes and Cardiovascular Disease

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that control the transcription of several genes involved in lipid and carbohydrate metabolism. Synthetic PPAR agonists have been shown to target some of the maladies in persons that are at extremely high risk for coronary artery disease (CAD), such as type 2 diabetes and the metabolic syndrome. These agents have clear anti-atherosclerotic effects by increasing insulin sensitivity and lowering triglyceride levels. Due to their wide-ranging effects, however, elucidation of their overall mechanism and clinical relevance remains a challenge.

PPARgamma impedes proliferation of VSMCs and activation of inflammatory cells

Excessive proliferation of vascular smooth muscle cells (VSMCs) contributes to the pathogenesis of atherosclerosis. PPARgamma is expressed and upregulated in human coronary arteries in response to injury of the arterial wall, though its role was previously unclear. Bruemmer et al (Bruemmer D. *Circ Res* 2003; 93:38) showed that over expression of PPARgamma induces apoptosis of human coronary VSMCs, thus providing protection from atherosclerosis. Another study found that ligand-induced activation of PPARs is also able to induce senescence in VSMCs by inhibiting telomerase (Ogawa et al. *Circ Res* 2006; 98:50). These findings support PPAR ligand therapy for the treatment of cardiovascular disease.

Inflammatory cell activation and migration is an important process in early atherogenesis. Marx et al (Marx N. *Circulation* 2003; 107:1954) demonstrated that in patients with type 2 diabetes and stable CAD receiving rosiglitzone, a PPAR agonist, had decreased levels of the inflammatory marker sCD40L. Similarly, this group also found that treating patients with pioglitazone, another PPARgamma agonist, significantly reduces neointima after coronary stenting in non-diabetic CAD patients (Marx N; *Circulation* 2005; 112:2792).

These studies represent some of the strongest evidence to date that PPARgamma activators exhibit anti-inflammatory and anti-atherogenic properties as shown by reductions in inflammatory biomarkers, improvements in vascular function, and stabilization effects on atherosclerotic lesions. Therefore, not only do these agonists exhibit metabolic effects by decreasing lipid profiles and increasing insulin sensitivity, but they also directly influence important processes in atherogenesis.

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considered in the Framingham risk score), to predict overall risk. Additionally, there has been recent interest in identifying novel risk markers that improve traditional risk factor assessment in a cost effective way.

Exercise testing can improve risk reduction in asymptomatic women

Physical fitness has long been known to reduce all-cause mortality from a plethora of diseases, most notably CVD and cancer. Investigators sought to determine if fitness tests could predict heart disease in asymptomatic women. In a study of 2,994 North American asymptomatic women aged 30 to 80, exercise capacity and heart rate recovery (HRR) was tested and correlated with cardiovascular and all-cause mortality (Mora S. *JAMA* 2003; 290:1600). After age-adjustment, women who were below the mean for exercise capacity and HRR had a 3.5-fold increased risk of cardiovascular death compared to women who had above average values for both tests. This large increase in risk justifies the use of exercise testing and HRR in predicting CVD in asymptomatic women, combined with traditional risk factors.

Other non-traditional markers improve risk prediction in women

Recent data has suggested that plaque burden can be predictive of CAD risk. In a cohort of 10,377 asymptomatic women, calcium scores >1000 were 4.03 times more likely to experience CVD-related death as women whose calcium scores were <10 (Shaw LJ. *Radiology* 2003; 228:826). Additional factors demonstrating promising correlations with increased risk of CV events are levels of the inflammatory marker C-reactive protein, the ankle brachial index (measurements of blood pressure in the ankle and the arm) and carotid-artery media and intima thickness. The ongoing MESA trial (Multi-Ethnic Study of Atherosclerosis), involving over 6,000 men and women between the ages of 45 and 84, will likely help us better understand the importance of sub-clinical disease measures in preventing CVD events, especially in women.

Cost considerations in CVD screening

The cost of CVD and stroke in the United States in 2006 is projected to be $403.1 billion including direct and indirect costs, according to the Centers for Disease Control and Prevention. The use of screening tests to decrease this economic burden is therefore attractive, as long as the screening strategies succeed. Possible reasons why a screening strategy might fail are: clinicians do not act on screening results, available therapy may be ineffective, or real-world application of therapy may not yield expected results. Conversely, there is also the possibility that screening strategies may themselves improve adherence to clinical guidelines, observes Vera Bittner, MD, Professor of Medicine from the University of Alabama in Birmingham. Currently, however, there is insufficient data on the benefits of screening methods for CVD. In the future, studies must correlate screening tests not only to increases in risk, but to actual health benefits.

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What are the endogenous ligands of PPARs?

Finally, since most PPAR agonists were happened upon by chance, comments Jorge Plutzky, Assistant Professor at Harvard Medical School in Boston, MA, one way to better understand these synthetic agonists is to ask about the nature of the endogenous ligands. Dr. Plutzky's group found that endothelial lipase limits the expression of soluble adhesion molecules that are predictive of cardiovascular risk by hydrolyzing HDL and subsequently activating PPARalpha. Currently available PPAR-alpha agonists include fibrates such as fenofibrate. Construing these pathways could lead to the development of more effective and more physiologically relevant drugs.