Is Asymmetric Dimethylarginine a Marker for Diabetes, Coronary Artery Disease, and Death/Myocardial Infarction? Results of the Intermountain Heart Collaborative Angiographic Registry Study

Jeffrey L. Anderson, John F. Carbullito, William L. Roberts, Benjamin D. Horne, Tami L. Bar, Ed Hoehn, Marcia Pasquali, Joseph B. Muhlstein, LDS Hospital, Salt Lake City, UT, University of Utah, Salt Lake City, UT

Background: Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide synthase that has generated interest as a potential cause or marker of endothelial dysfunction and its clinical consequences, including diabetes, coronary artery disease (CAD), and renal failure.

Methods: We tested whether ADMA distinguishes patients (pt) with normal (NFG; <110 mg/dL), or impaired fasting glucose (IGF: 110-125), or diabetes (DM; ≥126 mg/dL); angiographic CAD; and death (D) or nonfatal myocardial infarction (MI) in a case-control cohort of 442 pt selected from the 3 glycemic categories from among 3000 pt entered in the Intermountain Heart Collaborative Registry. Consenting pt had fasting blood drawn for FG and ADMA during angiographic assessment and were followed for 2.6 ± 1.4 y. ADMA was assayed from cryogenically stored samples by high-pressure liquid chromatography with pre-column derivatization and fluorescence detection. Non-parametric (KW) tests were compared ADMA among groups. Logistic regression was used for predictive modeling.

Results: The study cohort consisted of equal numbers of NFG (146), IGF (148), and DM (148), matched for age (±5 y) and gender. Overall, age averaged 61 years; 72% were male, 56% had angiographic CAD, 61% smokers, 58% hypertension, 58% hyperlipidemia; 24%; prior MI. During follow-up, 137 events occurred. Distribution of ADMA was broad and rightward skewed, with median 0.85 µM (range: 0.30). Mean (median) ADMA levels increased progressively by glycemic category (p<0.001): NFG=2.3 (1.74), IGF=3.0 (1.77), DM=3.4 (2.72). When adjusted for standard risk factors, CAD severity, and presenting diagnosis. In ADMA independently predicted DMI (odds ratio [OR] 1.29 /ln unit, CI 1.07-1.54, p=0.006) and, less strongly, CAD (OR 1.21, CI 1.01-1.5, p=0.06). Ln ADMA trended higher in those DMI (adjusted OR 1.17, CI 0.99-1.39, p=0.08).

Discussion: Among a high coronary risk case-control cohort, TADMA predicted risk of IFG, DM, and CAD. Thus, ADMA might contribute to endothelial dysfunction associated with these conditions. Further research should determine whether ADMA is a causal factor or passive marker and determine causes of interpatient variability.

The Predictive Value of Parental History of Coronary Disease

Pamela Ouyang, Lisa R. Yanek, Daniele Fallin, Taryn F. Moy, Lewis C. Becker, Diane M. Becker, Johns Hopkins University School of Medicine, Baltimore, MD, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

Background: Parental history of coronary disease (CHD) is a well-known risk factor for CHD. However the risk conferred by the gender of an affected parent is controversial and data are sparse. This prospective study in high risk families was designed to determine the extent to which a maternal or paternal history of CHD contributed independently to the risk of incident CHD after adjusting for known risk factors.

Methods: Unaffected sibs (SIBS) of probands were identified from hospitalized index family member. SIBS were followed for incident CHD events. SIB events were documented from medical records and adjudicated by an external endpoints committee. Parental family history was elicited by self-report and confirmed by another family member. SIBS were followed for incident CAD, and renal failure.

Results:Among a high coronary risk case-control cohort, TADMA predicted risk of IFG, DM, and CAD. Thus, ADMA might contribute to endothelial dysfunction associated with these conditions. Further research should determine whether ADMA is a causal factor or passive marker and determine causes of interpatient variability.

The Independent Impact of FBG in the Upper Normal Range as a Risk Factor for Subclinical Coronary Atherosclerosis

Khurram Nasir, Roger S. Blumenthal, Joel B. Braunstein, Romeu Meneghello, Jose A. Maluf, Wendy S. Post, Matthew J. Budoff, Raul D. Santos, Johns Hopkins Medical Institutions, Baltimore, MD, Albert Einstein Hospital, Sao Paulo, Brazil

Background: Non-diabetic individuals with high fasting blood glucose (FBG) are at high risk for experiencing the metabolic syndrome, which includes insulin resistance, hypercholesterolemia, and a procoagulant state. While emerging evidence suggests that impaired FBG (FBG<110 mg/dl) may accelerate atherosclerosis, we sought to evaluate the independent impact of FBG in the upper normal range (<110 mg/dl) as a risk factor for subclinical coronary atherosclerosis assessed by coronary artery calcification (CAC) in an asymptomatic non-diabetic population.

Methods: We studied 531 consecutive asymptomatic, non-diabetic males (46±7 yrs; range 29-65 yrs) with FBG<110 mg/dl in the study who presented for electron-beam computed tomography (EBCT) between 1999 and 2002 in Sao Paulo, Brazil. The population was divided into 2 categories; highest quartile of FBG (≥85 mg/dl, n=119) and the lowest three quartiles (n=412).

Results: Individuals in the highest quartile of FBG were more likely to have higher body mass index (28±4 vs. 26±3, p<0.001), waist to hip ratio (0.93±0.06 vs. 0.90±0.06, p=0.01), triacylglycerides (410±116 vs. 180±132, p<0.001) and systolic blood pressure (131±14 vs.121±13, p<0.001), where as no significant difference was observed in high density lipoprotein, low density lipoprotein and total cholesterol levels respectively. Overall median, 75th percentile and 90th percentile CAC scores were 3, 34 and 156 among individuals with highest FBG quartile compared to 0, 6 and 56 among patients with lowest three quartiles (p<0.05). After adjusting for potential confounders, the odds ratio for any calcification (CAC>0) with FBG≥85 mg/dl was 2.5% (95% CI: 1.15-5.4, p=0.02) and 1.8 (1.1-3.2, p=0.01) for ≥75th percentile CAC, respectively.

Conclusions: FBG in the upper normal range ≥85 mg/dl appears to be an important independent predictor of presence and severity of CAC in non-diabetic apparently healthy young/middle aged men.

Increased Urinary 8-Isoprostaglandin F2alpha Excretion Predict Cardiac Events in Patients With Type 2 Diabetes

Yusuke Nakagawa, Yosihyuki Kijima, Akira Nishibe, Nobuyuki Ogawara, Tamayo Ishiko, Megumi Kunishige, Takeshi Hata, Higashiosaka City General Hospital, Higashiosaka, Japan

Background: Increased oxidant stress may play a key role in the etiology of diabetic cardiovascular complications. We hypothesized that increased production of 8-isoprostaglandin F2alpha (8-iso-PGF2alpha), a marker for in vivo oxidant stress, predicts future cardiac events in type 2 diabetic patients.

Methods: We studied 148 patients aged 30-85 (62±10) with type 2 diabetes. Baseline level of urinary 8-iso-PGF2alpha excretion were measured and the patients were followed up for a mean period of 1380 days. Cardiac events were defined as hospitalization for acute myocardial infarction, unstable angina, revascularization, and worsening heart failure.

Results: One hundred thirty-nine patients completed the follow-up period, while 2 died of non-cardiac causes. Of the remaining 137 patients, cardiac events were occurred in 16. Urinary 8-iso-PGF2alpha excretion above the median value of 287.5 pg/ml creatinine was