CVD As The #1 Causes of Death In USA

Obesity/Diabetes = Common Soil for Cardiovascular Disease

- Hypertension
- Heart failure
- Stroke
- CHD
- Arrhythmia

Disorder of Glucose Metabolism
Disorder of Lipid Metabolism

OBESITY
What Matters More?

Quantity
Vs.
Quality
Obese Adipose tissue Dysregulation

**Anti-Inflammatory Profile:**
- IL-4, IL-10, IL-13
- Normal metabolic function
- Normal vascularization

**Immune cells:** M2 macrophages, eosinophils, and Tregs

**Pro-Inflammatory Profile:**
- IFN-γ, TNF-α, MCP-1, IL-6, IL-1β
- Metabolic dysfunction, Severe hypoxia, Adipocyte necrosis

**Immune cells:** M1 macrophages (crown-like structures), CD4+ T lymphocytes, CD4+ T lymphocytes, B lymphocytes, and mast cells
Adipose Tissue Dysfunction

Positive Energy balance → Subcutaneous Adipose tissue expansion

- Adipogenesis intact (minimal hypertrophy)
- Sufficient storage capacity
- Regulated lipolysis
- No inflammation
- Insulin sensitive

Decreased adipogenesis (adipocyte hypertrophy)
- Storage capacity compromised
- Increased lipolysis
- Low-grade inflammation
- Insulin resistance

Pro-inflammatory adipokine profile → Increased visceral adipose tissue → Free fatty acids → Adverse Impact Upon Liver, Skeletal Muscle, Endothelial Cells, and Cardiomyocytes
Free Fatty Acids
Lysophospholipid
Lactate
Glutamine

Cytokines
(TNFα, Interleukins, PAI-1)

Growth Factors
(TGFβ, IGF-1, IGFBP
FGF, EGF, IGF-1
IGFBP, FGF, EGF)

Hormones
(Angiotensin, Estrogen, Prostaglandins)

Adipokines, Adipocytokines

Leptin 1994

Adiponectin 1995
Largest Endocrine Organ

Adipose Derived Hormones

Leptin
Adiponectin
Is Adipocyte Endocrine Function Altered in Obesity/Diabetes?
Association of Serum Leptin Concentration with BMS and Waist Circumference in Non-Diabetic and Diabetic Men and Women

BMJ 1996;313:965-969
Correlations between Serum Leptin and BMS and WBGU

European Journal of Endocrinology (1998) 139 598–604
Paradoxical Decrease of Adiponectin in Obesity

Non-obese subjects: men; 7.7 ± 3.1 µg/ml, women; 10.6 ± 7.3, p < 0.0001
Obese subjects: men; 2.8 ± 2.1 µg/ml, women; 4.8 ± 4.0, p < 0.0001

Arita, et al., BBRC 257;79,1999
Reduced Plasma Concentrations of Adiponectin in Type 2 Diabetic Patients

Figure 1. Plasma levels of adiponectin and leptin in normal and diabetic patients with and without CAD. The plasma levels of adiponectin (A) and leptin (B) in normal and diabetic patients without and with CAD were determined as described in Methods. Data are presented as mean ± SEM.

Arterioscler Thromb Vasc Biol 2000;20;1595-1599
Obesity/Diabetes

Leptin

Adiponectin
Does Adipocyte Endocrine Unbalance Play Important Roles in Diabetic Heart Injury?
Leptin
From a Fat Fighter to a Risk Factor

Ob/ob
Db/db

Reduces Appetite

Hypothalamus

Stimulation
Inhibition
Travel

Heart & Vasculature

Hypertension
Atherosclerosis
LV Hypertrophy

Inhibition removed by leptin resistance

Leptin

Peripheral Resistance?

Free fatty acid, lipid deposition

Reactive Oxygen Species

Nitric Oxide

Endothelin-1

Angiotensin II
Tumor Necrosis Factor-α
Other Cytokines

Adipocytes

↑ Appetite
↓ Energy Expenditure
Reduced Adiponectin Level is Associated with Severity of Coronary Artery Disease

Figure. Correlations between the severity of stenosis in patients with coronary artery disease and plasma adiponectin levels. The severity of stenosis in the coronary artery was measured using the Gensini score.
High Molecular Weight Adiponectin as a Predictor of Long-Term Clinical Outcome in Patients With Coronary Artery Disease

Am J Cardiol 2007;100:569–574
Serum Adiponectin is A Predictor of Coronary Heart Disease: A Population-Based 10-Year Follow-up Study in Elderly Men

**Fig. 1.** Kaplan-Meier survival curves for incident CHD during 10.4 yr of follow-up in groups defined by baseline serum adiponectin levels below (solid line) or above (broken line) the median. The risk for CHD was most pronounced in the group with adiponectin levels below the median ($P = 0.03$ for difference).
Future Adverse Cardiac Events Can Be Predicted by Persistently Low Plasma Adiponectin Concentrations in Men and Marked Reductions of Adiponectin in Women after Acute Myocardial Infarction

Usefulness of Adiponectin to Predict Myocardial Salvage Following Successful Reperfusion in Patients with Acute Myocardial Infarction

Am J Cardiol 2008;101:1712–1715
Three Questions for A Top-Down Translational Research

Causative?
Mechanisms?
Target?
Obesity/Diabetes

Adiponectin

Vascular Injury
Morbidity of IHD

Cardiomyocyte Injury
Mortality of IHD

Adiponectin Biological Functions

AMPK Agonists

Anti-Oxidative/Anti-Nitrative

Anti-Oxidative/Anti-Nitrative Stress

AMPK

Anti-Inflammatory

Metabolic/Insulin Sensitization

APPL1
nCDase
Insulin Sensitization
Metabolic Regulation
Anti-Inflammatory
Anti-Oxidative/Nitrative
AMPK

Normal Heart

Diabetic Heart

Cardioprotection

Loss of Cardioprotection

Wang et al, ATVB, 32:934-942, 2012
Obesity/Diabetes: Adipose Endocrine Dysfunction

Leptin

Adiponectin
APN in HF Is Controversy

Plasma Adiponectin, Body Mass Index, and Mortality in Patients With Chronic Heart Failure

Caroline Kistorp, MD; Jens Faber, MD, DMSc; Søren Galatius, MD, DMSc; Finn Gustafsson, MD, PhD; Jan Frystyk, MD, PhD, DMSc; Allan Flyvbjerg, MD, DMSc; Per Hildebrandt, MD, DMSc

Background—Recent studies have suggested that higher body mass index (BMI) is associated with improved prognosis in chronic heart failure (CHF). The adipocytokine adiponectin is inversely associated with BMI, and in healthy subjects, low adiponectin is a predictor of mortality. In a prospective study, we therefore evaluated the association between plasma adiponectin levels and mortality among patients with CHF.

Methods and Results—In 195 CHF patients (age 69.5±10.2 years, BMI 27.3±5.2 kg/m², left ventricular ejection fraction 30±8.9%, mean±SD), plasma adiponectin and N-terminal pro brain natriuretic peptide (NT-proBNP) were measured at baseline. Adiponectin was positively associated with NT-proBNP (β=0.47, P<0.001), and both biomarkers were negatively associated with BMI (β=-0.43, P<0.001 for adiponectin and β=-0.38, P<0.001 for NT-proBNP, respectively) During a median follow-up of 2.6 years, 46 (23.5%) of the patients died. After adjustment for clinical variables associated with CHF severity (age, systolic blood pressure, left ventricular ejection fraction <25%, duration of CHF, and creatinine clearance) and for NT-proBNP, the hazard ratio of mortality for values in the 2 upper tertiles relative to the lowest tertile of adiponectin was 3.23 (P=0.032). BMI predicted mortality independently of clinical parameters of CHF severity (hazard ratio=0.63, P=0.012), but this association became insignificant after additional adjustment for NT-proBNP (hazard ratio=0.74, P=0.13).

Conclusions—A high adiponectin level was a predictor of mortality, independent of risk markers of CHF severity, presumably because of its role as a marker for wasting. BMI was also associated with mortality, but a part of this relation may be mediated by adiponectin and NT-proBNP levels. (Circulation. 2005;112:1756-1762.)
High Adiponectin Levels Are Associated with Increased Mortality and Heart Failure

Fig. 2. Survival free of cardiovascular events or death by adiponectin quartile. Cardiovascular events or death includes myocardial infarction, heart failure, or death from any cause. \( p < 0.0001 \) for difference between quartile I and quartile IV.
GRK2-Mediated AdipoR1 Phosphorylation Contributes to the Development of Ischemic Heart Failure

Wang et al, Circulation. 2015;131:1392-1404
Systemic Adiponectin Dysfunction

Novel Player in Post-MI Cardiac Remodeling
Post-Ischemic Remodeling

- Hypertrophy
- Apoptosis
- Fibrosis
- Autophagy
- Stem Cell Deficiency
**Fold Over Sham MI/R**

**WT**

**APNKO**

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**LC3**

**αSA**

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**p62**

**αSA**

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**Beclin-1**

**αSA**

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**LAMP2**

**αSA**

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**αSA**
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Ma’s Laboratory

Current Members
Yajing Wang, MD, PhD
Wayne Bond Lau, MD
Yaping Guo, MD
Yue Chen, MD
Han Wang, MD
Wenjun Yan, MD, PhD
Lu Gan, PhD
Bernard Lopez, MD, MS
Theodore A. Christopher, MD

Past Key Members
Feng Gao, MD, PhD
Huirong Liu, MD, PhD
Ling Tao, MD, PhD
Jun Pu, MD, PhD
Wei Yi, MD, PhD
Yang Sun, MD, PhD

Key Collaborators
Erhe Gao, MD, PhD
Walter Koch, PhD