Depot-Specific Differences and Insufficient Subcutaneous Adipose Tissue Angiogenesis in Human Obesity

Summary: One of the most important functions of adipose tissue is to provide sufficient storage for excess calories in the form of triglycerides. Insufficient storage leads to increased circulating free fatty acids and ectopic lipid deposition, factors that are thought to result in insulin resistance and subsequently lead to type 2 diabetes mellitus. The storage capacity of adipose tissue is determined by the combination of adipocyte hypertrophy and hyperplasia, which gives rise to expanded tissue mass. However, in humans the expansion of adipose tissue in response to excess caloric intake is not always uniform. In some individuals, a disproportionate expansion of visceral relative to subcutaneous adipose tissue occurs. This manifests as an increased waist-to-hip ratio and is associated with elevated risk of metabolic disease. The mechanisms that support or limit the expandability of specific adipose tissue depots are not known. However, like the growth of any tissue, adipose expansion must require an adequate vascular supply. Thus, it is possible that adipose tissue angiogenesis might play a role in determining adipose tissue expandability. In this article, we describe an approach to investigate adipose tissue angiogenesis, in which angiogenic capacity correlates with insulin resistance, suggesting that impairment of subcutaneous adipose tissue angiogenesis may contribute to metabolic disease pathogenesis.

Conclusions: These data imply that subcutaneous adipose tissue has a higher capacity to expand its capillary network than visceral tissue, but this capacity decreases with morbid obesity. The decrease correlates with insulin resistance, suggesting that impairment of subcutaneous adipose tissue angiogenesis may contribute to metabolic disease pathogenesis.

Relation of Obesity to Circulating B-Type Natriuretic Peptide Concentrations in Blacks: The Jackson Heart Study

Summary: In this community-based cohort of blacks, we established that higher body mass index is associated with lower B-type natriuretic peptide concentrations. The relation was present in both sexes and in both nonhypertensive and hypertensive participants.

Our findings extend the concept of a natriuretic handicap of obesity to blacks. Augmentation of the natriuretic peptide system may reduce the susceptibility of obese individuals to the development of hypertension; the loss of this protective mechanism may predispose this group to persistent elevations in blood pressure.

Effects of Weight Loss and Long-Term Weight Maintenance With Diets Varying in Protein and Glycemic Index on Cardiovascular Risk Factors: The Diet, Obesity, and Genes (DiOGenes) Study: A Randomized, Controlled Trial

Summary: Food components are well known to affect cardiovascular risk, for which blood pressure, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and the inflammatory marker C-reactive protein (CRP) are established biomarkers. In the present randomized, multicenter study, the separate effects of 11 kg weight loss achieved during an 8-week low-calorie diet as well as a subsequent 26-week intake of diets varying in protein and glycemic index on these biomarkers were studied. The choice of food was ad libitum but was strictly controlled by nutritional advice concerning the targeted fat and protein content as well as glycemic index. Expectedly, the initial weight loss significantly reduced systolic and diastolic blood pressure, triglycerides, high-density lipoprotein cholesterol, and CRP. The subsequent consumption of different low-fat isocaloric diets resulted in moderate increases of blood lipids and blood pressure, which, however, were independent of the protein content and glycemic index of the diet. This clearly indicated that the beneficial effects on blood lipids and blood pressure were driven by the weight reduction itself but not by the dietary composition. In explicit contrast to the other biomarkers, consumption of low-glycemic-index diets led to a further decrease of CRP compared with high-glycemic-index diets. A low protein content enhanced the CRP-lowering effect, whereas a high protein content diminished it. Thus, the combination of low glycemic index and low protein intake appears to be most effective to reduce CRP, an established marker of low-grade inflammation and cardiovascular risk.
Conclusions: This large-scale intervention study clearly separates weight loss from dietary composition–related effects. Low-glycemic-index carbohydrates and, to a lesser extent, low-protein intake may specifically reduce low-grade inflammation and associated comorbidities in overweight/obese adults.

Body Mass Index and Adverse Cardiovascular Outcomes in Heart Failure Patients With Preserved Ejection Fraction: Results From the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) Trial

Summary: Obesity is a major risk factor for incident heart failure (HF). Paradoxically, in HF with reduced left ventricular ejection fraction (HFREF) a high body mass index (BMI) appears to be beneficial. However, approximately 50% of HF patients have a preserved left ventricular ejection fraction (HFPEF). Compared with HFREF, patients with HFPEF are usually older and more frequently female. The relationship between BMI and adverse cardiovascular (CV) outcomes was studied in the HFPEF patient cohort (n=4109) from the I-PRESERVE trial (mean age, 72 years, >60% female, mean BMI, approximately 30 kg/m²). Depending on their BMI, the patients were characterized by multiple differences in clinical variables. After adjustment for 21 key variables, patients in the lowest (BMI <23.5 kg/m²) and those in the highest BMI categories (BMI ≥35 kg/m²) had the highest CV event rate and the highest mortality. The lowest event rates were seen in overweight patients, that is, those with a BMI between 26.5 and 30.9 kg/m², indicating a U-shaped relationship. Only HF hospitalization was less frequently seen in normal-weight patients with HFPEF. This is the largest cohort of HFPEF patients studied so far, showing a significant impact of BMI on adverse CV outcomes. Whether weight changes, for example, weight gain in underweight and weight reduction in severe obesity, influence LVM, such as hypertension and insulin resistance. Our study underscores the benefits of maintaining and improving fitness regardless of BMI change.6

Long-Term Effects of Changes in Cardiorespiratory Fitness and Body Mass Index on All-Cause and Cardiovascular Disease Mortality in Men: The Aerobics Center Longitudinal Study

Summary: If overweight or obese persons, who comprise two thirds of the US population, can reduce the risk of premature mortality by improving physical activity or fitness, this carries a large clinical and public health implication. Studies of cardiorespiratory fitness (hereafter fitness) change and mortality are sparse, and long-term effects of body mass index (BMI) change on mortality are inconsistent. Also, the combined associations of changes in fitness and BMI with mortality remain controversial and uncertain. This study found that maintaining or improving fitness was associated with a lower risk of death from all-causes and cardiovascular disease in 14,345 men during 11.4 years of follow-up, after accounting for possible confounding effects of baseline risk factors, changes in lifestyle factors and medical conditions, and simultaneous BMI change. Men who lost fitness also had a higher mortality risk regardless of BMI change in our combined analyses. Given the great difficulties of losing weight and maintaining a reduced weight over the long term, this study underscores the benefits of maintaining and improving fitness to reduce mortality risk independent of weight change, and is important for the development of health recommendations and policies. To date, extensive attention has been given to weight loss. However, the long-term effect of fitness change, primarily resulting from increasing physical activity, is likely to be at least as important as weight loss for reducing premature mortality. Increased attention needs to be placed on strategies to maintain or improve fitness.

Conclusions: Maintaining or improving fitness is associated with a lower risk of all-cause and CVD mortality in men. Preventing age-associated fitness loss is important for longevity regardless of BMI change.

Association of Adiponectin With Left Ventricular Mass in Blacks: The Jackson Heart Study

Summary: Compared with whites, blacks have a higher prevalence of left ventricular hypertrophy and lower circulating levels of adiponectin, an adipokine inversely related to adiposity. In animal model studies, adiponectin has antihypertrophic effects on the heart. Similarly, several human studies have reported an inverse relationship between adiponectin levels and left ventricular mass (LVM); however, the association between adiponectin and LVM in blacks has yet to be defined. We examined the association between serum adiponectin and echocardiography-measured LVM in 2649 black participants in the Jackson Heart Study cohort and queried whether this association is modified by selected covariates known to be determinants of LVM. In the overall sample, we observed a modest negative correlation between adiponectin and LVM that was modified by hypertension and insulin resistance. Among normotensive participants, the inverse association was explained by body mass index and insulin resistance. In contrast to previous reports, we observed a direct association between adiponectin and LVM among blacks with hypertension and insulin resistance. Overall, this cross-sectional study indicates that in blacks the adiponectin-LVM relationship is contextual and depends on the status of risk factors that also influence LVM, such as hypertension and insulin resistance. Our results are consistent with previous reports of increased cardiac expression and circulating levels of adiponectin in the context of hypertension, activation of the renin-angiotensin-aldosterone system, and diastolic dysfunction. Future longitudinal studies are necessary to further define the prognostic significance of adiponectin levels as predictors of LVM in various clinical contexts and race/ancestry groups.

Conclusions: The association between serum adiponectin and LVM among blacks in the Jackson Heart Study cohort was dependent on hypertension and insulin resistance status. Normotensive blacks exhibited an inverse adiponectin-LVM association, whereas participants with hypertension and insulin resistance had a direct association.

Wrist Circumference Is a Clinical Marker of Insulin Resistance in Overweight and Obese Children and Adolescents

Summary: One of the major priorities of clinical practice is to identify young people at increased risk for obesity and insulin resistance, representing the metabolic basis for future cardiovascular disease. This study introduces a new clinical marker of insulin resistance in overweight/obese children and adolescents: the wrist circumference. This measurement has been historically included in the calculation of frame size, which is a parameter in evaluating the free fat mass to correct misclassification introduced by the use of body mass index. We produce the first evidence that wrist circumference is highly correlated with insulin resistance parameters (fasting insulin and homeostasis model assessment of insulin resistance index) in a population of overweight/obese children and adolescents. The association of wrist circumference with insulin resistance is explained only by the transversal wrist bone tissue–related areas and not by the wrist adipose tissue ones, reflecting the anabolic role of insulin on transversal bone growth. Wrist circumference is easily accessible and measurable by the doctor, minimiz-
ing the collaboration required of the patient, and its reproducibility is higher than that of waist circumference. Therefore, taking into account the high collinearity between the 2 parameters, wrist circumference could be considered in the classification of obesity for the prediction of insulin resistance and cardiovascular risk. The identification of youths with increased risk for insulin resistance–related complications could be achieved with minimal effort by measuring wrist circumference, thus avoiding testing the entire population of overweight/obese children for insulin resistance. Our findings open new perspectives in the prediction of cardiovascular risk.

Conclusions: Our findings suggest a close relationship among wrist circumference, its bone component, and insulin resistance in overweight/obese children and adolescents, opening new perspectives in the prediction of cardiovascular disease.7

Association of Maternal Diabetes Mellitus in Pregnancy With Offspring Adiposity Into Early Adulthood: Sibling Study in a Prospective Cohort of 280 866 Men From 248 293 Families

Summary: Maternal diabetes mellitus in pregnancy results in greater offspring adiposity at birth. However, it is unclear whether it results in greater adiposity into adulthood in humans. We undertook a large record-linkage prospective-cohort study of 280 866 singleton-born Swedish men from 248 293 families in order to explore the intrauterine effect of maternal diabetes mellitus on offspring body mass index (BMI) in early adulthood. Maternal diabetes mellitus during pregnancy was associated with greater mean BMI at age 18 in their sons. The difference in BMI was similar within brothers and between unrelated individuals. BMI of men whose mothers had diabetes mellitus during their pregnancy was on average 0.94 kg/m2 greater (95% confidence interval, 0.35–1.52) than in their brothers born before their mother was diagnosed with diabetes. This association was independent of maternal early-pregnancy BMI. Our results show that maternal diabetes mellitus in pregnancy has long-term consequences that are, at least in part, driven by intrauterine mechanisms for greater BMI in offspring. These findings highlight the clinical importance of identifying and adequately treating gestational diabetes mellitus not only for the short-term health benefit of mother and baby, but also potentially for the longer-term prevention of obesity in offspring.

Conclusions: Maternal diabetes mellitus has long-term consequences for greater BMI in offspring; this association is likely to be via intrauterine mechanisms, and is independent of maternal BMI in early pregnancy.8

Rhesus Macaques Develop Metabolic Syndrome With Reversible Vascular Dysfunction Responsive to Pioglitazone

Summary: The metabolic syndrome (MetS) is a constellation of clinical features that include central obesity, hypertension, atherogenic dyslipidemia, and insulin resistance and is clinically important both because of its prevalence and because it increases the risk for cardiovascular disease and type 2 diabetes mellitus (T2D). However, the concept remains controversial, and there is a need for better understanding of how MetS predisposes to cardiovascular disease and T2D. Here, we devised and implemented a strategy to establish a spontaneous nonhuman primates model of MetS, investigated the emergence of MetS in relation to vascular dysfunction, and determined the response to an established pharmacological treatment for diabetes mellitus. By identifying MetS-predisposed animals among 408 rhesus monkeys of 12.7 years age and acclimating them to standardized laboratory conditions for 18 months, we established a nonhuman primates model of spontaneous MetS that faithfully reproduced salient features of human MetS. During the transition from pre-MetS to onset MetS, individual components of MetS emerged together, indicating common shared underlying processes rather than simultaneous occurrence of independent risk factors. Importantly, vascular dysfunction (60% impairment of flow-mediated dilation of brachial artery) tracked with development of MetS. Pioglitazone, a peroxisome proliferator–activated receptor γ agonist, reversibly improved atherogenic dyslipidemia and insulin resistance and fully restored flow-mediated dilation with persistent effect, suggesting the benefit for early treatment of MetS before frank T2D develops. This unique nonhuman primate model of MetS, as demonstrated here, should be highly valuable in mechanistic and translational studies on the pathogenesis of MetS in relation to cardiovascular disease and T2D.

Conclusions: Coemergence of metabolic and cardiovascular components during MetS progression and complete normalization of vascular dysfunction with peroxisome proliferator-activated receptor γ agonists suggest shared underlying mechanisms rather than separate processes, arguing for the benefit of early intervention of MetS components. Predictive nonhuman primate (NHP) models of MetS should be highly valuable in mechanistic and translational studies on the pathogenesis of MetS in relation to cardiovascular disease and diabetes mellitus.9

Association of Vascular Risk Factors With Cervical Artery Dissection and Ischemic Stroke in Young Adults

Summary: Cervical artery dissection (CEAD), although rare in the general population, is a major cause of ischemic stroke (IS) in young adults. Little is known about its risk factors. Our aim was to compare the prevalence of vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, current smoking, overweightness, and obesity) in CEAD patients versus referents and patients with IS of a cause other than CEAD (non-CEAD IS) in a multicenter setting. Compared with country-, gender-, and age-matched referents, CEAD patients were more frequently hypertensive and had a lower prevalence of hypercholesterolemia, obesity, and overweightness. All vascular risk factors were less frequent in CEAD patients compared with country-, gender-, and age-matched non-CEAD IS patients. These patients were more frequently hypertensive, diabetic, and current smokers compared with referents, as described in older cohorts of non-CEAD IS patients. Our findings, if confirmed in independent data sets, could improve the understanding of the mechanisms underlying CEAD, a major cause of IS in young adults, in whom the impact of stroke-related disability is particularly dramatic from a personal and socioeconomic point of view. They suggest that hypertension could be a risk factor of CEAD, although the relationship seems weaker than with non-CEAD IS. The inverse association of CEAD with hypercholesterolemia could have implications in terms of secondary stroke prevention because statins are commonly prescribed after an ischemic stroke, including in CEAD patients, in some instances.

Conclusions: These results, from the largest series to date, suggest that hypertension, although less prevalent than in patients with a non-CEAD IS, could be a risk factor of CEAD, whereas hypercholesterolemia, obesity, and overweightness are inversely associated with CEAD.10

Increased Adipose Tissue Oxygen Tension in Obese Compared With Lean Men Is Accompanied by Insulin Resistance, Impaired Adipose Tissue Capillarization, and Inflammation

Summary: The increase in adipose tissue mass during the development of obesity is accompanied by impaired adipose tissue function, which may underlie type 2 diabetes mellitus and cardiovascular disease. The inciting event causing the metabolic and endocrine derangements in adipose tissue of obese individuals remains to be established. Recent cell culture experiments suggest that a reduced
oxygen tension in adipose tissue (adipose tissue hypoxia) may be involved. It has been proposed that the expansion of adipose tissue mass during weight gain may lead to adipose tissue hypoxia because angiogenesis is insufficient to maintain normoxia. Although adipose tissue hypoxia has been demonstrated in rodent models of obesity, evidence for this in humans is scarce. We hypothesized that decreased adipose tissue blood flow in obese humans may lower adipose tissue oxygen tension, thereby affecting adipose tissue inflammation and insulin sensitivity. In the present study, we describe a novel system for the continuous monitoring of adipose tissue oxygen tension in humans using microdialysis. Using both pharmacological and physiological approaches, we demonstrate that adipose tissue blood flow regulates adipose tissue oxygen tension in humans. Nevertheless, obese individuals exhibit adipose tissue hyperoxia (increased oxygen tension) despite lower adipose tissue blood flow, which seems to be explained by lower oxygen consumption in adipose tissue. This was accompanied by insulin resistance, impaired adipose tissue capillarization, and higher adipose tissue gene expression of inflammatory cell markers. Although these findings are preliminary in nature and require confirmation, this work sheds new light on the role of adipose tissue oxygen tension in metabolic disease.

Conclusions: Our findings establish adipose tissue blood flow (ATBF) as an important regulator of AT oxygen partial pressure. Nevertheless, obese individuals exhibit AT hyperoxia despite lower ATBF, which seems to be explained by lower AT oxygen consumption. This is accompanied by insulin resistance, impaired AT capillarization, and higher AT gene expression of inflammatory cell markers.

Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008

Summary: Defining the characteristics of uncontrolled hypertensive patients may facilitate efforts to improve blood pressure control. Data were analyzed for 13,375 hypertensive adults from the National Health and Nutrition Examination Surveys for 1988 to 1994, 1999 to 2004, and 2005 to 2008. Multivariable logistic regression was used to identify clinical characteristics associated with untreated hypertension, hypertension uncontrolled on 1 to 2 blood pressure medications, and apparent treatment-resistant hypertension on ≥3 blood pressure medications. More than half of uncontrolled hypertensives were untreated, including 52.5% in 2005 to 2008, with about two thirds of them unaware of their hypertension. Untreated hypertensive patients were more often men, infrequent users of primary health care, lean, and without clinical cardiovascular or renal disease. Most treated uncontrolled patients reported taking 1 to 2 blood pressure medications, a proxy for therapeutic inertia. This group, which was older and had higher 10-year coronary heart disease risk than patients controlled on 1 to 2 medications, comprised 34.4% of all uncontrolled and 72.0% of treated uncontrolled patients in 2005 to 2008. Apparent treatment-resistant hypertension increased from 15.9% (1998–2004) to 28.0% (2005–2008) of treated patients (P < 0.001). Clinical characteristics associated with apparent treatment-resistant hypertension included ≥ 4 visits a year, obesity, chronic kidney disease, and 10-year coronary heart disease risk > 20%. Adherence to health lifestyles and medications is important for all patients. Raising hypertension awareness among infrequent users of primary health care and linking them to a medical home could reduce untreated hypertension. Uncontrolled patients on 1 to 2 blood pressure medications could benefit from an additional antihypertensive medication. More effective selection of antihypertensive combination therapy is important for the growing proportion of patients with apparent treatment-resistant hypertension.

Conclusions: Untreated, undertreated, and apparent treatment-resistant hypertension (aTRH) patients have consistent characteristics that could inform strategies to improve blood pressure control by decreasing untreated hypertension, reducing therapeutic inertia in undertreated patients, and enhancing therapeutic efficiency in aTRH.

Colchicine Reduces Postoperative Atrial Fibrillation: Results of the Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) Atrial Fibrillation Substudy

Summary: Postoperative atrial fibrillation (POAF) is the most common complication after cardiac surgery; it is reported in 10% to 65% of cases. POAF increases patient morbidity, length of hospital stay, and management costs. Its prevention is an important management goal. Systemic and local inflammatory responses are believed to contribute to the pathogenesis of POAF. Inflammation, inhomogeneity of atrial conduction, and the incidence of POAF are decreased by corticosteroids. Because of its anti-inflammatory effects for the treatment and prevention of pericarditis, colchicine has the potential to prevent POAF. The Colchicine for the Prevention of the Postpericardiotomy Syndrome (COPPS) POAF substudy is the first trial designed to assess the efficacy and safety of colchicine for POAF prevention. It is a substudy of the COPPS trial, in which colchicine halved the occurrence of the postpericardiotomy syndrome. On the third postoperative day, consecutive adult patients undergoing cardiac surgery and without contraindications to colchicine were randomized to receive placebo or colchicine on top of standard therapy. The substudy primary efficacy end point was the incidence of POAF on placebo/colchicine treatment at 1 month. Patients on colchicine had a reduced incidence of POAF (12.0% versus 22.0%, respectively; P = 0.021; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4 ± 5.7 versus 10.3 ± 4.3 days; P = 0.040) and rehabilitation stay (12.1 ± 6.1 versus 13.9 ± 6.5 days; P = 0.009). Side effects were similar in the study groups. Such findings may be particularly important for clinical practice because colchicine might represent a cheap and relatively safe option for the prevention of both the postpericardiotomy syndrome and POAF, 2 common and troublesome complications of cardiac surgery.

Conclusions: Colchicine seems safe and efficacious in the reduction of POAF with the potentiality of halving the complication and reducing the hospital stay.

Long-Term Dipeptidyl-Peptidase 4 Inhibition Reduces Atherosclerosis and Inflammation via Effects on Monocyte Recruitment and Chemotaxis

Summary: The incretin hormones glucagon-like peptide and glucose-dependent insulotropic polypeptide play a key role in the regulation of postprandial glycemia and satiety. Incretin hormones are inactivated by the exopeptidase dipeptidyl-peptidase 4 (DPP-4). Both small-molecule inhibitors of DPP-4 and DPP-4–resistant incretin analogs are increasingly common treatments for type II diabetes mellitus, although their effects in reducing long-term cardiovascular complications remain to be established. An expanding list of potential beneficial effects of DPP-4 inhibition on the cardiovascular system includes glucagon-like peptide–mediated effects on cardioprotective pathways, nitric oxide–dependent vasodilation, and non–glucagon-like peptide effects that relate to a pathophysiological role for DPP-4 in regulating inflammation. In this study, we investigated the net effects of long-term DPP-4 inhibition with alogliptin in a model of atherosclerosis and insulin resistance. DPP-4 activity was increased in atherosclerosis with a reduction in response to treatment. DPP-4 inhibition improved insulin resistance, blood pressure, and visceral adiposity with reductions in atherosclerosis and inflammation (evidenced by a reduction in plaque and adipose inflammatory macrophage content) and a shift to an alternately activated macrophage phenotype. DPP-4 inhibition prevented monocyte migration and actin polymerization in vitro via Rac-dependent mechanisms and prevented in vivo migration of labeled monocytes to the aorta in response to exogenously administered tumor necrosis factor–α and DPP-4. These data support a net effect of DPP-4 inhibition in reducing adipose and vascular inflammation with a concomitant reduction in atherosclerosis and support a
therapeutic role for these agents in preventing cardiovascular complications in type II diabetes mellitus.

**Conclusions:** DPP-4i exerts antiatherosclerotic effects and reduces inflammation via inhibition of monocyte activation/chemotaxis. These findings have important implications for the use of this class of drugs in atherosclerosis.

### Adipose Tissue ATP Binding Cassette Transporter A1 Contributes to High-Density Lipoprotein Biogenesis In Vivo

**Summary:** Adipose tissue is a major pool of whole-body free cholesterol (FC) and abundantly expresses ATP binding cassette transporter A1 (ABCA1), a membrane protein necessary for high-density lipoprotein (HDL) particle formation. Although adipocytes abundantly express ABCA1, their contribution to HDL production in vivo is unknown. Using adipocyte-specific ABCA1 knockout mice, we demonstrate for the first time that adipocytes make nascent, discrete-sized HDL particles that represent a significant (~15%) source of plasma HDL. Furthermore, deletion of ABCA1 in adipocytes results in a 2-fold increase in FC content, suggesting that other FC export mechanisms cannot compensate for loss of ABCA1. Adipose tissue ABCA1 expression varies over a 5-fold range among different adipose depots in wild-type mice and is significantly correlated with adipose tissue FC content, suggesting an important role for ABCA1 in adipose tissue FC homeostasis. Because adipocyte FC content increases with obesity and adipocyte hypertrophy, we speculate that ABCA1 is upregulated in adipocytes to maintain optimal FC balance between the lipid droplet and plasma membrane and adipocyte function. Accretion of FC during adipocyte expansion may sequester FC on lipid droplets, shunting it away from ABCA1-mediated HDL particle formation, resulting in decreased plasma HDL concentrations with development of obesity. In contrast, rapid weight loss may result in FC mobilization to the adipocyte plasma membrane, resulting in increased ABCA1-mediated HDL particle formation and increased plasma HDL concentrations. Thus, adipocyte ABCA1 quantitatively contributes to plasma HDL levels and may be critical as a negative regulator of obesity and metabolic syndrome by preventing adipocytes from abnormal FC accumulation and dysfunction.

**Conclusions:** We provide in vivo evidence that AT ABCA1-dependent cholesterol efflux and nascent HDL particle formation contribute to systemic HDL biogenesis and that AT ABCA1 expression plays an important role in adipocyte cholesterol homeostasis.

### Insulin Receptor Substrate 1 Gene Variation Modifies Insulin Resistance Response to Weight-Loss Diets in a 2-Year Randomized Trial: The Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) Trial

**Summary:** Although recent data from gene–environment interaction analyses provide support for the notion of a personalized nutrition approach, evidence from clinical trials is scarce. Genome-wide association studies have identified common genetic variants in the IRS1 locus associated with insulin resistance and hyperinsulinemia, as well as type 2 diabetes mellitus and coronary heart disease. In a 2-year randomized weight-loss trial, the Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial, we genotyped the best associated variant (single nucleotide polymorphism rs2943641) in 738 overweight adults, to examine the modifications of the IRS1 gene variation on the long-term changes in body weight, fasting insulin, and insulin resistance in response to weight-loss diets with different compositions of macronutrients. Our results indicated that participants with the IRS1 rs2943641 CC genotype might obtain more benefits in weight loss and improvement of insulin resistance than those without this genotype in response to a high-carbohydrate/low-fat diet. Our data may provide novel information for the development of effective dietary intervention strategies based on genetic background in preventing diseases related to obesity and insulin resistance, such as type 2 diabetes mellitus and cardiovascular disease.

**Conclusions:** Individuals with the IRS1 rs2943641 CC genotype might obtain more benefits in weight loss and improvement of insulin resistance than those without this genotype by choosing a high-carbohydrate and low-fat diet.

### Physical Activity and the Risk of Incident Atrial Fibrillation in Women

**Summary:** Although young, highly trained athletes are at increased risk of atrial fibrillation (AF), physically active middle-aged and older men and elderly women are at reduced risk of the arrhythmia. This association does not appear to be mediated by overweight/obesity. The relationship between physical activity and AF in middle-aged women is less well understood and may be mediated by physical activity’s beneficial effects on a number of AF risk factors, such as cardiovascular disease, high blood pressure, or overweight/obesity. Regular physical activity in the middle-aged is associated with a lower risk of AF. Although this association is independent of hypertension and the development of cardiovascular disease, it does not appear to be independent of body mass index. These data suggest that decreases in body mass index associated with increasing physical activity may underlie the association between moderate levels of physical activity and AF in middle-aged women.

**Conclusions:** In middle-aged women, physical activity was associated with a modestly reduced risk of AF. However, this relationship was no longer significant after controlling for body mass index.

### Consumption of Added Sugars and Indicators of Cardiovascular Disease Risk Among US Adolescents

**Summary:** Consumption of added sugars (caloric sweeteners), which contribute calories but no other nutrients to the diet, are the source of more than one fifth of the calories consumed by US adolescents. The results of our study show that higher consumption of these sugars is associated with blood lipid levels that may place adolescents at increased risk of future cardiovascular disease. We also found that the risks associated with added sugar consumption may be higher among overweight or obese adolescents because higher consumption among this group was also associated with increased insulin resistance. Our findings highlight the prominence of added sugars in the diets of adolescents and suggest that reducing this consumption could be a strategy for modifying cardiovascular disease risk factors and helping to prevent cardiovascular disease. The associations demonstrated in our cross-sectional study point to the need for controlled trials to determine if reducing consumption of added sugars can improve cardiovascular disease risk factors in adolescents and prevent future disease.

**Conclusions:** Consumption of added sugars among US adolescents is positively associated with multiple measures known to increase cardiovascular disease risk.

### Mice With Cardiac Overexpression of Peroxisome Proliferator–Activated Receptor γ Have Impaired Repolarization and Spontaneous Fatal Ventricular Arrhythmias

**Summary:** Diabetes mellitus and obesity confer an increased risk of sudden cardiac death and are associated with cardiomyocyte lipid accumulation and altered cardiac electric properties (demonstrated by prolongation of the QRS and QT intervals). In order to study the effects of metabolic abnormalities on arrhythmias without the complex systemic effects of diabetes mellitus and obesity, we studied a mouse model with cardiac-specific overexpression of
peroxisome proliferator–activated receptor γ (PPARγ), a transcription factor that is a key regulator of glucose and lipid metabolism. These PPARγ transgenic mice develop abnormal accumulation of intracellular lipids and die as young adults, before any significant reduction in systolic function. We found that these mice have prolongation of the QT interval and spontaneous ventricular arrhythmias, including polymorphic ventricular tachycardia and ventricular fibrillation. Isolated cardiomyocytes demonstrated prolonged action potential duration caused by reduced potassium currents, which are responsible for repolarization. Short-term exposure to pioglitazone, a PPARγ agonist, had no effect on mortality or rhythm in wild-type mice but further exacerbated the arrhythmic phenotype and increased mortality in the PPARγ mice. Our findings support an important link between PPARγ activation, cardiomyocyte lipid accumulation, ion channel remodeling, and increased cardiac mortality. This mouse model may help identify the molecular mechanisms leading to sudden death in diabetic and/or obese patients.

Conclusions: Our findings support an important link between PPARγ activation, cardiomyocyte lipid accumulation, ion channel remodeling, and increased cardiac mortality.19

Common Variation at the 11β Hydroxysteroid Dehydrogenase Type 1 Gene Is Associated With Left Ventricular Mass

Summary: A number of lines of evidence point toward an important role of corticosteroid metabolism in cardiovascular and metabolic risk. At the extremes, patients with Cushing syndrome resulting in greatly excessive circulating cortisol exhibit all the features of severe metabolic syndrome; however, variation in cortisol metabolism within the conventionally accepted normal range also could be important in determining interindividual differences in cardiovascular risk. Among the most studied proteins involved in this process is 11β hydroxysteroid dehydrogenase type 1 (11β-HSD1). A microsomal enzyme, 11β-HSD1 converts inactive cortisone to active cortisol. It is strongly expressed in all target tissues for cortisol, chiefly liver and adipose tissue, as well as in cardiomyocytes. Actions of 11β-HSD1 have been implicated in the pathogenesis of diabetes and metabolic syndrome; 11β-HSD1 inhibitors are a novel class of drugs with promising effects in animal models that are under intensive investigation for benefit on these conditions in humans. Left ventricular hypertrophy is a frequent accompaniment of the metabolic syndrome; the hypothesis that 11β-HSD1 actions independently affect left ventricular hypertrophy hitherto has not been investigated. In the present investigation, genetic polymorphisms in the HSD11B1 gene, which codes for the 11β-HSD1 protein, were examined for association with left ventricular mass in a study of 255 hypertensive families. Association was found with a polymorphism in the 11β-HSD1 in the human cardiomyocyte, which may be of therapeutic importance.20

S100A9 Differentially Modifies Phenotypic States of Neutrophils, Macrophages, and Dendritic Cells: Implications for Atherosclerosis and Adipose Tissue Inflammation

Summary: It has previously been demonstrated that elevated plasma levels of S100A9 (also known as myeloid related protein-14) in complex with its binding partner S100A8 (myeloid related protein-8) predict increased risk of future cardiovascular events in healthy postmenopausal women and recurrent events in patients with acute coronary syndromes. Furthermore, apolipoprotein E–deficient mice that are also deficient in S100A9 exhibit reduced atherosclerosis. These important findings suggest that S100A9 is both a biomarker and a mediator of atherosclerosis and cardiovascular events. Most of the constitutively secreted S100A9 is believed to be derived from myeloid cells. We demonstrate that low-density lipoprotein receptor–deficient mice that lack S100A9 in bone marrow–derived cells, including myeloid cells, are not protected against diet-induced atherosclerosis or insulin resistance. Furthermore, S100A9 deficiency differentially modifies phenotypic states of myeloid cell populations. S100A9-deficient neutrophils exhibit a reduced secretion of cytokines, whereas S100A9-deficient dendritic cells show an exacerbated release of cytokines. The effect of S100A9 deficiency on atherosclerosis and other inflammatory diseases is therefore predicted to depend on the relative contribution of these cell types at different stages of disease progression. Furthermore, S100A9 expression in nonmyeloid cells is likely to contribute to atherosclerosis. Further study is needed to fully understand the functions of S100A9 in specific cell populations and disease states before S100A9 and S100A9 are considered therapeutic targets.

Conclusions: S100A9 differentially modifies phenotypic states of neutrophils, macrophages, and dendritic cells. The effect of S100A9 deficiency on atherosclerosis and other inflammatory diseases is therefore predicted to depend on the relative contribution of these cell types at different stages of disease progression. Furthermore, S100A9 expression in nonmyeloid cells is likely to contribute to atherosclerosis.21

Association of Health Professional Shortage Areas and Cardiovascular Risk Factor Prevalence, Awareness, and Control in the Multi-Ethnic Study of Atherosclerosis (MESA)

Summary: Residents living in areas with a shortage of primary care physicians often have difficulty obtaining preventive health care. This article is the first to examine whether living in an area with a shortage of primary care physicians is associated with the prevalence, awareness, or control of cardiovascular risk factors. Although people living in primary care shortage areas have a higher prevalence and lower awareness and control for many cardiovascular risk factors, these findings appear to be due to differences in race/ethnicity and socioeconomic status (SES), not the lack of primary care physicians. Simply increasing the number of primary care physicians in these shortage areas will not improve cardiovascular risk factors. Instead, interventions must also take into account other barriers to cardiovascular health.

Conclusions: This study suggests that increased prevalence of cardiovascular disease risk factors in PC-HPSAs are explained by the demographic and socioeconomic characteristics of their residents. Future interventions aimed at increasing the number of primary care physicians may not improve cardiovascular risk without first addressing other factors underlying health care disparities.22

Ethnic Differences in Out-of-Hospital Fatal Pulmonary Embolism

Summary: This report presents the first epidemiological study involving a large number of autopsy-based out-of-hospital fatal pulmonary embolism investigations in New York City, with its diverse ethnic population. New data presented should alert and aid clinicians in evaluating patients at risk for acute and fatal pulmonary embolism on the basis of different ethnic backgrounds. Because blacks and Hispanics suffer fatal pulmonary embolism at a significantly younger age than whites, physicians should closely monitor these populations for known risk factors (such as body mass index) and counsel healthy lifestyles, especially at younger ages. Because of the large number of prothrombin G2010A carriers observed in white and Hispanic out-of-hospital pulmonary embolism decedents, testing for prothrombin G20210A in high-risk patients is indicated. Finally, our results clearly point to the need for additional research to identify...
Exploring Determinants of Secular Decreases in Childhood Blood Pressure and Hypertension

Summary: The dramatic reduction in mortality from stroke and coronary heart disease observed over several decades in many countries is due partly to declines in blood pressure (BP) and hypertension. Medical treatment and behavioral changes have contributed to the declines. However, there may be important childhood determinants of the reduction in BP and hypertension, considering reports showing that BP tracks from childhood to later life and high adolescent BP is important risk factors for adult cardiovascular disease. One way to unravel childhood determinants of BP and hypertension is to track secular trends in childhood BP because childhood BP is largely uninfluenced by medical treatment and behavioral changes associated with hypertension diagnosis. In the present analyses, on the basis of 4 waves of the Korean National Health and Nutrition Examination Survey between 1998 and 2008, age- and height-adjusted mean systolic BP decreased by 8.7 to 10.0 mm Hg among boys and girls. Childhood hypertension and prehypertension/hypertension prevalences decreased by 52% to 86%. These remarkable decreases were found among all age and socioeconomic groups and were not explained by concomitant secular changes in childhood obesity, health behaviors, nutritional factors, psychological factors, and sociodemographic factors. These results have public health significance because they suggest that important population determinants of secular declines in BP and associated diseases may lie in early life before 10 years of age. Healthcare providers need to keep in mind that, although medical treatment and behavioral changes among adults are important to reduce the disease burden of elevated BP, prevention of BP-related diseases may begin earlier in childhood.

Conclusions: We observed important population declines in blood pressure in Korea over a 10-year period in children 10 to 19 years of age, but the likely causes for these secular trends remain to be determined.

Molecular Basis of Autosomal Dominant Hypercholesterolemia: Assessment in a Large Cohort of Hypercholesterolemic Children

Summary: Autosomal dominant hypercholesterolemia (ADH) is characterized by severely elevated low-density lipoprotein cholesterol levels from birth on, enhanced atherosclerosis progression, and premature cardiovascular events. Functional and morphological changes of the arterial wall are observed in children with ADH, which indicates that the atherosclerotic process has already been initiated. Early diagnosis and treatment of ADH are pivotal because therapy with lipid-lowering agents strongly decreases the risk for cardiovascular events. If possible, a clinical diagnosis of FH should preferably be confirmed by molecular genetic testing. Furthermore, the impression of any current clinical screening strategy for ADH emphasizes the relevance of genetic testing for definite diagnosis of ADH and screening purposes in affected families. This study shows that, if stringent criteria are used, a functional mutation can be found in 95% of children. We therefore feel that children are better suited for the definition of the molecular basis of a dyslipidemic phenotype. This knowledge can help clinicians establish the definite diagnosis of FH in families. Once a child is identified as having ADH, cascade screening can be performed to screen more distant relatives using the inheritance pattern across the pedigree. Furthermore, these data strongly suggest that most of the large-effect genes underlying ADH have been found, at least in the Netherlands. This is of importance because any novel gene implicated in the pathogenesis of ADH and cardiovascular disease could become a pharmacological target in itself; hence, it is important to establish whether a large proportion of ADH patients still carry unexplained molecular defects.

Conclusions: In the vast majority of children with an ADH phenotype, a causative mutation can be identified, strongly suggesting that most of the large-effect genes underlying ADH are known to date.

References


Circulation Editors’ Picks: Most Read Articles on the Topic of Obesity and Cardiovascular Disease
The Editors

Circulation. 2012;126:e301-e308
doi: 10.1161/CIRCULATIONAHA.112.148445
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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