Recent Highlights of ATVB

The Growing Problem of Obesity
Mechanisms, Consequences, and Therapeutic Approaches

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Obesity is a significant problem in the United States and worldwide and one that is not sufficiently abating despite extensive entreaties in the press and in public service announcements. Hence, great attention has been paid to understanding obesity—from its epidemiology, pathobiology, and to therapeutic approaches. To optimally interpret published reports on obesity, it is necessary to adhere to the definitions of the term. The Centers for Disease Control (CDC) define obesity according to criteria aligned directly with subject age. Specifically, in infants and toddlers (age range, birth to age 2 years), high weight for recumbent length is defined as weight for length at or above the 95th percentile of the sex-specific CDC growth charts. In the age range from 2 to 19 years, obesity is defined as body mass index (BMI) at or above the sex-specific CDC BMI-for-age growth charts, and in subjects age≥19 years, obesity is defined as BMI≥30. Based on these definitions, the CDC reported that the percentage of individuals meeting the definition of obesity in 2011 to 2012 within these specific age ranges was 8.1%, 16.9%, and 34.9%, respectively. In addition to the potential for great toll on health and self-esteem, the associated complications of obesity, such as type 2 diabetes mellitus, cardiovascular disease, stroke, and certain forms of cancer, impose a high burden on healthcare delivery. The CDC reported that in 2008, the cost of obesity was $147 billion. Notably, the medical costs for those with obesity were $1429 greater annually than for those who were not classified as obese. Of significant concern, the rise in obesity in young people seems to carry significant complications when diabetes mellitus ensues, such as increased levels of low-density lipoprotein cholesterol, hypertension, retinopathy, and microalbuminuria that, although comparable with rates observed in obese adults, seems to progress at accelerated paces compared with those observed in obese adults, according to the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study. These considerations underscore the urgency of elucidating mechanisms and therapeutic approaches in obesity to ward off the cardiometabolic, oncological, and other complications that limit health and lifespan.

In the past 2 years, multiple reports published in Arteriosclerosis, Thrombosis, and Vascular Biology (ATVB) addressed the problem of obesity in organisms, such as mice, monkeys, and human subjects. From basic mechanisms of disease, to translational studies and to therapeutic approaches, reports in the journal have provided novel insights on the causes and consequences of obesity. In the sections to follow, we highlight these reports and conclude with new insights into therapeutic strategies.

Tracking Obesity and Its Consequences
From Birth to Adulthood: Does Risk Begin in the Womb?

Published evidence in ATVB from the Cardiovascular Risk in Young Finns study suggests that cardiovascular risk attributed to increased body weight may begin by birth. The authors addressed the effect of high birth weight (defined as weight at birth greater than the 90th percentile) and found that those born large for gestational age had higher BMI throughout childhood, adolescence, and in young adult years with overall 2-fold greater risk of obesity when compared with a control group with normal birth weight. The investigators reported that carotid intima-media thickness was higher in subjects born large for gestational age versus normal birth weight and that this was independent of other cardiovascular risk factors. In a distinct cohort, the 1946 British Birth Cohort Study, the authors examined the role of BMI and height from infancy to adulthood in subjects presenting with high adult carotid intima-media thickness. Although no associations of BMI and height were elucidated in women, the authors found that in men, there was a positive association of BMI at age 4 and 20 years (but negative associations with height) with high carotid intima-media thickness. The authors concluded that in men, early childhood may represent a particularly sensitive period for the development of atherosclerosis. Although these studies were not designed to capture the underlying mechanisms of these bad memories, it is plausible that epigenetic changes imparting maladaptive signatures in adipocytes or other metabolic tissues may contribute to these findings. What about the reports in ATVB on the consequences of obesity in human subjects?

Ageno et al performed a meta-analysis of both case–control and cohort studies to evaluate the risk of metabolic syndrome and venous thromboembolism. The authors found that in the case–control studies, both metabolic syndrome and obesity were better predictors of unprovoked venous thromboembolism versus obesity alone. However, when the results of 2 prospective cohort studies were included (comprising 26,531 subjects and 289 cases of unprovoked venous thromboembolism), the associated factors were age, obesity, and abdominal obesity but not metabolic syndrome. Additional analyses suggested that abdominal obesity was a strong risk factor for this complication.
The health of fat tissue with respect to metabolic risk factors has also been addressed. In 1985, Goodpaster et al reported on the skeletal muscle attenuation coefficient determined by computed tomography, a noninvasive measure of muscle density in which lower values reflect increased muscle lipod content. Goodpaster used that measure to test the relationship of muscle content to strength in older subjects. In recently reported studies by Therkelsen et al in ATVB, the relationship between muscle attenuation coefficient with metabolic risk factors and additionally adjusted for BMI and visceral adipose tissue was addressed in subjects of the Framingham Heart Study. The authors showed that in both men and women, muscle attenuation was associated with dysglycemia, dyslipidemia, and hypertension. None of the associations, however, persisted after correction for BMI and visceral adipose tissue. In men, there remained an association between muscle attenuation and lipid levels and in women, an association between muscle attenuation and metabolic syndrome remained.13

In a distinct paper, the relationship of circulating C-reactive protein and interleukin (IL)-6 levels to expression of platelet-derived inflammatory gene mRNAs in 1625 subjects (46% male) of the Framingham Offspring Study was addressed. The authors reported that levels of C-reactive protein and IL-6 were associated with 10 of 15 studied platelet inflammatory factors, adjusting for cardiovascular disease risk factors. Importantly, further analyses of the data suggested that body weight may directly influence these associations.14

A key question, thus, is what are the underlying mechanisms linking obesity to cardiometabolic risk? Multiple studies in the past 2 years published in ATVB have addressed these issues—including studies related to immune cells, inflammation, oxidative stress, and lipid metabolism. In the sections to follow, we review the recently published evidence in ATVB that together add to our growing understanding of mechanisms of obesity and cardiovascular complications.

Inflammation and Oxidative Stress: Roles in Obesity and Metabolic Organs

Immune cell content in metabolic organs, particularly in adipose tissue, is suggested to be linked to metabolic dysfunction. In the past 2 years, several reports in ATVB addressed mechanisms of T-cell content and activity in metabolic organs. A report by McLaughlin et al in healthy overweight or obese human subjects showed that CD4 and CD8 T cells populate human adipose tissue and that the relative frequency of Th1 and Th2 display high associations with systemic inflammation and insulin resistance. Further, the authors showed that adipose tissue expression of IL-10, an anti-inflammatory cytokine, was inversely associated with insulin resistance in human subjects.15 In distinct studies in mice and humans, reports published in ATVB addressed the mechanisms driving T-cell content and activity in obesity.

In a mouse model, CXCR3 was shown to mediate T-cell content in peripancreatic adipose tissue in obese mice, which was related to distinct T-cell subsets that modulated systemic inflammation and metabolism.16 In other studies, the β2 integrin, CD11a was shown to be upregulated in CD8+ T cells of adult mice. In the setting of CD11a deficiency in mice, the resulting attenuation in tumor necrosis factor-α- and IL-12-producing macrophages in adipose tissue was associated with improvements in insulin resistance.17 In other studies in diet-induced obese mice, mice specifically lacking invariant natural killer T cells were studied. Jα18 null mice (devoid of invariant natural killer T cells) and wild-type controls were fed high-fat diet. Under obese conditions, the number of T cells and macrophages was lower in adipose tissue in the Jα18 null mice but inflammatory cytokine expression did not differ. However, the Jα18 null mice displayed lower adipose tissue weight, smaller adipocytes, accelerated lipogenesis, increased expression of hormone-sensitive lipase, and accelerated basal lipolysis versus the controls.18 The authors concluded that these intriguing data showed that invariant natural killer T cells do not affect glucose clearance but, rather, that they modulate lipid metabolism in liver and adipose tissue.

Beyond roles for T cells in obesity and metabolic dysfunction, other studies published in ATVB addressed roles for distinct cell types. Beaulieu et al reported on studies from the Framingham Heart Study subjects in whom it was shown that IL-1β-related genes in platelets were associated with increased BMI, and in mice, analogous observations were made. The authors showed that IL-1 receptor 1 and IL-1β mRNA transcripts, elevated in obesity, increased both macrophage and platelet functions particularly in mice treated with the periodontal pathogen, Porphyromonas gingivalis, thereby suggesting that these inflammatory factors promote a prothrombotic environment in infection and obesity.

Liu et al reported on novel insights on long intergenic noncoding RNAs (lncRNAs) in monocytes and adipocytes of healthy humans undergoing endotoxemia. They showed that adipocytes and monocytes were sources of 2 lipopolysaccharide-regulated lincRNAs and that, interestingly, 2 such lincRNAs (linc-DMRT2 and inc-TP53I13) were suppressed in the adipose of obese humans. Although the mechanistic and pathobiological implications are yet to be fully elucidated, the studies suggest, nevertheless, that obesity might modulate lincRNAs in metabolic tissues. It will be of great interest to learn how the modulation of these lincRNAs might contribute to or protect from the metabolic phenotype in obesity.

Beyond direct roles for inflammatory stress in obesity, oxidative stress is also linked to the pathogenesis of obesity.21–24 Three recent studies in ATVB addressed this concept. In the first study, Liang et al reported that in obese mice db/db mice, toll-like receptor 4 mediates endothelial dysfunction, at least in part through Nox1- and Nox4-linked oxidative stress. Murakami et al showed that mice heterozygous for the xanthine oxidoreductase gene, which catalyzes the production of uric acid, displayed increased lipid accumulation in adipocyte along with increased oxidative stress. These mice also displayed higher body weight, systolic blood pressure, and insulin resistance versus the wild-type controls. Epididymal white adipose tissue displayed increased adipocyte size and greater macrophage content (F4/80 immunostaining) versus the wild-type controls. The data therefore linked reduction in xanthine oxidoreductase to induction of obesity and insulin resistance, particularly in older aged mice.26 In a distinct study, Chen
et al showed that the aortas of obese ob/ob mice displayed increased pulse wave velocity and rigidity, in parallel with decreased expression of lysyl oxidase. In vivo, inhibition of lysyl oxidase in wild-type lean mice caused a significant increase in pulse wave velocity and elastin fragmentation. In human subjects and in mice, these authors showed that obesity was associated with aortic stiffening, thereby further supporting the mechanistic link between this enzyme and aortic tissue disease.

Interestingly, Gaens et al. showed that expression of the advanced glycation end product, carboxy methyl lysine AGE, and its principal cell surface receptor, receptor for AGE (RAGE), were highly expressed in human obese adipose tissue versus lean subject adipose tissue. Of note, carboxy methyl lysine (CML) may also form via oxidative stress through activation of the myeloperoxidase pathway. Thus, these studies link RAGE in adipocyte tissue expression to both inflammatory and oxidative stress mechanisms. Further work is required to make definitive mechanistic links between CML-AGE/RAGE, oxidative stress, and obesity.

Finally, the expansion of perivascular adipose tissue during obesity results in its increased inflammatory potential and a correlation with increased cardiovascular risk. In studies by Manka et al., aortic perivascular adipose tissue from high-fat fed obese mice to the carotid arteries of either high fat–fed or low fat–fed mice devoid of the low-density lipoprotein receptor resulted in increased neointimal expansion after guidewire injury, at least in part through monocyte chemoattractant protein 1–dependent mechanisms. In distinct studies in ob/ob obese mice, roles for leptin in exaggerated neointimal expansion were observed, suggesting that leptin biology may contribute to vascular phenotypes in arterial injury.

Taken together, the above studies from mice to human subjects strongly implicate inflammatory and oxidative stress mechanisms in the links between obesity, metabolic dysfunction, and cardiovascular risk. In the section to follow, we summarize recent studies examining obesity and lipid metabolism.

**Obesity and Lipid Metabolism**

Definitive roles for ABCG5 and ABCG8, mediators of biliary cholesterol secretion, were shown in obese db/db mice. In mice, adenooviral vectors encoding these molecules improved glycemic control and reduced levels of plasma triglycerides. These data revealed the benefits of accelerating biliary cholesterol secretion in obese mice. Studies in human subjects tested whether intestinal insulin resistance modified lipid and lipoprotein homeostasis in the intestine of obese subjects. The authors obtained duodenal samples from 20 obese subjects undergoing bariatric surgery. In these tissues and subjects, dysregulated intestinal insulin signaling was associated with increased lipogenesis and lipoprotein synthesis. Further, the authors found that evidence of abnormal cholesterol transport and metabolism, as suggested by reduced expression of the ATP-binding cassette A1 transporter and proprotein convertase subtilis/kexin type 9. Taken together, these findings from obese human duodenum suggested a mechanistic link between abnormal intestinal insulin signaling and atherogenic dyslipidemia.

To directly address the effect of dietary cholesterol on adipocyte properties, Chung et al. fed male African green monkeys diets of low, medium, or high cholesterol. The authors found that with increasing dietary cholesterol content, free cholesterol, and adipocyte size increased in parallel in visceral but not subcutaneous fat. In the visceral fat, dietary cholesterol intake also increased proinflammatory gene expression and macrophage recruitment, decreased expression of genes mediating cholesterol biosynthesis and lipoprotein uptake, and increased expression of proteins involved in free cholesterol efflux. Hence, despite the increase in free cholesterol and inflammatory signals, compensatory mechanisms in visceral fat are also triggered in an attempt, apparently, to counteract these consequences.

Taken together, these recently published papers in *ATVB* provided important insight on lipid metabolism and the intake of dietary cholesterol on insulin signaling and adipocyte properties. Clearly, the crosstalk between lipoprotein metabolism and inflammatory mechanisms contributes, at least in part, to the aberrant metabolic phenotypes observed in obesity.

Lastly, in the section to follow, we address potential solutions for the problem of obesity. In fact, 4 papers recently published in *ATVB* report on therapeutic strategies in obesity and may lay the groundwork for further study in human subjects.

**Solving the Problem of Obesity and Its Consequences**

Two papers published in *ATVB* highlighted the sequelae of weight loss on cardiometabolic factors in obesity. In the first, Petersen et al performed a systematic search of multiple literature databases to find intervention trials testing the effect of weight loss (induced by various means such as energy restriction, antiobesity drugs, and bariatric surgery) on pulse wave velocity. With respect to all arterial segments, the authors found that even modest weight loss (mean of 8% of baseline body weight) through diet and lifestyle improved pulse wave velocity. In other studies, the benefits of bariatric surgery in 22 obese subjects without diabetes mellitus undergoing the procedure were tested on triglyceride-rich lipoprotein metabolism. Benefits were observed in the reduction of triglyceride-rich lipoprotein-apoB 100 concentrations that were significantly associated with a reduction in plasma apoC-III. Together, the results implicated these mechanisms in the potential for reduced cardiovascular mortality. What about pharmacological approaches?

Two studies reported on such interventions. In the first, high dose resveratrol treatment for 2 weeks reduced intestinal and hepatic lipoprotein particle production in either overweight or obese human subjects. In the second study, treatment of mice fed high-fat diet with metformin inhibited endoplasmic reticulum stress and oxidative stress and improved nitric oxide bioavailability and thereby improved endothelial function. These benefits were shown to be because of the effects of metformin on activation of 5′-adenosine monophosphate–activated protein kinase/peroxisome proliferator–activated receptor α pathway.
Closing Notes

In summary, recent articles published in ATVB have highlighted fundamental mechanisms underlying obesity and its complications. In many of these publications, studies in human subjects reinforce key hypotheses and the translational relevance gained from rodent studies, such as the roles of epigenetics and intrauterine and birth weight, subsets of T cells, lipid metabolism, and potential roles for RAGE and IL-10 in human obesity.30–42

Future research directions are buoyed by these findings and set the stage for exploring novel mechanisms and for testing new therapeutic strategies, especially those combining efforts to combat inflammation and abnormal lipid handling in obesity.

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