OBESITY AND CARDIOVASCULAR DISEASE
ACP: Oklahoma Chapter Scientific Meeting 2017

Nicole Tintera Tran, M.D.
Assistant Professor of Medicine
Department of Cardiology
Relevant Disclosure

Under Accreditation Council for Continuing Medical Education guidelines disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Nicole Tintera Tran, M.D.

I have no relevant financial relationships or affiliations with commercial interests to disclose.
Learning Objectives

• Upon completion of this session, participants will be able to:
  – Understand the data supporting obesity as an independent risk factor for cardiovascular disease.
  – Identify the direct physiologic effects of obesity on the cardiovascular system.
  – Understand the contribution of obesity to hypertension and identify which pharmacologic therapies might be most effective in this population.
  – Recognize the concept of the “obesity paradox” in patients with existing cardiovascular disease, and identify a potential mechanism for this paradox as well as confounding factors.
Background

OBESITY AND CARDIOVASCULAR DISEASE
Epidemiology

- The prevalence of obesity in the USA has doubled since 1980
- CDC estimates that obesity cost the USA > $147 billion in 2008
- 68% of adults in the USA are either overweight or obese
- Childhood obesity often translates to obesity in adulthood
  - 80% of obese children become obese adults

Ogden CL, National Center for Health Statistics; 2010.
WHO Classification

- BMI = weight (kg)/(height (m)^2)

<table>
<thead>
<tr>
<th>Class</th>
<th>BMI (kg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 – 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25 – 29.9</td>
</tr>
<tr>
<td>Class I obesity</td>
<td>30 – 34.9</td>
</tr>
<tr>
<td>Class II obesity</td>
<td>35 – 39.9</td>
</tr>
<tr>
<td>Class III obesity (severe, morbid)</td>
<td>≥ 40</td>
</tr>
</tbody>
</table>

WHO Guidelines on Obesity. 2009;9
Limitations of BMI

• At lower BMIs does not distinguish well between lean body mass and adipose tissue
• Better predictive of amount of adipose tissue at higher BMIs
• Centripetal obesity (waist to hip ratio) may be more predictive of cardiovascular outcomes

Obesity as a Cardiovascular Risk Factor

• 27th Bethesda conference
  – **Category I:** risk factors for which interventions have been proved to reduce the incidence of coronary artery disease (CAD) events
  – **Category II:** a risk factor for which intervention is likely to lead to decreased likelihood of CAD events
  – **Category III:** risk factors clearly associated with increase risk of CAD which if modified might decrease risk of CAD events
  – **Category IV:** risk factors associated with increased risk which cannot be modified

Obesity is a *category II* risk factor for coronary artery disease.

Obesity as a Cardiovascular Risk Factory

- Obesity is associated with:
  - Insulin resistance/hyperinsulinemia
  - Diabetes type II
  - Dyslipidemia
  - Hypertension
  - Left ventricular hypertrophy
  - Sympathetic nervous system (SNS) dysfunction
  - Endothelial dysfunction
  - Obstructive sleep apnea

All of which are risk factors for cardiovascular disease...

Is obesity an independent risk factor for cardiovascular disease or is it associated with cardiovascular disease due to the above?

Obesity as an independent risk factor

OBESITY AND CARDIOVASCULAR DISEASE
Nurses Health Study

- 119,195 women in the USA between 30-55 yo
- Free of cardiovascular disease in 1976
- Among non-smokers, risk of death increased directly and significantly with increasing BMI

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Mortality (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 – 24.9</td>
<td>1.2</td>
</tr>
<tr>
<td>25 – 26.9</td>
<td>1.3</td>
</tr>
<tr>
<td>27 – 28.9</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt; 29</td>
<td>2.1-2.2</td>
</tr>
</tbody>
</table>

Framingham Heart Study

• 30 years of follow-up
• Strong positive and significant correlation between baseline weight and mortality
• Overweight, non-smoking men had 3.9 fold increase in mortality when compared to normal weight men

What about cardiovascular disease and cardiovascular mortality?

Garrison RJ, Ann Intern Med. 1985;103(6 (Pt 2)):1006.
Prospective study of over 1 million USA adults
- 457,785 males
- 588,369 females

Obesity significantly associated with increased all cause mortality and increased cardiovascular (CVS) mortality in men and women who were non-smokers with no baseline CAD.

- High BMI most strongly predicted CVS death in males
- Risk greatest in both men and women with BMI ≥ 40 kg/m²

What about “metabolically healthy” obesity?

- In Class I-III obese patients without evidence of any of the components of the metabolic syndrome
  - Impaired vasoreactivity
  - More echolucent carotid plaque
  - Increased left ventricular mass
  - Impaired coagulation/fibrinolytic systems

Obesity and Cardiovascular disease

- Conclusion: obesity is both an independent risk factor for cardiovascular disease as well as a facilitating causal agent through various associated co-morbidities
Direct cardiovascular effects of obesity

OBESITY AND CARDIOVASCULAR DISEASE
Physiologic Effects of Obesity

↑ total blood volume and central blood volume

↓ systemic vascular resistance*

↑ cardiac output

↑ left ventricular end-diastolic dimension

↑ wall stress

Eccentric hypertrophy

*normotensive obesity

Physiologic Effects of Obesity

↑ total blood volume and central blood volume

↑ systemic vascular resistance*

↑ cardiac output

↑ left ventricular end-diastolic dimension

↑ wall stress

↑ afterload

Concentric hypertrophy

*hypertensive obesity

Physiologic Effects of Obesity

• Class III obesity (morbid, severe)
  – Left ventricular end-diastolic pressure (LVEDP) and pulmonary capillary wedge pressure (PCWP) are increased
  – Increased left-heart filling pressures along with obstructive sleep apnea (OSH) and obesity hypoventilation syndrome → increased right-heart filling pressures
  – Exaggerated increased of LVEDP/PCWP with exercise
  – Pulmonary edema threshold can be exceeded

Obesity Cardiomyopathy

- Heart failure due predominantly or entirely to severe obesity
- Common in class III obesity, related to duration obesity
  - 70% at 20 years
  - 90% at 30 years
- Incidence diastolic dysfunction increases with obesity class
- Severe systolic dysfunction rare in uncomplicated obesity

Obesity-related hypertension

OBESITY AND CARDIOVASCULAR DISEASE
The Problem

- 60-70% of hypertension in adults attributable to obesity
- Obese individuals are 3.5 x more likely than normal weight individuals to develop hypertension
- Central obesity more strongly associated with hypertension than peripheral obesity in both men and women

• Through what mechanisms does obesity contribute to hypertension?
  – Insulin-resistance
  – Sodium retention
  – Altered vascular function
  – Increased sympathetic nervous system (SNS) activity
  – Increased renin-angiotensin-aldosterone (RAA) activity
Pathophysiology

Increased SNS activity
- Baseline SNS activity increased in obesity
- Most prominent in the kidney and skeletal muscle
- Increased renal SNS → sodium retention and activation of the renin-angiotensin-aldosterone (RAA) system

Renal factors
- Increased Na retention
- Impaired pressure natriuresis
- Increased intrarenal pressure due to abdominal obesity may also impair natriuresis

Pathophysiology

• Impaired endothelial function
  – Insulin resistance and central obesity are both associated with impaired endothelial function
  – Nitric oxide (NO) dependent vasodilation is impaired
  – This correlates most strongly with waist-hip ratio
  – Weight loss has been shown to improve endothelial function

## Treatment: Lifestyle Modifications

<table>
<thead>
<tr>
<th>INTERVENTION</th>
<th>DESCRIPTION</th>
<th>ANTICIPATED DECREASE IN SBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Sodium Restriction</td>
<td>&lt; 2.4 grams/day</td>
<td>4.8 mm Hg</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>BMI 18.5-24.9</td>
<td>1 mm Hg per pound lost</td>
</tr>
<tr>
<td>DASH Diet</td>
<td>High in vegetables, fruit, low fat dairy, whole grains, poultry, fish, nuts</td>
<td>6 mm Hg</td>
</tr>
<tr>
<td>Aerobic Exercise</td>
<td>40 minutes of moderate intensity exercise 3-4x a week</td>
<td>4-6 mm Hg</td>
</tr>
<tr>
<td>Limit Alcohol Intake</td>
<td>≤ 1 beverages/day women, ≤ 2 beverages/day men</td>
<td>2-4 mm Hg</td>
</tr>
</tbody>
</table>

Treatment: Anti-Hypertensive Therapy

- Obesity is not a specific population in JNC-8
- ACE inhibitors and angiotensin receptor blockers (ARBs) are associated with increased insulin sensitization and decreased diabetic risk
- Adverse metabolic effects of diuretics are dose dependent
- Beta blockers may be more effective in treating hypertension in obesity due to SNS over activity but are still not first line agents in the treatment of hypertension

The obesity paradox

OBESITY AND CARDIOVASCULAR DISEASE
The Obesity Paradox and Heart Failure

- Meta-analysis of 9 observational studies of patients with heart failure where BMI and mortality reported
- 28,209 patients, mean follow-up 2.7 years
- Overweight and Class I-II obesity were associated with a reduction in mortality
- This remained true when adjusted for baseline risk
- There was a very high mortality in the underweight group

- **Overweight (BMI 25 – 29.9):** all-cause mortality RR 0.84 (0.79 – 0.90)
- **Obese (BMI 30-39.9):** all-cause mortality RR 0.67 (0.62 – 0.77)

The Obesity Paradox and Heart Failure: Discussion

• Selection bias:
  – Obese patients may be identified earlier in the disease due to comorbidities
  – Only the “healthiest” obese may be surviving long enough to get heart failure
  – Obese patients were younger, less likely to smoke, had a lower incidence of previous MI, had higher EF, higher systolic BP and higher rate of beta blocker use

• Chronic heart failure is a catabolic state

The Obesity Paradox and Coronary Disease

- Meta-analysis of 40 studies of patients with CAD which reported BMI and all-cause mortality
- 250,152 patients with mean follow-up of 3.8 years

- **Underweight (BMI ≤ 20):** RR all-cause mortality 1.37 (1.32 - 1.43), CVS mortality 1.45 (1.16 – 1.81)
- **Overweight (BMI 25 – 29.9):** RR all-cause mortality 0.87 (0.81-0.94), no significant reduction CVS mortality
- **Class III obesity (BMI ≥ 40):** RR CVS mortality 1.88 (1.85 – 3.34)

The Obesity Paradox and Coronary Disease: Discussion

• BMI not optimal for distinguishing between lean mass and adipose tissue in the overweight category
• Fewer cardiovascular risk factors in lower BMI groups
• Risk factors potentially identified earlier in obese
• Underweight have decreased muscle mass which is associated with decreased exercise capacity

The Obesity Paradox and Cardiorespiratory Fitness

- Poor cardiorespiratory fitness (CRF) measured in METs may be the strongest cardiovascular risk factor.
- 1 MET increase in CRF is associated with a 13% reduction in CVS mortality and 15% reduction in all-cause mortality (2).
- 1 MET increase in CRF is associated with a 17% reduction in heart failure hospitalization (2).

The Obesity Paradox and Cardiorespiratory Fitness

• In heart failure, the obesity paradox is only present in individuals with low CRF
• 2066 patients with systolic heart failure (2)
  – CRF (peak VO2 max) was ≥ 14 ml/kg/min
    • No obesity paradox
    • Low mortality
  – CRF (peak VO2 max) < 14 ml/kg/min
    • Obesity paradox present
    • High mortality

Rapid Weight Fluctuations and Outcomes

• Post hoc analysis of the Treating to New Targets Trial
  – Patients with established cardiovascular disease
  – Each 1 SD of body weight variability was associated with an increased risk of any coronary or any cardiovascular event (HR 1.04)
  – Higher body weight variability was associated with higher risk
  – Body weight variability also associated with increased risk of new onset diabetes

Conclusions

OBESITY AND CARDIOVASCULAR DISEASE
Conclusions

- Obesity is an independent risk factor for the development of cardiovascular disease.
- Obesity is associated with an increased risk of hypertension, congestive heart failure, coronary heart disease, and cardiovascular mortality.
- Visceral obesity (measured by waist hip ratio) is associated with increased cardiovascular risk at any level of BMI.
Conclusions

• Purposeful weight loss is associated with:
  – Decreased total and central blood volume
  – Decreased oxygen consumption
  – Decreased stroke volume
  – Decreased cardiac output
  – Decreased blood pressure

• Improved CRF is associated with decreased cardiovascular and all-cause mortality
ACC/AHA/ACP Guidelines

- Recommend regular assessment of BMI and waist circumference
- Recommend counseling on weight management at each patient visit with goal BMI 18.5 – 24.9 kg/m2
- Recommend initial goal weight low of 10% of baseline weight
- Recommend lifestyle changes and treatment strategies for metabolic syndrome in:
  - Men with waist ≥ 40”
  - Women with waist ≥ 35”

Questions?

Nicole-Tran@ouhsc.edu
References


References

References

The Obesity Paradox and Heart Failure: Possible Mechanism

- Obesity is associated with increase TNF-α which promotes cardiac apoptosis, but adipose tissue also produces soluble TNF-α receptors
- Increased BNP and NT pro-BNP levels are associated with worse outcomes in heart failure
- Obesity associated with increased systolic blood pressure
- BMI when mildly elevated is not optimal for distinguishing between adipose tissue and lean body mass

American College of Sports Medicine Guidelines

- Recommendations for physical activity in obese patients
  - 5-7 days per week of aerobic physical activity
  - 150 minutes/week to maintain weight/improve health
  - 150 – 250 minutes/week to prevent weight gain
  - 225 – 450 minutes/week to promote weight loss
  - 200 – 300 minutes/week to prevent weight gain after weight loss