Treating Obesity Can Treat the Heart and much more: 200+ Obesity Complications

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Disclosures

Company	Disease State/Topic	Role
Novo Nordisk	Obesity	Promotional speaker Advisory board
Acella	Thyroid	Advisory board Promotional speaker
Currax	Obesity	Advisory board Promotional speaker
Lilly	Obesity and Sleep apnea	Advisory Board Promotional speaker
BI	Obesity	Advisory Board
WW	Obesity	Advisory board

- All relevant financial relationships have been mitigated.

Objectives

- ✓ List the current identified complication of obesity
- ✓ Discuss the pathophysiology of obesity and how it causes various complications
- ✓ Review the treatment including pharmacology for obesity and this effect on some complications

“And in the absence of relevant trial data f
individual
ledge to care for people with diabetes.”

Semenkovich 2017

The same is true for obesity… Golden ☺

Organizational statements

- AACE
  - complications centric approach, the primary endpoint is improvement in adiposity-related complications, not preset decline in body weight
    - List: 16 discrete diseases
- OMA:
  - algorithm “clinical manifestations: fat mass disease”, Adiposopathic or fat mass pathologies
    - List: 19 cancers, 17 GU and reproductive manifestations, 15 metabolic and other diseases

Steele, C. B., Thomas, C. C., Henley, S. J., Massetti, G. M., Galuska, D. A., Agurs-Collins, T., Puckett, M., & Richardson, L. C. (2017). Vital Signs: Trends in Incidence of Cancers Associated with Overweight and Obesity - United States, 2005-2014. *MMWR. Morbidity and mortality weekly report*, *66*(39), 1052–1058. https://doi.org/10.15585/mmwr.mm6639e1

Problem

- Study of interest
  - Health Effects of Overweight and Obesity in 195 Countries over 25 Years
  - Findings
    - 2015, obesity affected 107.7 million children and 603.7 million adults worldwide
    - High BMI accounted for 4.0 million deaths globally
    - More than two-thirds of deaths related to high BMI were due to cardiovascular disease
    - High BMI accounted for 28.6 million years lived with disability of all-cause.
      - DM was the leading cause of YLDs related to BMI - 19.3 million
      - MS disorders - 5.7 million
      - CV disease 3.3 million

GBD 2015 Obesity Collaborators (2017). Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *New England Journal of Medicine. 377*:13-27.

Problem

- Study of interest
  - Associations of Weight Gain From Early to Middle Adulthood With Major Health Outcomes Later in Life (2017)
    - 118,140 health professionals
    - Findings: In these cohorts of health professionals, weight gain during adulthood was associated with significantly increased risk of major chronic diseases and decreased odds of healthy aging.

Zheng, Y., Manson, J., Yuan, C., Liang, M., Grodstein, F., Stampfer, M., & Willett, W. Hu. (2017). Associations of Weight Gain From Early to Middle Adulthood With Major Health Outcomes Later in Life. *Journal of American Medical Association, 318*(3), 255-269.

Problem

- Study of interest
  - The Genetic Basis of Obesity Complications
    - Weight loss modifies at least 100 genes involved
      - production of cytokine, interleukins, complement components, acute phase proteins

Zheng, Y., Manson, J., Yuan, C., Liang, M., Grodstein, F., Stampfer, M., & Willett, W. Hu. (2017). Associations of Weight Gain From Early to Middle Adulthood With Major Health Outcomes Later in Life. *Journal of American Medical Association, 318*(3), 255-269.

SEMINAL STUDY

T-P-3166: A systematic review and evaluation of current evidence reveals 236 obesity-associated disorders (ObAD)

Michele M. Yuen[1,2], Rebecca L. Earle[1], Nitya Kadambi[1], Joseph Brancale[1], David T. Lui[2], Scott I. Kahan[3], Lee M. Kaplan[1]

[1]Massachusetts General Hospital, Boston, MA, [2]Queen Mary Hospital, The University of Hong Kong, [3]George Washington University, Washington, DC

Background

The breadth of comorbid conditions associated with obesity has not been comprehensively described. Using a systematic approach, we performed an extensive, systematic review of the literature to evaluate the extent of obesity-associated disorders (ObAD).

Aims

- To assess the **relationship between the severity of obesity**, using *body mass index (BMI) categories* and *waist circumference (WC)* as measures, **and the risk of having the ObAD** (manuscript in preparation)
- To assess the **population-attributable risk** of obesity in the major ObAD (manuscript in preparation)
- To assess the **benefit of weight loss** (to be addressed in Part 2 of this study)
- To evaluate the **strength of evidence** of the association between obesity and each ObAD using a modified **Grading of Recommendations Assessment, Development & Evaluation (GRADE)** approach

Methods I

Generated list of candidate ObAD based on *a priori* knowledge

↓

Searched PubMed using MeSH terms with Boolean logic
Example: comorbidity/epidemiology[MAJR] AND obesity/epidemiology[MeSH]

↓

Applied filters: "Human", "English", "Adults:19+years"

↓

Narrowed or broadened search by adding or removing MeSH terms

- 1 or more articles reporting an OR, RR or HR → Characterized strength of association by a modified **GRADE** approach
- No report of OR, RR or HR → Removed from final ObAD list

Methods II

Modified Grading of Recommendations Assessment, Development & Evaluation (GRADE)

Consider study design

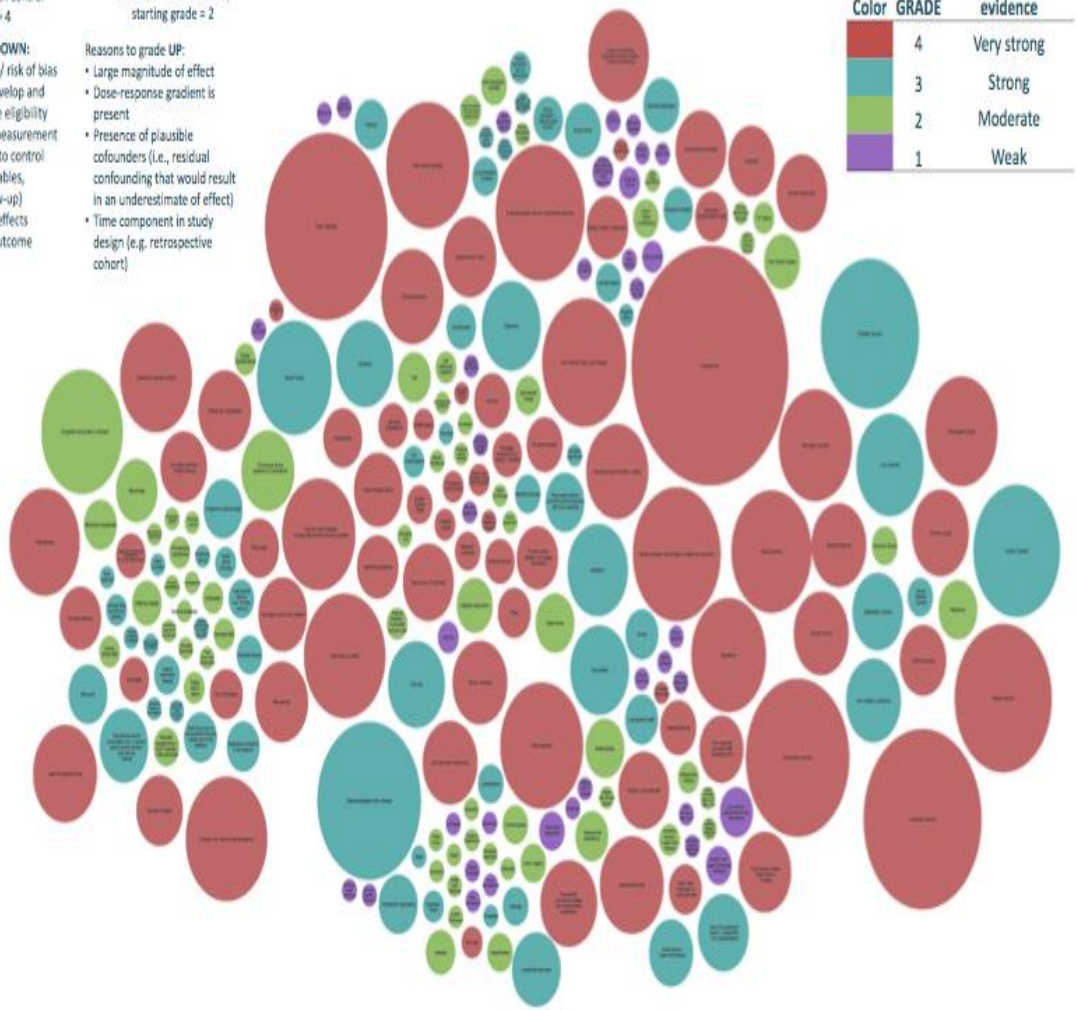
- Randomized control / Prospective cohort with control — starting grade = 4
- Other (ie. observational) — starting grade = 2

Reasons to grade **DOWN:**
- Study limitations / risk of bias (e.g. failure to develop and apply appropriate eligibility criteria, flawed measurement methods, failure to control confounding variables, incomplete follow-up)
- Inconsistency of effects
- Indirectness of outcome
- Imprecision

Reasons to grade **UP:**
- Large magnitude of effect
- Dose-response gradient is present
- Presence of plausible cofounders (i.e., residual confounding that would result in an underestimate of effect)
- Time component in study design (e.g. retrospective cohort)

Figure: Strength of evidence for each of the 236 ObAD

- ObAD are clustered by discipline and organ system affected (if applicable)
- Size of the dot represents number of article retrieved for the individual ObAD.
- Color of the dot represents the highest GRADE of retrieved articles



Results

- 236 ObAD were identified
- Strongest associations (≥50-100 relevant, high-quality articles each) were observed for **cardiovascular disorders, cancers, selected infections, obstetric conditions**
- Moderate associative evidence (10-50 articles each) was found for **GI, renal, orthopedic, psychiatric and dental** disorders
- Weak evidence (<10 qualifying articles) was identified for **hematological, pulmonary, neurological, rheumatological, ENT, surgical and ophthalmological** ObAD
- Weakest evidence (10-50 cross-sectional studies) was found for **quality of life** disturbances **and dermatological** ObAD

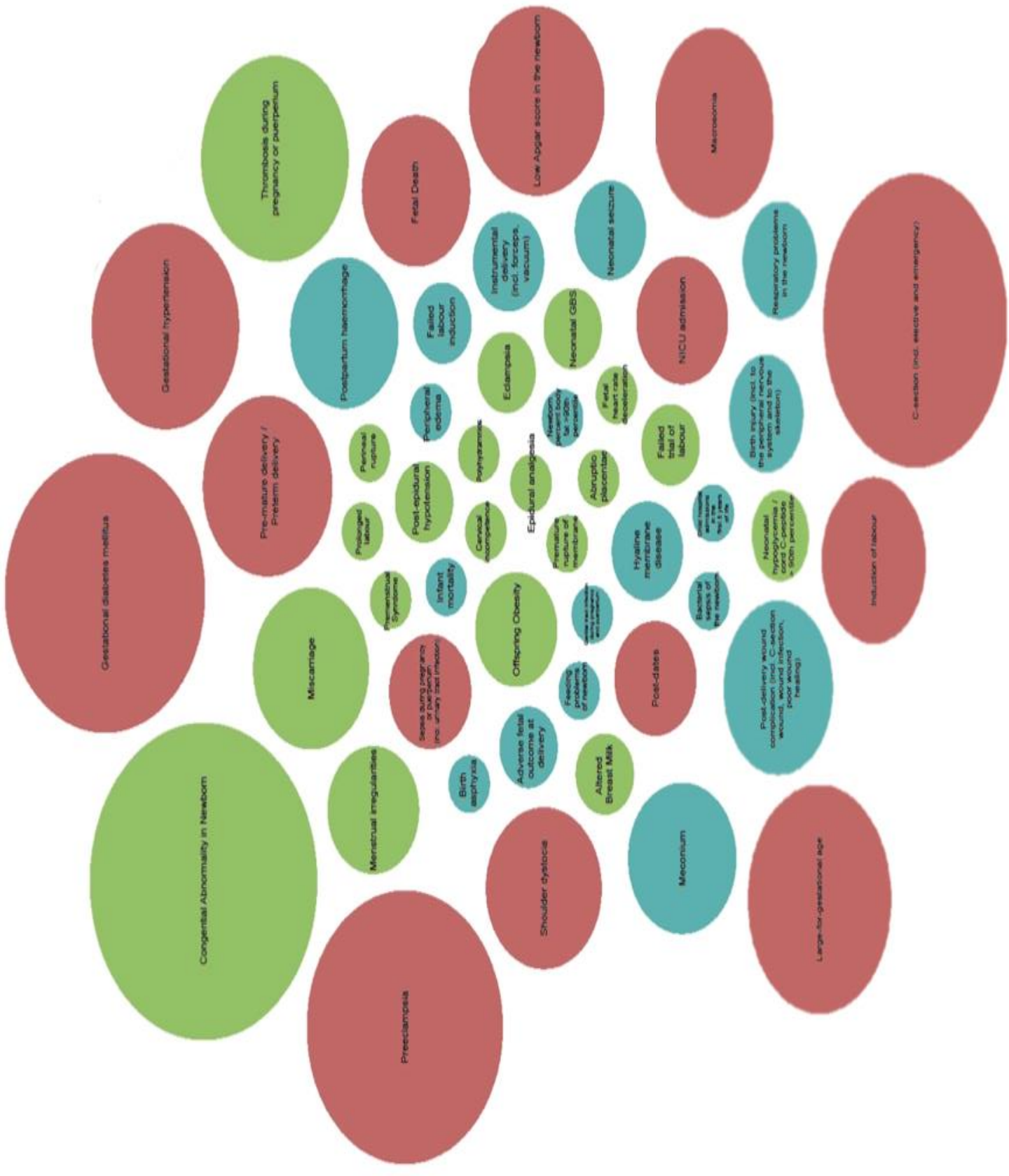
Conclusions and Implications

- Obesity is linked to over 200 discrete disorders
- This number is far greater than previously reported
- The diseases that obesity is linked to comprise 35% of non-fatal global burden of disease and 38% of causes of global causes of death based on data from 2015 (retrieved from http://www.healthdata.org/gbd)
- This methodology provides a framework for further study to more precisely define these clinical relationships and to explore their pathophysiological basis and health policy implications.

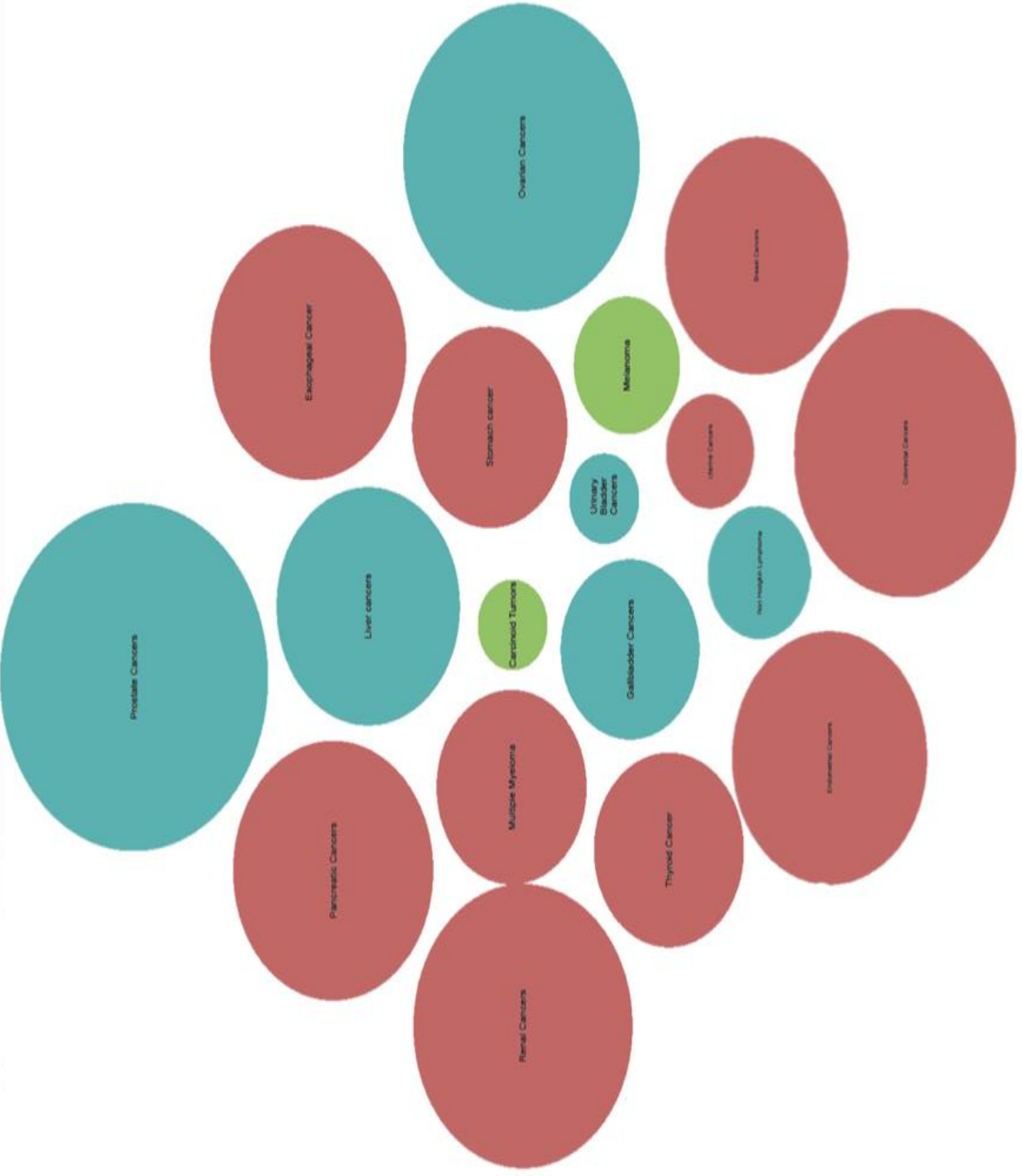
Contacts

Michele M. Yuen, MBBS, FHKCP, FHKAM: micheleyuen@hotmail.com
Lee M. Kaplan, MD, PhD: lmkaplan@mgh.harvard.edu

Women's Health



Cancers


Ovarian Cancers
Esophageal Cancer
Stomach cancer
Melanoma
Urinary Bladder Cancers
Liver cancers
Carcinoid Tumors
Gallbladder Cancers
Prostate Cancers
Pancreatic Cancers
Multiple Myeloma
Renal Cancers
Thyroid Cancer

All Cause Mortality

- Adults with obesity
  - die 3.7 years earlier from all causes
  - die 1.6 years earlier from CVD
  - Most at risk adults aged 45 years to 64 years with obesity
    - die up to 12.8 years earlier than those who are at normal weight
- Most, if not all, of these sequelae could be reduced w relatively mod. Wt. loss of just 5%-10%
  - Stage 2 and 3 obesity were both associated with significantly higher all-cause mortality
  - Overweight was associated with significantly lower all-cause mortality

Flegel, K., Kit, B., Orpana, H., & Graubard, B. (2013). Association of all-cause mortality with overweight and obesity using standard body mass index categories: A systematic review and meta-analysis. *The Journal of the American Medical Association*, *309*(1): 71-82.
Flegal, K., Graubard, B., Williamson, D., & Gail, M. (2007). Excess deaths associated with underweight, overweight, and obesity. *The Journal of the American Medical Association*, *298*(17): 2028-2037.
Visaria, A., & Setoguchi, S. (2023). Body mass index and all-cause mortality in a 21st century U.S. population: A National Health Interview Survey analysis. *PloS one*, *18*(7), e0287218. https://doi.org/10.1371/journal.pone.0287218

Epidemiology of Obesity Related to Cancer

- According to the CDC
  - Obesity increases the risk of 13 cancers
  - Account for 40% of all cancers diagnosed in the US
  - 55 percent of all cancers diagnosed in women and 24 percent of those diagnosed in men
- 2030 estimates
  - every state 44% of population with obesity
  - 13 states > 60%
- 6% new cases of cancer a year

Pati, S., Irfan, W., Jameel, A., Ahmed, S., & Shahid, R. K. (2023). Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers*, *15*(2), 485. https://doi.org/10.3390/cancers15020485

Obesity Related Cancers

- Pathophysiology: cytokines = chronic inflammation = influencing neoplastic process
- Study of interest:
  - Metabolic Dysregulation and the Risk of Obesity-related Cancers (2013)
    - 4615 participants
    - finding: IFG time exposure > risk of obesity-related cancers, particularly colorectal cancer
- 2004 Dr. Bray wrote about obesity and cancers relationships

Pati, S., Irfan, W., Jameel, A., Ahmed, S., & Shahid, R. K. (2023). Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers*, *15*(2), 485. https://doi.org/10.3390/cancers15020485

Obesity Related Cancers

- Study of interest: Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States (2016)
  - 73,913 women
  - Findings
    - being overweight for a longer duration during adulthood
    - increases incidence of all obesity-related cancers

Arnold, M., Jiang, L., Stefanick, M., Johnson, K., Lane, D., LeBlanc, E., Prentice, R., Rohan, T., Snively, B., Vitolins, M., Zaslavsky, O., Soerjomataram, I., & Anton-Culver, H.. (2016). Duration of Adulthood Overweight, Obesity, and Cancer Risk in the Women's Health Initiative: A Longitudinal Study from the United States. PLoS Med 13(8): e1002081. doi:10.1371/journal.pmed.100208, last accessed August 12, 2017.

Obesity Related Cancers
Clinical Implications

- IFG
  - consider treatment to reduce risk continuing IFG – thereby reducing cancer risk
    - AACE tx recommendation
      1. Lifestyle therapy with goal of 10% weight loss
      2. Medication assist: with phentermine/topiramate ER, liraglutide 3mg, or orlistat (if at risk for DM2) again with 10% loss (with lifestyle therapy)
      3. NOTE: post 2016 semaglutide 2.4mg and tirzepatide 15mg
      4. High risk patients: consider metformin, acarbose and thiazolidinediones if 1 and 2 not effective and remain glucose intolerant

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice*, *22*(3), 1-203. Last accessed Septembr 18, 2024 https://www.aace.com/files/final-appendix.pdf

Obesity Related Cancers
Clinical Implications

- ACCE guideline:
  - women with weight-related complications, any weight loss was associated with a 20% reduction in all-cause mortality due to reduced mortality from cancers and diabetes
- Attention to CA screening – esp. colon, prostate and breast
- Amount of time overweight or obesity important role in cancer risk
  - highlights the importance of obesity prevention at all ages and from early onset

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice*, *22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Neurodegenerative Disorders

- Neurodegenerative disease
  - multifactorial interaction between environmental factors and genetic predisposition
  - Obesity connection
    - increase in reactive oxygen species – oxidative stress
    - dysfunction in the ATP production

      = cognitive impairment

Kueck, P. J., Morris, J. K., & Stanford, J. A. (2023). Current Perspectives: Obesity and Neurodegeneration - Links and Risks. *Degenerative neurological and neuromuscular disease*, *13*, 111–129. https://doi.org/10.2147/DNND.S388579

Neurodegenerative Disorders

- Obesity connection
  - Chronic hyperglycemia and insulin resistance risk factors – neuronal death
  - Increase FFA adds to increase in insulin resistance
  - changes in insulin signaling – impairs neuronal excitability, nerve cell metabolism, cell survival, and changes in insulin-like growth factor
  - Long term increase in IL-6 causes neuronal death

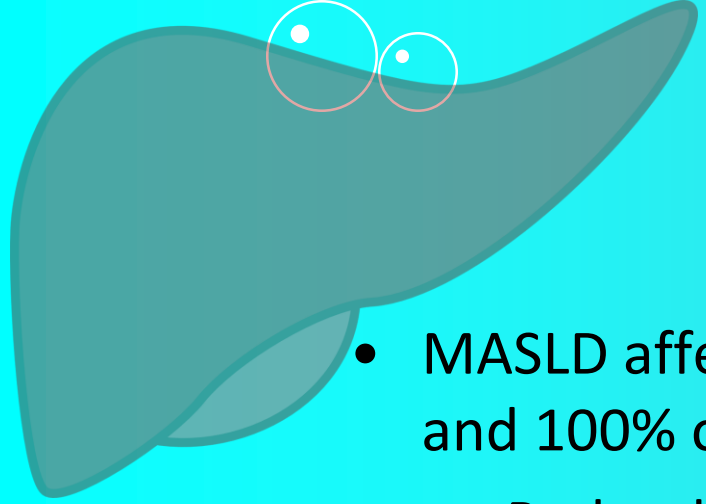
Kueck, P. J., Morris, J. K., & Stanford, J. A. (2023). Current Perspectives: Obesity and Neurodegeneration - Links and Risks. *Degenerative neurological and neuromuscular disease*, *13*, 111–129. https://doi.org/10.2147/DNND.S388579

Clinical Implications

- Weight reductions
  - improves cognitive improvement
    - verbal memory
    - executive function
    - cognition
    - language
  - High % of population is above normal weight as aging and obesity can be an aggravation to AD and PD

Horie, N., Serrao, V., Simon, S., Gascon, M., Xavier dos Santos, A., Zambone, M., Merenciana del Bigio de Freitas, M., Cunha-Neto, E., Marques, E., Halpern, A., Edna de Melo, M., Mancini, M., & Cercato, C. (2016). Cognitive Effects of Intentional Weight Loss in Elderly Obese Individuals With Mild Cognitive Impairment, *The Journal of Clinical Endocrinology & Metabolism*, *101*(3); 1104–1112.

Kueck, P. J., Morris, J. K., & Stanford, J. A. (2023). Current Perspectives: Obesity and Neurodegeneration - Links and Risks. *Degenerative neurological and neuromuscular disease*, *13*, 111–129. https://doi.org/10.2147/DNND.S388579

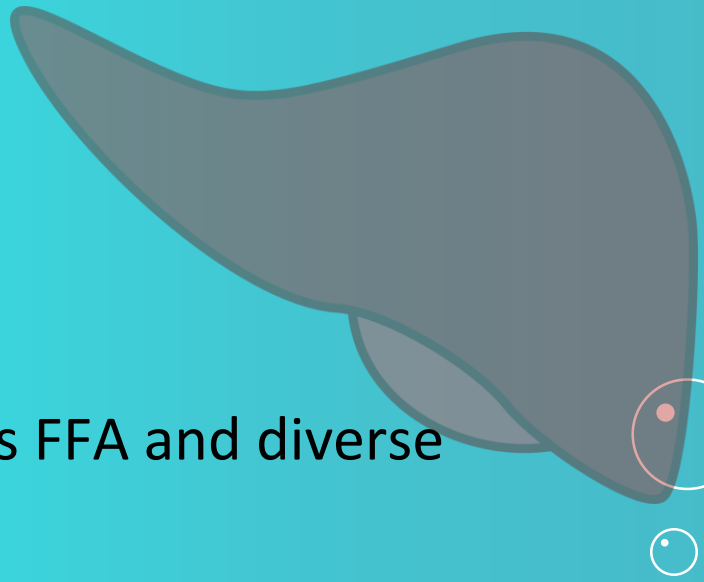


Liver

- MASLD affects 60-80% of patients with DM + obesity and 100% of people with severe obesity
  - Pathophysiology of NAFLD includes genetic, dietary, metabolic and hormonal factors
  - Ectopic fat accumulation combined with low-grade chronic inflammatory in an organ not able to accumulate fat
  - Hepatocytes become vulnerable to lipid oxidation, impaired apoptosis, and cytokine activity

Chen, Y., Wang, W., Morgan, M. P., Robson, T., & Annett, S. (2023). Obesity, non-alcoholic fatty liver disease and hepatocellular carcinoma: current status and therapeutic targets. *Frontiers in endocrinology*, *14*, 1148934. https://doi.org/10.3389/fendo.2023.1148934

Liver



- Obesity connection
  - Visceral adipose tissue produces FFA and diverse adipokines
    - increased: TNF-a, resistin, interleukin-6
    - decreased adiponectin
  - All this increases ectopic fat accumulation and inflammation – including in the liver

Chen, Y., Wang, W., Morgan, M. P., Robson, T., & Annett, S. (2023). Obesity, non-alcoholic fatty liver disease and hepatocellular carcinoma: current status and therapeutic targets. *Frontiers in endocrinology*, *14*, 1148934. https://doi.org/10.3389/fendo.2023.1148934

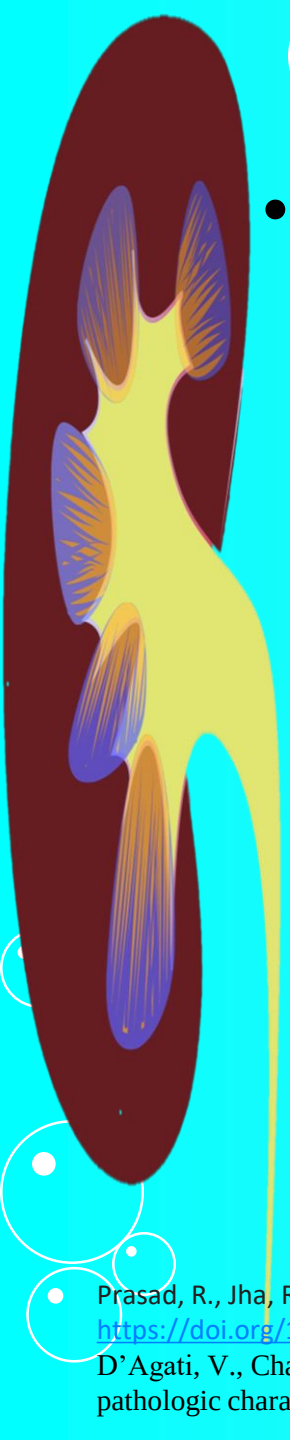
Clinical Implications

- MASLD treatment is directed at obesity
  - lifestyle modifications
    - 7% weight loss of baseline – significant improvements in steatosis and lobular inflammation
    - 9% body weight loss showed histologic improvement (may require as high as 40%)
  - Bariatric surgery
    - Some patients experience complete resolution of NASH
  - Medication: orlistat, liraglutide
  - NOTE: post 2016 semaglutide 2.4mg and tirzepatide 15mg

Clinical Implications

- MASLD treatment as directed at obesity
  - Supplements
    - PIVENS study demonstrated Vitamin E improved steatohepatitis, enzyme levels and inflammation
    - Curcumin – showed decreased BMI, HgBA1C
    - Flavonoids – positive effect on lipid metabolism, insulin resistance, inflammation and oxidative stress
  - Eating plan
    - Mediterranean-type effect on hepatosteatosis independent of weight loss

Sanyal, A. J., Chalasani, N., Kowdley, K. V., McCullough, A., Diehl, A. M., Bass, N. M., … for the NASH CRN. (2010). Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. *The New England Journal of Medicine*, 362(18), 1675–1685. http://doi.org/10.1056/NEJMoa0907929



Kidney

- Obesity Connection
  - obesity- related glomerulopathy (ORG)
  - Risk factor for CKD (adults and children) occurrence and progression, nephrolithiasis, and kidney CA
  - “Fatty Kidney” – triglyceride accumulation
  - Pathophysiology
    - glomerulus enlarges d/t increases in glomerular filtration rate, renal plasma flow, filtration fraction and tubular sodium reabsorption
    - podocytes strain, shear, and fail = sclerosis
    - adiponectin, leptin, and resistin abnormal = inflammation, oxidative stress, activation of RAAS, and insulin resistance

Prasad, R., Jha, R. K., & Keerti, A. (2022). Chronic Kidney Disease: Its Relationship With Obesity. *Cureus*, *14*(10), e30535. https://doi.org/10.7759/cureus.30535

D’Agati, V., Chagnac, A>, de Vries, A., Levi, M., Porrini, E., Herman-Edelstein, M., & Praga, M. (2016). Obesity-related glomerulopathy: Clinical and pathologic characteristics and pathogenesis. *Nature Reviews* ***Nephrology***, doi:10.1038/nrneph.2016.75.

ORG

- criteria BMI ≥30 kg/m2 + glomerulomegaly with or without FSGS.
- Clinical features - Isolated proteinuria
- Common findings: hypertension and dyslipidemia
- Clinical course: stable or slowly progressive – 1/3 develop renal failure and ESRD

Prasad, R., Jha, R. K., & Keerti, A. (2022). Chronic Kidney Disease: Its Relationship With Obesity. *Cureus*, *14*(10), e30535. https://doi.org/10.7759/cureus.30535

D'Agati, V., Chagnac, A>, de Vries, A., Levi, M., Porrini, E., Herman-Edelstein, M., & Praga, M. (2016). Obesity-related glomerulopathy: Clinical and pathologic characteristics and pathogenesis. *Nature Reviews* ***Nephrology***, doi:10.1038/nrneph.2016.75.

CKD

- impairment of intestinal barrier function and changes in composition of the gut microbiome contributes to…
  - Insulin resistance common feature
- intraglomerular pressure creates damage over long term

Prasad, R., Jha, R. K., & Keerti, A. (2022). Chronic Kidney Disease: Its Relationship With Obesity. *Cureus*, *14*(10), e30535. https://doi.org/10.7759/cureus.30535

D'Agati, V., Chagnac, A>, de Vries, A., Levi, M., Porrini, E., Herman-Edelstein, M., & Praga, M. (2016). Obesity-related glomerulopathy: Clinical and pathologic characteristics and pathogenesis. *Nature Reviews* ***Nephrology***, doi:10.1038/nrneph.2016.75.

Clinical Implications

- High fat diets cause consistent inflammation of kidney with albuminuria and lipids in glomerulus
- Lifestyle interventions with weight loss
  - amount
  - eating plan: high fiber promotes SCFA producing bacteria and decreases inflammation

Prasad, R., Jha, R. K., & Keerti, A. (2022). Chronic Kidney Disease: Its Relationship With Obesity. *Cureus*, *14*(10), e30535. https://doi.org/10.7759/cureus.30535

D'Agati, V., Chagnac, A>, de Vries, A., Levi, M., Porrini, E., Herman-Edelstein, M., & Praga, M. (2016). Obesity-related glomerulopathy: Clinical and pathologic characteristics and pathogenesis. *Nature Reviews **Nephrology***, doi:10.1038/nrneph.2016.75.

Clinical Implications

- Bariatric surgery
- Fecal microbiota transplant
- Medications:
  - RAAS blockade – fatigues
  - SGLT2 ? renal protective + weight loss
- OMs
  - ESRD – orlistat and liraglutide with caution
  - avoid orlistat and phentermine/topiramate ER with risk of stones
  - NOTE: post 2016 semaglutide 2.4mg and tirzepatide 15mg

Prasad, R., Jha, R. K., & Keerti, A. (2022). Chronic Kidney Disease: Its Relationship With Obesity. *Cureus*, *14*(10), e30535. https://doi.org/10.7759/cureus.30535

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IR/Prediabetes/DM

- Adipose tissue overwhelmed with FFAs - leads to fatty acid deposition in muscle, liver and pancreatic beta cells
- Leads to decreased insulin sensitivity to glucose and insulin resistance
- Leptin from adipocytes – releases aldosterone causing increase in SNS – increasing angiotension II
- Hyperaldosterone leads to insulin resistance
  - IR – prediabetes – DM… Continuum

Klein, S., Gastaldelli, A., Yki-Järvinen, H., & Scherer, P. E. (2022). Why does obesity cause diabetes?. *Cell metabolism*, *34*(1), 11–20. https://doi.org/10.1016/j.cmet.2021.12.012

Chandrasekaran, P., & Weiskirchen, R. (2024). The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. *International journal of molecular sciences*, *25*(3), 1882. https://doi.org/10.3390/ijms25031882

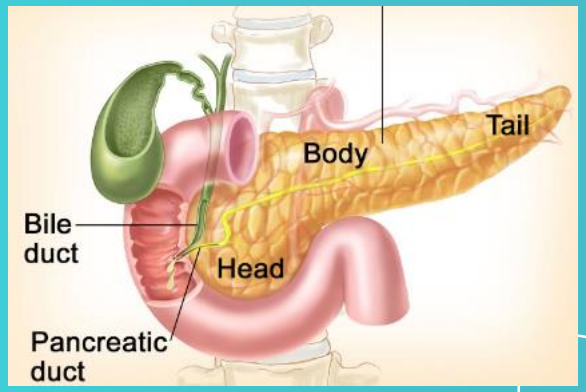
Insulin Resistance

- dysfunctional insulin resistant adipocytes
  - diminished ability to store lipids
  - redistribution of fat to the intra-abdominal compartment
  - accumulation of lipid in muscle and hepatocytes
  - cornerstone factor affecting insulin insensitivity is the release of NEFAs

Klein, S., Gastaldelli, A., Yki-Järvinen, H., & Scherer, P. E. (2022). Why does obesity cause diabetes?. *Cell metabolism*, *34*(1), 11–20. https://doi.org/10.1016/j.cmet.2021.12.012

Chandrasekaran, P., & Weiskirchen, R. (2024). The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. *International journal of molecular sciences*, *25*(3), 1882. https://doi.org/10.3390/ijms25031882

Prediabetes



- The World Health Organization has defined prediabetes as a state of intermediate hyperglycemia
- diagnosed with IFG, IGT, 2 hour post-OGTT, HgBA1C
- Insulin resistance with impairment of β-cell function leads is the next continuum
  - ? due to continuous exposure to NEFAs – reduced insulin synthesis and increasing resistance

Klein, S., Gastaldelli, A., Yki-Järvinen, H., & Scherer, P. E. (2022). Why does obesity cause diabetes?. *Cell metabolism*, *34*(1), 11–20. https://doi.org/10.1016/j.cmet.2021.12.012
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Pancreas image https://nci-media.cancer.gov/pdq/media/images/636528.jpg

Diabetes

- Diabesity
- endothelial dysfunction worsens
- β-cells can no longer compensate
- hyperglycemia results
- Studies of interest
  - Nurses' Health Study - 2014 (275,000 participants) and Health Professionals Follow-up Study (2014)
  - Findings: individuals who gained 5-9.9 kg as young adults have 1.5-to-3-fold risk for DM, CVD, and HTN – increased risk with larger weight gain

Yashi K, Daley SF. Obesity and Type 2 Diabetes. [Updated 2023 Jun 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK592412/

Clinical Implications

- Study of Interest: Diabetes Prevention Program
  - Findings Subjects achieved approximately 6% mean weight loss at 2 years and 4% weight loss at 4 years in the lifestyle intervention arm, and, in post-hoc analysis, a progressive 16% reduction in T2DM risk was seen with every kilogram of weight loss
  - These combined data suggest that 10% weight loss will reduce the risk of future T2DM by ~80%
- IFG may relate to impaired liver functioning “hepatic insulin resistance” ? r/t ectopic fat deposits

Hamman, R. F., Wing, R. R., Edelstein, S. L., Lachin, J. M., Bray, G. A., Delahanty, L., Hoskin, M., Kriska, A. M., Mayer-Davis, E. J., Pi-Sunyer, X., Regensteiner, J., Venditti, B., & Wylie-Rosett, J. (2006). Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes care*, *29*(9), 2102–2107. https://doi.org/10.2337/dc06-0560

Clinical Implications - Prediabetes

- Reduced calorie, health meal plan and physical activity with aerobic and resistance – prevention of progression to DM
- ACEE:
  - OM recommendation: orlistat, phentermine/topiramate ER, or liraglutide 3mg for patients at risk of DM + ILI to obtain 10% weight loss
  - NOTE: post 2016 semaglutide 2.4mg and tirzepatide 15mg
  - DM medication to add if above not successful: metformin, acarbose or thiazolidinediones

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Clinical Implications - DM

- Treat with ILI for 5-15% weight loss OR MORE to achieve lowering of A1C
- OMs considered in all patients with T2DM regardless of length of disease (AACE, 2016)
  - phentermine/topiramate ER – 10% weight loss at one year with 0.4% decrease in A1C in mild T2DM, 1.6% in more severe, long standing T2DM
- Utilize weight neutral or weight loss causing DM meds if possible
- Bariatric surgery if fail above – Roux-en-Y, sleeve gastrectomy, or biliopancreatic diversion

Garvey, T,, Ryan, D., Bohannon, N., Kushner, R., Rueger, M., Dvorak, R., & Troupin, B. (2014. Weight-Loss therapy in type 2 diabetes: Effects of phentermine and topiramate extended release. *Diabetes Care*, *37*, 3309-3316. DOI: 10.2337/dc14-0930.

CV

- Obesity Connection: low systemic inflammation contributes to atherosclerotic processes
- Adults with obesity – age 45 to 64 – die up to 12.8 years earlier than those of normal weight
- Pathophysiology – adipose tissue hypoxia is likely major component of CV disease associated with obesity

Volpe, M., & Gallo, G. (2023). Obesity and cardiovascular disease: An executive document on pathophysiological and clinical links promoted by the Italian Society of Cardiovascular Prevention (SIPREC). *Frontiers in cardiovascular medicine*, *10*, 1136340. https://doi.org/10.3389/fcvm.2023.1136340

CV

- Specific types of adipose tissue
  - PAT: periaortic adipose tissue
    - found around the aorta and other systemic vessels (except the brain)
  - EAT: epicardial adipose tissue
    - located around the coronary arteries

Jing, L. et al (2016). Cardiac remodeling and dysfunction in childhood obesity: a cardiovascular magnetic resonance study. *Journal of Cardiovascular Magnetic Resonance, 18*(28), 1-12.

Volpe, M., & Gallo, G. (2023). Obesity and cardiovascular disease: An executive document on pathophysiological and clinical links promoted by the Italian Society of Cardiovascular Prevention (SIPREC). *Frontiers in cardiovascular medicine*, *10*, 1136340. https://doi.org/10.3389/fcvm.2023.1136340

CV

- EAT
  - Normal state: Cardioprotective
    - anti-inflammatory and pro-inflammatory balance of adipokines
      - adiponectin – antidiabetic, antiatherogenic, antioxidative and anti-inflammatory properties
    - Regulates vascular tone
      - adrenomedullin – vasodilator peptide
    - Immunologic protection
  - Enlarged – obesigenic state
    - increased production of saturated FFA – pro-inflammatory predominately – IL-6 and TNF
  - Communicates with coronary blood vessels without a barrier – vasocrine or paracrine cross talk

Iacobellis, G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol* **19**, 593–606 (2022). https://doi.org/10.1038/s41569-022-00679-9

CV

- Study of interest:
  - 60 children (Jing, et al, 2016)
  - Findings: Cardiac remodeling can begin to occur in children as young as 8 years old.
- Study of interest:
  - Inter99 study (Jansen, et al. 2017)
  - 6238 adults
  - Findings
    - obesity is associated with higher incidence of IHD irrespective of metabolic status
    - “question the feasibility of denoting a subgroup of obese individuals as metabolically healthy”

Jing, L. et al (2016). Cardiac remodeling and dysfunction in childhood obesity: a cardiovascular magnetic resonance study. *Journal of Cardiovascular Magnetic Resonance, 18*(28), 1-12.

Jansen, L., Netterstrom, M., Johansen, N., Ronn, P., Vistisen, D., Husemoen, N., Jorgensen, M., Rod, N., & Faerch, K. (2017). Metabolically healthy obesity and ischemic heart disease: A 10-Year follow-up of the Inter99 study. *Journal of Clinical Endocrinology of Metabolism, 102*(6): 1934-1942.

Iacobellis, G. Epicardial adipose tissue in contemporary cardiology. *Nat Rev Cardiol* **19**, 593–606 (2022). https://doi.org/10.1038/s41569-022-00679-9

Clinical Implications

- Pediatric obesity is critical for treatment earlier
- Weight loss interventions including bariatric surgery show reductions in EAT
- Medications
  - OM's
    - orlistat 24% VAT volume decrease with LDL, Trig and FBG
  - Other meds
    - statins have pleiotropic effects including decrease in adipose tissue inflammation and impact in EAT thickness and inflammation in T2DM women independent of lipid lowering
    - incretin may directly target VAT and EAT regulation as well as insulin resistance – also encourage differentiation to BAT
    - PPARy agonists may reduce pro-inflammation of EAT

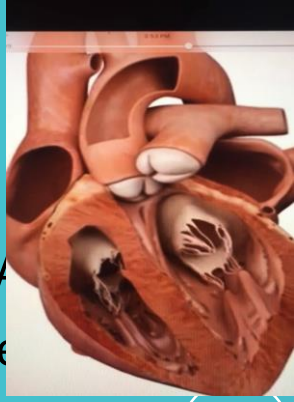
Gujral J, Gupta J. Pediatric Dyslipidemia. [Updated 2023 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK585106/

Clinical Implications

- Controversy
  - AACE “R42 Weight loss therapy is not recommended based on available data for the expressed and sole purpose of preventing CVD events or to extend life, although evidence suggests that the degree of weight loss achieved by bariatric surgery can reduce mortality (Grade B; BEL 2)
  - “Q8.5. Cardiovascular disease and cardiac arrhythmia R94 In patients with established atherosclerotic cardiovascular disease, orlistat and lorcaserin are preferred weight-loss medications (Grade A; BEL1)

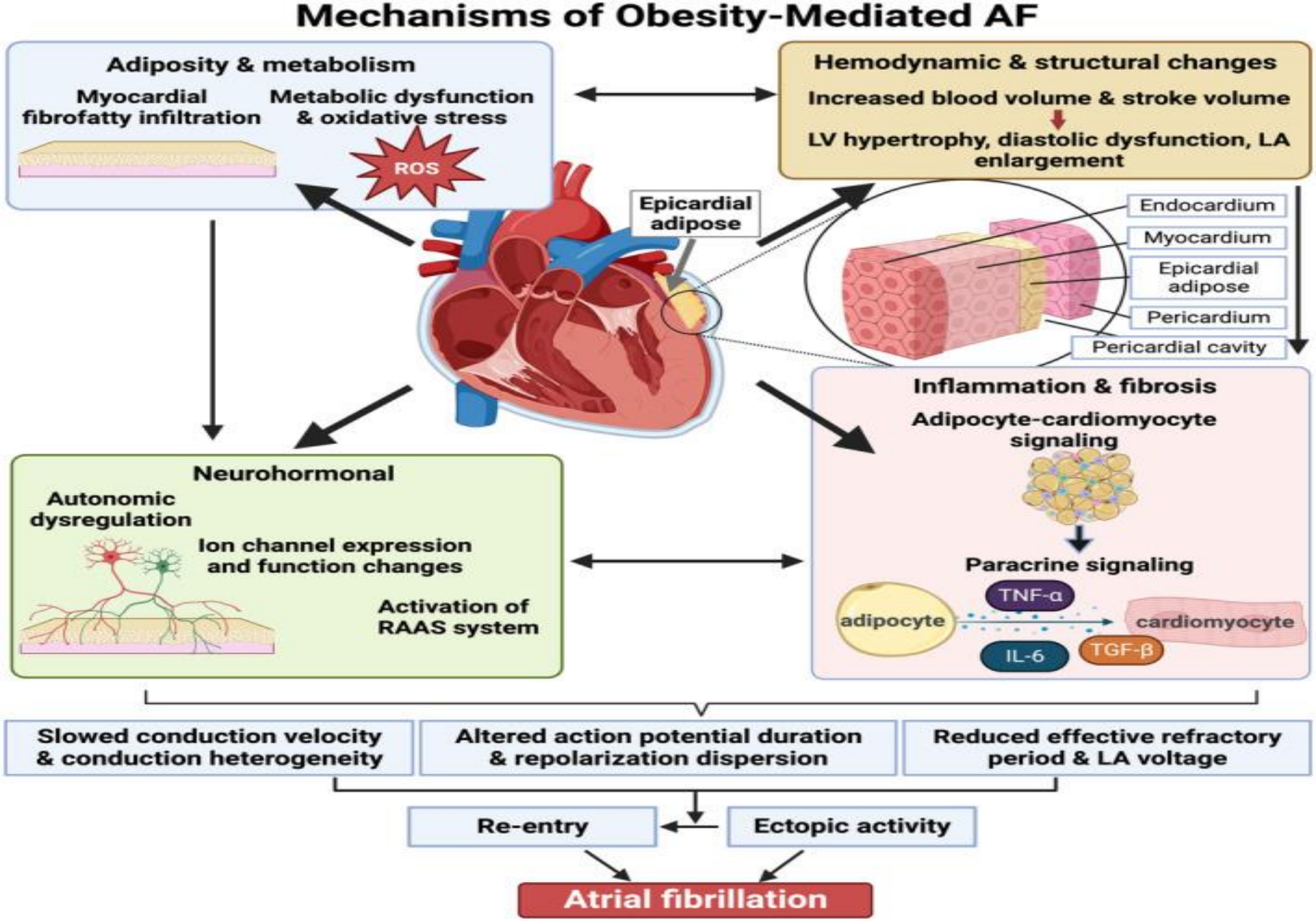
Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

AFib



- Obesity Connection:
  - obesity is correlated with a greater frequency of developing A
  - risk factors include structural and electrical remodeling of the – macro and micro level
- EAT amount contributes thru structural and electrical remodeling of myocardium
  - worsens chronicity, recurrence after ablation and cardioversion and symptom burden
  - induces fibrosis of myocardium – profibrotic mediators (inflammatory cytokines)
  - increases the SNS tone
- Obesity induced hemodynamic changes as well as the low-grade inflammation and oxidative stress add to risk

Sha, R., Baines, O., Hayes, A., Tompkins, K., Kalla, M., Holmes, A. P., O'Shea, C., & Pavlovic, D. (2024). Impact of Obesity on Atrial Fibrillation Pathogenesis and Treatment Options. *Journal of the American Heart Association*, *13*(1), e032277. https://doi.org/10.1161/JAHA.123.032277

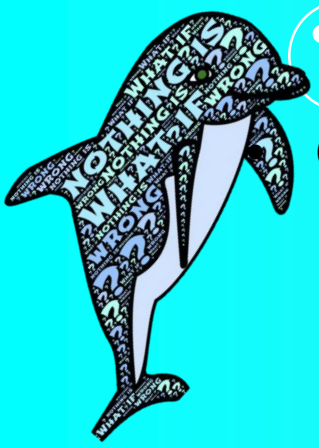


Sha, R., Baines, O., Hayes, A., Tompkins, K., Kalla, M., Holmes, A. P., O'Shea, C., & Pavlovic, D. (2024). Impact of Obesity on Atrial Fibrillation Pathogenesis and Treatment Options. *Journal of the American Heart Association*, *13*(1), e032277. https://doi.org/10.1161/JAHA.123.032277 open access Figure 1

Clinical Implications

- Atrial fibrosis is reversible in early stages
- Study of interest:
  - LEGACY (Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort) (2015, Pathak, et al.)
  - 1415 participants
  - Findings:
    - benefit of weight loss was does-dependent with 10% being associated with 6-fold greater probability of AF free survival as compared to those who didn't lose weight.
    - absence of weight fluctuation was important

Rajeev, P, Middeldorp, M., Meredith, M., Mehta, A., R., Mahajan, R., Wong, C., Twomey, D., Elliott, A., Kalman, J., Abhayaratna, W., Lau, D., & Sanders, P. (2015). Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort. *Journal of the American College of Cardiology*, *65* (20) 2159-2169; DOI: 10.1016/j.jacc.2015.03.002.



Heart Failure

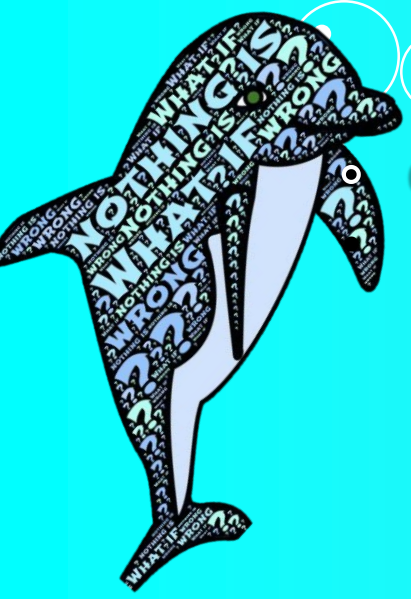
Obesity connections

- **Obesity paradox** – higher BMI lower rates of hospitalization and mortality (2005) HOWEVER
- study of interest: Association between obesity and heart failure symptoms in male and female patients (Heo et al, 2017)
  - 302 patients
  - Findings:
    - did not support obesity paradox in the relationships between obesity and HF symptoms
    - higher levels of BMI were associated with more severe HF symptoms in both males and females
- study of interest: Body Mass Index and Mortality in Acutely Decompensated Heart Failure Across the World (Shah,et al 2014)
  - 6,142 patients with acute decompensated HF
  - "obesity paradox" confined to older persons w decreased cardiac function, less cardiometabolic illness, and new onset HF

Aryee, E. et al. (2023). Heart Failure and Obesity: The Latest Pandemic. *Progress in cardiovascular diseases*, *78*, 43–48. https://doi.org/10.1016/j.pcad.2023.05.003

Heo, S., Moser, D., Pressler, S., Dunbar, S., Lee, K., Kim, J., & Lennie, T. (2017). Association between obesity and heart failure symptoms in male and female patients. *Clinical Obesity*, *7*, 77-85.

Shah, R., et al. (2014). Body Mass Index and Mortality in Acutely Decompensated Heart Failure Across the World. *Journal of the American College of Cardiology*, *63*(8), 778–85.



Heart Failure

Obesity paradox

study of interest: Meta-Analysis of the Relation of BMI to All-Cause and Cardiovascular Mortality and Hospitalization in Patients With CHF (2015, Sharma, et al)

- 22,807 patients
- Findings:
  - risk for total mortality and CV mortality and hospitalization was highest in underweight patients with chronic HF
  - risk for CV mortality and hospitalization was lowest in overweight subjects. (BMI 25 to 29.9)
  - Increasing degree of obesity failed to achieve a statistically significant effect on CV mortality and on hospitalization

- Obesity remains a risk factor for HF due to the oxidative stress and chronic inflammation

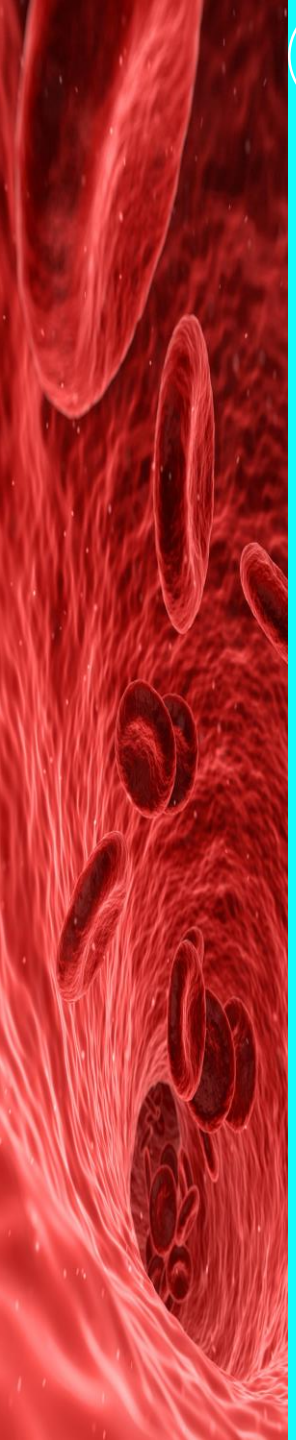
Aryee, E. et al. (2023). Heart Failure and Obesity: The Latest Pandemic. *Progress in cardiovascular diseases*, *78*, 43–48. https://doi.org/10.1016/j.pcad.2023.05.003

Sharma, A. et al. (2015). Meta-Analysis of the Relation of Body Mass Index to All-Cause and Cardiovascular Mortality and Hospitalization in Patients With Chronic Heart Failure, The American Journal of Cardiology, 115(10), 1428-1434.

Clinical Implications

- PREVENTION of obesity is the starting point
- Excess adiposity **within limits** may reflect a metabolic safety net for catabolic needs in heart failure
- Maintenance of wt especially in specific individuals (elders w decreased cardiac function, fewer comorbidities, and new onset HF
- Obesity paradox consideration with the risk of other complications when determining if treating obesity

Aryee, E. et al. (2023). Heart Failure and Obesity: The Latest Pandemic. *Progress in cardiovascular diseases*, *78*, 43–48. https://doi.org/10.1016/j.pcad.2023.05.003



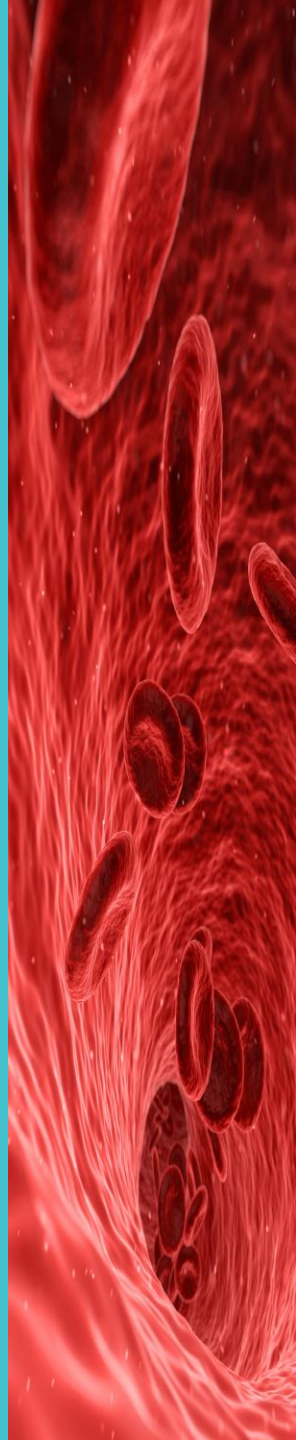
Dyslipidemia

- Obesity connection:
  - hypothesis – high CHO consumption drives hepatic VLDL production
  - insulin resistance also elevates triglycerides
  - HDL becomes dysfunctional due to the inflammation and oxidative stress – the ability to cause cholesterol efflux lowers – HDL clearance occurs faster than production
  - Down regulation of Apo-A occurs

Bays, H. E., Kirkpatrick, C. F., Maki, K. C., Toth, P. P., Morgan, R. T., Tondt, J., Christensen, S. M., Dixon, D. L., & Jacobson, T. A. (2024). Obesity, dyslipidemia, and cardiovascular disease: A joint expert review from the Obesity Medicine Association and the National Lipid Association 2024. *Journal of clinical lipidology*, *18*(3), e320–e350. https://doi.org/10.1016/j.jacl.2024.04.001

Dyslipidemia

- Obesity connection:
  - FFAs form adipose tissue increases the amount of VLDL – leading to more TG
  - the relationship between BMI and circulating lipids is complex
  - Insulin and leptin are secreted in direct proportion, and adiponectin in negative proportion, to the size of the adipose mass



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Clinical Implications

- Lifestyle therapy
  - physical activity, meal plan with reduced calories, minimizing sugar and refined CHO, avoiding trans fats and limits ETOH
  - PUPFAs decrease TG
- 5 to 10% weight loss or more as needed to achieve therapeutic targets
- OM with life- style therapy
- Meds for hyperlipidemia if above unsuccessful (AACE)

Bays, H. E., et al (2024). Obesity, dyslipidemia, and cardiovascular disease: A joint expert review from the Obesity Medicine Association and the National Lipid Association 2024. *Journal of clinical lipidology*, *18*(3), e320–e350. https://doi.org/10.1016/j.jacl.2024.04.001

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Clinical Implications

- Study of interest: POUNDS LOST (2009)
  - 811 “free-living overweight or obese adults”
  - Findings:
    - weight loss after six months and two years similar all four diets
    - Craving, fullness, hunger, and diet satisfaction similar
    - All diets improved risk factors for CV disease at 6 months and 2 years (reduced levels of TG, LDL, lowered BP, and increased HDL)
    - heart-healthy, reduced-calorie diets, regardless of which macronutrients they emphasize, can help achieve and maintain weight loss with CV outcomes

Williamson, D. A., Anton, S. D., Han, H., Champagne, C. M., Allen, R., LeBlanc, E., Ryan, D. H., McManus, K., Laranjo, N., Carey, V. J., Loria, C. M., Bray, G. A., & Sacks, F. M. (2010). Adherence is a multi-dimensional construct in the POUNDS LOST trial. *Journal of behavioral medicine*, *33*(1), 35–46. https://doi.org/10.1007/s10865-009-9230-7

Hypertension

- Obesity connection
  - Excessive reactive oxygen species production
  - abnormal RAAS, especially aldosterone
  - pro-inflammatory signaling
    - monocytes promote the inflammatory response changing the vascular endothelium
    - MCP-1 is elevated and a possible target for treatment
  - reduced nitric oxide bioavailability and activity

Shariq, O. A., & McKenzie, T. J. (2020). Obesity-related hypertension: a review of pathophysiology, management, and the role of metabolic surgery. *Gland surgery*, *9*(1), 80–93. https://doi.org/10.21037/gs.2019.12.03

Hypertension

- Obesity connection
  - PVAT – layer of adipose tissue around blood vessels
    - with normal adiposity – primarily anti-contractile enhancing NO bioavailability within endothelium
    - with obesity – reduction in NOS expression in vascular tissues + increase in inflammation (TNF) = increase in oxidative stress and more inflammation so increase in contractile state of vascular bed
  - leptin elevation increases SNS activation in CNS as well as receptors in peripheral endothelium and smooth muscle vasculature – further promotion of inflammation = development of arterial wall stiffening

Shariq, O. A., & McKenzie, T. J. (2020). Obesity-related hypertension: a review of pathophysiology, management, and the role of metabolic surgery. *Gland surgery*, *9*(1), 80–93. https://doi.org/10.21037/gs.2019.12.03

Clinical Implications

- Weight loss can partially or completely reverse the vascular consequence of obesity even after they are occurred
- AACE, 2016
  - Lifestyle interventions for 5-15% weight reduction to achieve BP reduction
- 2023 SELECT trial showed 20% reduction in MACE with semaglutide 1.7 and 2.4mg doses
  - Label change to patients with obesity and prior history of non fatal MI or stroke or PAD

Shariq, O. A., & McKenzie, T. J. (2020). Obesity-related hypertension: a review of pathophysiology, management, and the role of metabolic surgery. *Gland surgery*, *9*(1), 80–93. https://doi.org/10.21037/gs.2019.12.03

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Clinical Implications

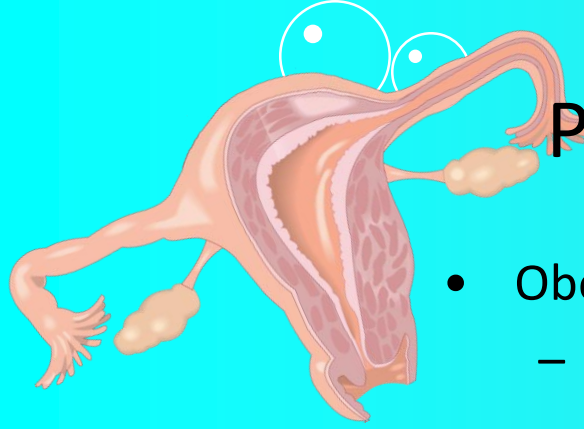
- AACE, 2016
  - OM should be considered
    - orlistat, phentermine/topiramate ER and liraglutide 3mg
    - monitor HR and BP closely with phentermine/topiramate ER
    - NOTE: post 2016 semaglutide 2.4mg and tirzepatide 15mg
    - naltrexone ER/bupropion ER avoided if others can be used as no expectation of BP reduction and contraindicated in uncontrolled HTN
  - Bariatric surgery considered: Roux-en-Y or sleeve gastrectomy recommended

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Clinical Implications

- AACE, 2016
  - Other medications
    - ACE-I, ARBS first line for HTN if weight loss is not effective with above
    - Combination therapy add Ca Channel (beta-blockers and thiazide diuretics may be considered but can have adverse effects on metabolism, beta blockers and alpha blockers promote weight gain)
- Poddar, et al
  - aldosterone antagonists for resistant hypertension

Poddar, M., Chetty, Y., & Chetty, V. (2017). How does obesity affect the endocrine system? A narrative review. *Clinical Obesity, 7*:136-144.
Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf



PCOS/Female Infertility

- Obesity connection:
  - PCOS
    - hyperinsulinemia, low SHBG, changes to the HPA (reproductive)
      - increase insulin levels increase ovarian androgen production
    - Leptin has a role in ovulation with releasing GnRH from hypothalamus – anovulation
    - Adipose tissue causes conversion and increase in oestrone = endometrial hyperplasia
    - SHBG decrease causes increase of bioavailable testosterone
  - Infertility
    - anovulation and elevated testosterone

Barber TM, Franks S. Obesity and polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2021; 95: 531–541. https://doi.org/10.1111/cen.14421

Clinical Implications

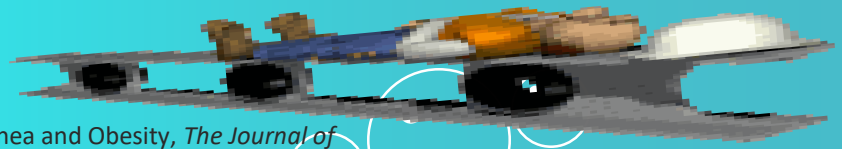
- 5-15% weight loss (or more) to improve hyperandrogenism, oligomenorrhea, anovulation, insulin resistance, and hyperlipidemia
- AACE recommends treatment with orlistat, metformin or liraglutide alone or in combination and/or bariatric surgery
- Studies suggest insulin sensitizing effects of weight loss or medications are reasons for outcomes

Barber TM, Franks S. Obesity and polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2021; 95: 531–541. https://doi.org/10.1111/cen.14421

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Obstructive Sleep Apnea

- Obesity connection:
  - vicious cycle of obesity leading to OSA and reciprocally OSA leading to obesity
  - Suspected mechanisms
    - adipokine effects on the lung
    - mechanical effects on upper airway collapsibility
    - chest wall compliance especially with severe obesity
    - effects on respiratory drive
  - OSA is associated with decreased leptin and increased ghrelin… increases hunger …. leading to weight gain.
  - New information is hypothesizing a role in the central orexin system



Emily Jane Meyer, Gary Allen Wittert, Approach the Patient With Obstructive Sleep Apnea and Obesity, *The Journal of Clinical Endocrinology & Metabolism*, Volume 109, Issue 3, March 2024, Pages e1267–e1279, https://doi.org/10.1210/clinem/dgad572

Clinical Implications

- Need greater than 10% weight loss based on Sleep AHEAD study
- AACE lists lifestyle + OM of phentermine/topiramate ER or bariatric surgery
- All patients with obesity should be evaluated for sleep apnea
  - STOP BANG
- SURMOUNT OSA
  - 42% and 51% disease resolution without excessive sleepiness
  - Label indication for tirzepatide: moderate to severe OSA with obesity

Kuna, S. T., Reboussin, D. M., Strotmeyer, E. S., Millman, R. P., Zammit, G., Walkup, M. P., Wadden, T. A., Wing, R. R., Pi-Sunyer, F. X., Spira, A. P., Foster, G. D., & Sleep AHEAD Research Subgroup of the Look AHEAD Research Group (2021). Effects of Weight Loss on Obstructive Sleep Apnea Severity. Ten-Year Results of the Sleep AHEAD Study. *American journal of respiratory and critical care medicine*, *203*(2), 221–229. https://doi.org/10.1164/rccm.201912-2511OC

Garvey, W., et al. (2016). American association of clinical endocrinologists and american college of endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocrinology Practice, 22*(3), 1-203. Last accessed September 18, 2024 https://www.aace.com/files/final-appendix.pdf

Psychological Implications

- Obesity connection:
  - Obesity causes systemic inflammation and dysregulation of the HPA axis, and these are factors in depression
  - Additionally, obesity can lead to social stigmatization with society bias, body dissatisfaction, diminished self-esteem and stress in society
  - Poor eating, disability and pain associated with obesity can increase the risk of depression and anxiety

Fu, X., Wang, Y., Zhao, F., Cui, R., Xie, W., Liu, Q., & Yang, W. (2023). Shared biological mechanisms of depression and obesity: focus on adipokines and lipokines. *Aging*, *15*(12), 5917–5950. https://doi.org/10.18632/aging.204847

Clinical Implications

- Weight loss has demonstrated an improvement in depression symptoms
- Monitor patients closely for mood disorders and suicidal ideation
- AACE, 2016:
  - orlistat, liraglutide 3mg and phentermine/topiramate ER at initiation and low dose may be considered for patients with depression – lorcaserin and naltrexone ER/bupropion ER used with caution or avoided if patient taking an antidepressant
  - NOTE: post 2016 semaglutide 2.4mg and tirzepatide 15mg
  - caution with obesity and anxiety and the use of maximal dose of phentermine/topiramate ER
  - Metformin may be beneficial for patients with psychotic disorders taking antipsychotics
- Consider use of non obesigenic medications for depression and anxiety

Fu, X., Wang, Y., Zhao, F., Cui, R., Xie, W., Liu, Q., & Yang, W. (2023). Shared biological mechanisms of depression and obesity: focus on adipokines and lipokines. *Aging*, *15*(12), 5917–5950. https://doi.org/10.18632/aging.204847

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THANK YOU

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