Obesity

Presented by
Gerard S. Letterie, DO
Associate Clinical Professor, Department of Obstetrics and Gynecology
University of Washington – Seattle WA

Disclosure: Dr. Lynch has no significant financial interest in any of the products or manufacturers mentioned.
Lifestyle, Obesity and PCOS: Objectives

- Relationship: between western life style, weight, PCOS and reproduction
- Factors: hormonal and epigenetic influences on obesity
- Shared relationships: hormonal and otherwise between obesity and PCOS
- Management: current options and future trends
Definitions: BMI (kg/m²)

- **NL**: 20 to 25
- **Overweight**: 26 to 29
- **Obese**:
  - I: 30 to 34
  - II: 35 39
  - III: > 40 (Morbid)
Tools for Treatment

Formula:
Hormone + receptor + enzyme = drug

Examples:
- Endometriosis: GnRH analogs
- Depression: SSRIs
- Fibroids: RU 486 and SPRM (asoprinil)
Obesity: A Modern Day Epidemic

- Most common nutritional disease in US
- Associated with increased morbidity and mortality, IR, dyslipidemia, DM, HTN, CVD
- 65% with BMI @ 27: at least one co-morbid condition
- Treatments: evolving medical and surgical options
Deaths Attributable to Obesity

- Variable ranges: 120,000 to 450,000 annually
- BMI > 30
- Multiple factors and co-morbidities: ischemic heart disease, HTN, DM and dyslipidemias
- Public health problem that crosses disciplines
Obese Adolescent: Next Wave

- 22 million children under 5 years
- 1971: 6% vs 2009: 23% (USA)
- International Obesity Task Force: 25% of 10 year olds are obese
- Processed food proliferation
- Establishment of brain enteric pathways
- Cross over with reproductive hormones
Transitions and graduations

- Normal to overweight: 20%
- Overweight to obese: 60%
- Duration: 2 to 4 years
- Risk factor: diet and activity
- Regardless of BMI: activity and diet will assure movement into the next weight category
Diet and lifestyle contributions

- Parallel increases in the incidence of obesity, proliferation of processed foods and the fast food industry
- Paradoxical increase in awareness of activity, exercise and risk factors
- Stratification according to demographics and lifestyle
- Built in assurances of continued epidemic of obesity and its sequelae on well being and reproduction
Contemporary Living and Age-Old Metabolism

- Collision between lifestyle and metabolism
- Programmed for thrift (not sure of next meal)
- Current lifestyle: heavy on consumption and low on expenditure
- What may kill us off is our food
Falling Down - I want breakfast
Hamburgers
Obesity: The Fast Food Industry

- Spent more on fast food than on movies, books, magazines, newspapers, videos and music combined
- Transformed American diet
- McDonald’s: 1,000 (1968) to 58,000
SUPER SIZE AMERICA
HOW OUR WAY OF LIFE IS KILLING US
Since when have portion sizes increased?

- Over the past 1,000 years
- Study of “The Last Supper” in 52 versions
- 69% increase in entrée; 23 % in bread portion and 65% in plate size
- “Does art imitate life?”

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Give Them the Business

"When C.E.O.'s are expelled they get huge payments — for not doing their job they get rewarded! ... It's all hush money."

Why is this, comparatitively, the so-called welfare queen of the Reagan years provoked much more anger on Main Street than white-collar criminals do now?

This outrage was fueled by people like Reagan. There are not many top politicians who are fueling outrage against corporate crime and white-collar crime, so that's one difference.

The second difference is that people can identify with someone who's ripping off welfare, i.e., their taxes, rather than a very complex corporate scheme, off-the-books partnerships, that are very remote. There is plenty of outrage out there, but the political system is not organized, because the political system is funded by corporate interests.

Tyco's C.E.O. was just indicted for failing to pay sales tax on paintings worth $13 million. He's also going to get a huge severance package.

Like all of them. When C.E.O.'s are expelled they get huge payments — for not doing their job they get rewarded! Ortiz in thrown out of Disney and gets $100 million. The head of Columbia/HCA, a healthcare company, got $10 million. It's all hush money. I would like to give shareholders the right to determine how much they want to pay their employees at the top. You can be sure that shareholders would never approve these crazy, wild, huge compensation packages that have nothing to do with performance.

What product on the market today makes you think Corvair every time you see it?

McDonald's double cheeseburgers, a weapon of mass destruction.

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Has anyone ever approached you to become a TV pitchman?

Years ago, someone wanted to put my name on a chain of restaurants.

McNader's? Is there any product that you would endorse?

Southwest Airlines. Superb airline. The lowest fares, the highest profits, the best service.

You go to great pains to deny that you cost Al Gore the election. Why not just say: "I cost Al Gore the election, and I'm proud of it. I persuaded the Democratic Party to take notice of progressives."

Did Tennessee cost Gore the election? Did Gore's performance on the debates cost Gore the election? There's a lot of that too. It's a sterile debate. The whole thing was satirized beautifully in a cartoon, which showed George W. Bush looking at a guy holding up a sign: "A Vote for Nader Is a Vote for Bush." And Bush says: "Really? I think I'll vote for Nader."

Are you more or less optimistic than you were when you came to Washington at age 29?

I am not affected by optimism or pessimism. They are not in my lexicon. I'm not in the mood game, because moods affect your output, and the thing is, you must keep striving because there is no alternative to striving for greater justice.

At 68, you can say that age has not mellowed you one bit!

Why should it? Experience informs one's judgment. Judgment is very motivational.
NEWS ITEM: U.S. OBESITY GROWING.
Hormones and Obesity

- Not strictly and “overeating” phenomenon
- Close association of brain-enteric sensors/secretions and reproduction
- Central Control of Food Intake
- Could there be a circuit that is established that contributes to perpetual weight gain?
Gut derived signals in the regulation of satiety

Novel hormonal and neurosensory cues that contribute to feedback loops governing energy balance

Combination of peripheral and central hormonal signals that result on satiety or lack of

Intimate sharing of hormonal cues between weight, energy homeostasis and reproduction

May be prenatally determined
**How we become obese: two possibilities**

*Hormones*: Intake vs output disproportion
- Energy balance and storage as adipose tissue is narrowly regulated
- Hormonal signals may be disrupted and establish a new set point and food choices
- Self perpetuation and vicious cycle of diet and obesity

*Prenatal:*
- May be determined in utero (epigenetic)
The Hormones

- Insulin
- Leptin
- Ghrelin
- Cholecystokinin
- Peptide YY
- Glucagon
- Adiponectin
- Urocortin
Insulin

- Metabolism’s primary hormone
- Secreted in response to glucose
- Structure and receptor well defined
- IR: genetic defect in receptor vs obesity induced increased demand
- Increased appetite in cases of IR may be related to cross over changes with other obesity/satiety hormones
Insulin like growth factors

- Family of peptides and binding proteins within ovary
- Regulates dynamic responses for ovulation
- Concentrations vary depending on phase of cycle
- Persistently elevated levels of insulin may cross over and bind to IGF I and II receptors and blunt response:
  - End result: anovulation
Obesity: Hormonal basis: Leptin

- Produced/released by adipocytes
- Acts to inhibit food intake and increase energy expenditure
- Corrects obesity in mice: decrease in weight, glucose, insulin and cortisol
- Correlations not strong in humans
Obesity Hormonal basis: Ghrelin

- Produced by stomach
- Increase food intake and participates in adaptive response to weight loss: rises during dieting
- Role in long-term regulation of body weight
- Suppression with gastric bypass surgery possibly contributing to the weight-reducing effect of the procedure
Ghrelin

- Decreased during anorexia and chemotherapy
- Antagonists described that are anti-obesity and anti-diabetic
- Structure, source and receptors are well described
- Focus of future weight loss programs
- Supersede bariatric surgery
Hormonal basis: Adiponectin:

- One of several adipocytokines (TNF and plasminogen activator inhibitor)
- Improved vascular profiles: intimal thickness, conduction, compliance.
- Predictor of CVD in obesity
Signals:
Long term control: leptin

- Acts at hypothalamus
- Favors energy expenditure and reduce food intake
- Mutation: in leptin gene or receptor induces a persistent state of polyphagia and obesity
Signals: Medium term: insulin and ghrelin

Insulin:
- Rises in response to feeding
- Considerable variation throughout the day

Ghrelin:
- Increased in fasting and decreases in response to meals

Both:
- Increased energy expenditure and sympathetic activity
- Reduced food intake
Signals: short term and immediate:

- Neuroendocrine event
- May be secreted in response to gut distention, meal size and content
- Hormones:
  1. PYY3-36 as a neurotransmitter to reduce food intake
  2. Amylin: pancreatic signal to centrally decrease food intake
  3. Secretion of both may be influenced by the action of leptin and insulin (neuropeptide Y)
Epigenetic influences

- Prenatal contributions to childhood obesity
- Increased methylation at birth correlated with childhood obesity
- Influenced by maternal weight, GDM, diet (carbohydrate content)
- Obesity may be environmentally induced
- Perpetuation of problem: preprogrammed obesity assures continuation of the problem
Epigenetic influences: animal model

- Unbalanced maternal diet during pregnancy
- Changes in DNA methylation
- Reflected in changes in body composition and metabolic phenotype
- Translated to humans
Epigenetic influences

- Metabolic pre-programming in fetal environment
- Allow the developmental environment to modulate gene transcription
- Example: DNA methylation and histone modification

Roles:
1. Cell differentiation
2. Impact developmental trajectory with long term effects
3. Impact phenotypic expression
Obesity and Offspring

- Gestational exposure to overweight mothers: risk of obesity on adulthood
- Pre-program multiple aspects of energy balance in adults
- Tip scales toward metabolic predisposition to obesity
- Perpetual circle of morbidity: collision course of maternal lifestyle, diet contributing to obesity in offspring
PCOS: Old vs New concepts

- Isolated cases—clinical curiosities (Stein and Leventhal, 1948)
- Connection between obesity and PCOS
- Intersection of co-morbidities: IR, C-V disease
- Increasing incidence internationally and across all age ranges
Where does obesity end and PCOS start?? Tale of two problems

- Two entities are closely related
- Both are endocrine issues
- Progressive process of one condition impacting another
- Should be considered as one: if there is obesity, there is probably PCOS
- Shared co-morbidities
PCOS: Old Philosophy

OLD PHILOSOPHY
◆ Local problem
  ● Organ-specific etiology
  ● Organ-specific therapy

NEW PHILOSOPHY
◆ Systemic Problem:
  ● Multiple end-organs involved
  ● Systemic therapy
PCOS: Contemporary Diagnosis

- Initial definition too restrictive
- Ovarian morphology: sensitive marker
- Diagnosed with menstrual irregular, mild hyperandrogenism and US findings
- Broader clinical implications regarding cardiovascular disease, well being and pregnancy outcomes
- All correlated with weight
Cross over between obesity and reproduction: PCOS

- Shared hormones: insulin and leptin among others
- Novel hormones:
  
  **Kisspeptin:**
  1. To enhance GnRH production neuropeptide
  2. Leptin deficient model: no kisspeptin and GnRH expression

  **Vaspin:**
  1. Adipokine to preserve insulin sensitivity
  2. Increased in IR and PCOS (attempt to relieve IR)
PCOS: Insulin Resistance

- Initial clinical description in 1975; nucleotide alteration described in 1990
- Various clinical phenotypes described associated with insulin-receptor mutations
- Classic, type A syndrome: acanthosis nigricans, severe insulin resistance, ovarian hyperandrogenism (PCOS)
- Various names: Metabolic syndrome, Syndrome X
PCOS and Hyperinsulinism

- Association of PCOS and hyperinsulinism
- Association of androgens and IR
  - Insulin as a “general augmenter”
- Steroidogenesis through Insulin like growth factors and LH secretion
- Elevated insulin and increase androgens
PCOS and Insulin: Dual hypothesis

- Hyperinsulinemia may drive pituitary gonadotrophs to hypersecrete LH
- Increased amplitude and frequency of LH pulses
- Pituitary LH hypersecretion: Increased ovarian androgen production
- ANOVULATION
Metabolic Problems and PCOS

- Hyperlipidemia
- C-V Disease
- Sleep Apnea
- Diabetes
- Nonalcoholic Fatty Liver Disease
- Depression
PCOS and Metabolic Problems: Mental Illness

- Depression: related to weight and body image
- Anxiety
- Eating disorders
- Lowered performance on “cognitive tests”: related to elevated free T
- Decreased libido
Obesity and PCOS

TREATMENT OPTIONS
Obesity Management: Surgical

- Effective options for those who failed medical or lifestyle modifications
- Lap band: simplest
- Requires special considerations during pregnancy
- Clear trend toward surgical vs medical
here are three patients who will probably be helped by weight reduction:

- the hypertensive
- the pregnant
- the diabetic

You will find 'Dexedrine' most useful for controlling appetite in these patients during the weight-reducing regimen. Numerous studies indicate that 'Dexedrine' can be used safely in the vast majority of such patients. If you have any doubts, write to us and we will send you the pertinent reprints and abstracts.

Smith Kline & French - Montreal 9

Dexedrine*
dextro-amphetamine sulfate, S.K.F.
Tablets
Capsules

*Reg. Can. T. M. ON.
Obesity Drug Therapy: Anti-Obesity Agents

- Goal: reduce comorbidities
- Association of fen/phen with valvular heart disease: limits role of drug
- Only for those at medical risk or unresponsiveness to traditional care
- No long-term studies
- Weight loss of 10-15% followed by plateau and gradual gain
Drug Therapy:
Antiquated Anti-Obesity Agents

◆ Sibutramine (Meridia, Knoll Pharm)
  ● Noradrenaline and serotonin-reuptake inhibitor (1998)
  ● Effective when used intermittently: 75% on/25% off
  ● Elevates BP and pulse

◆ Orlistat (Xenical, Roche Pharm)
  ● Inhibitor of pancreatic lipase reducing fat absorption by 30%
  ● 5-10% weight loss
Syndrome of IR and PCOS
Medical Management: Metformin

◆ Increases peripheral sensitivity to insulin
◆ Decreases gluconeogenesis and intestinal absorption
◆ Reduction in: insulin, androgen and leptin concentrations;
◆ Weight loss (visceral adipose)
Treatment: Central Targets I: Reprogram

- Transplant leptin responsive cells into receptor deficient hypothalamus of mildly obese mice
- Differentiation and integration
- Restoration of leptin responsiveness
- Alleviation of obesity and hyperglycemia
- Restore signaling and alleviate obesity and associated problems
Cannabinoid receptor: block the urge to eat/hunger signal

Leptin receptor mimetics: improve signals for lowered glucose, insulin and hyperglycemia; improved energy balance

Ghrelin antagonists: reduce the urge to consume
Adipotide: ligand specific peptide-mimetic for sclerosing blood vessels of white fat tissue

Targeted apoptosis within the blood vessels of white fat tissue

Result: rapid weight loss and improved IR in three monkey models

Prototype of a new class of candidate drugs for obesity treatment
Crossover from obesity to PCOS and reproduction

- Redundancy in defining dual platforms
- Improvement in obesity should be first step
- Add-on options include reproductive specific interventions that manipulate oocytes and embryos and avoiding any complicated interventions for ovarian stimulation
PCOS Treatments: IVF

- Trend away from any form of injectable treatments and toward IVF
- Minimize if not eliminate the risk of twins by elective single embryo transfer (eSET)
- Risk of obesity also extends to a reduction in pregnancy rates with increasing weight
PCOS Treatments: In vitro maturation

- Minimal stimulation and retrieval of immature oocytes
- Side step the complexities of ovarian stimulation and possible hyperstimulation syndrome
- Specialized needle, suction and lab for maturation process
- Transfer of only one embryo
Eating is a complicated matter
Current management options for both obesity and PCOS are limited
Compelling data on well being and obstetric outcomes with no effective deterrent
Western lifestyles are driving us in the wrong direction in many regards
Encouraging trends however
Obesity and PCOS: Final Thoughts

- Suggestion that we may have effective analogs or re-programming tools is an oversimplification
- Education regarding empowerment and self management
- Fertility options will be away from standard IVF with multiple embryo transfers to a very pared down stimulation protocol with single embryo transfer and liberal use of cryotechnology
PCOS: Diagnosis of IR

- G/I ratio > 4-5
- Peak insulin > 100 on OGTT
- Fasting insulin > 15-22

No easy method to detect IR.
PCOS: Cardiovascular Disease

- Increased incidence of PCOS with confirmed CAD
- Association may occur regardless of androgen profiles
  - GnRH suppression impacts lipids minimally
  - No change in IR after GnRH suppression
- Enhanced production of plasminogen activator inhibitor in PCOS
PCOS: Three areas to manage

- **Metabolic:** Obesity, Cholesterol and glucose metabolism,
- **Cosmetic:** Hirsutism, acne, acanthosis nigricans
- **Reproductive:** Anovulation and infertility

Unifying Concept: Lifestyle
PCOS: Medical Treatment Options For Fertility

- Antiestrogens: clomiphene
- Aromatase Inhibitor: letrazole
- Gonadotropin therapy: rec FSH
- IVF
- Immature oocytes/in-vitro maturation
PCOS: Summary And Management Plan

General Principles

- Evaluation and treatment thus far: Inadequate
- Type II diabetes: 25%-35% of PCOS by age 30
- Two to sevenfold increase in myocardial infarction
- Three to fivefold increase in endometrial carcinoma
PCOS: Management Plan: History

Life style:

- Weight loss counseling
- Psycho-social screening
- Possible increased monitoring for well being
- Fertility discussions
PCOS: Summary and Management Plan

Initial Laboratory Evaluation

- Exam for hirsutism, acne, weight and BP
- Fasting glucose; ? oral glucose tolerance testing (OGTT)
  - ? insulin resistance: Fasting greater than 70 microunits/ml; peak greater than 350 microunits/ml.
- Cholesterol and lipid profile
PCOS: Summary and Management

Plan - Ongoing Laboratory Evaluation

- Periodic screens for diabetes (DM)
- Continuous monitoring of cholesterol and lipids
- Assessment of endometrial stripe in anovulatory patients
- Evaluation for ovulatory dysfunction
- Discussion of reproductive plans
PCOS: Diagnosis of IR

- G/l ratio > 4-5
- Peak insulin > 100 on OGTT
- Fasting insulin > 15-22

- No easy method to detect IR.
Nonalcoholic fatty liver:

- Progressive liver disease associated with IR, obesity and metabolic syndrome
- May progress to cirrhosis
- Treatments include weight reduction, insulin sensitizers and statins