OBESITY MEDICINE:

OPTIMIZING AN ORTHO SURGICAL PATIENT

Josh Porter, PA-C
Optimize U Chattanooga
Optimized Health

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Avoidable human misery is more often caused not so much by stupidity as by ignorance, particularly our ignorance about ourselves.

- Carl Sagan

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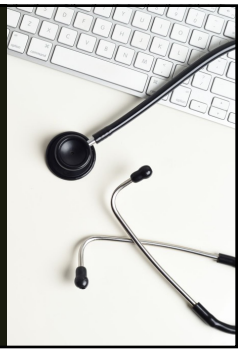
Background

- PA for 13 years
- Orthopaedics for 11 years
  - *Sports Med for 6 years*
  - *Foot & Ankle for 5 years*
- Served on the board of PAOS as the Southeast Regional Director and VP
- Emergency Medicine – moonlighting throughout my career
- Preventative medicine the past 2 years (Hormone Replacement Therapy, Peptides, Healthy Aging Medicine)



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I KNOW WHAT YOU ARE THINKING….HE OWNS A HORMONE CLINIC, SO

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I must be one of these guys….

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WHY THE CHANGE?

WHAT LEAD ME TO LEAVE ORTHOPAEDICS AND PURSUE PREVENTATIVE HEALTH?

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A TALK ABOUT OBESITY WITHOUT A PERSONAL STORY?

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Objectives of Lecture

- Understand the epidemic we call obesity and how it is impacting healthcare globally
- Understand how obesity is impacting orthopaedic outcomes
- Consider that you might play a role in combating this issue
- Discuss GLP-1 meds such as Semaglutide and Tirzepatide and their potential impact on fighting obesity
- Some promising results
- Discuss potential side effects, problems, and complications in the orthopaedic patient population
- Where do we go from here? What is your potential role?

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"YOU MAY HAVE NOT SEEN IT…BUT IT HAS SEEN YOU"

Clint Hill, MD

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Normal is not optimal

- Normal is not the same as healthy
- Reference ranges for many tests we use (A1C, LFTs, testosterone, thyroid, etc…) are based on current percentiles of the general population SO → as the population becomes less healthy, the average will be less than optimal.
- Typically "normal" means between the 2.5th and the 97.5th percentiles (WIDE RANGE)

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Obesity defined…

Overweight = BMI > 25

Obesity = BMI > 30

Not the most accurate metric of excess fat but it is easy to assess and a simple way for providers to assess quickly.

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What would you think is the most common problem you see in your clinic?

- Osteoarthritis of any joint (26% of population aged 45-64)
- Rotator Cuff (20% of population)
- Carpal tunnel (6% of population)

- Obesity = makes up what _____% of the population

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The obesity pandemic

- Worldwide: Obesity has tripled since 1975
- In the 1970s, the average adult male weighed 173 pounds. Currently, the average adult male weighs 200 pounds.
- Higher in women at any age but highest between the ages of 50-65
- 42% of the US population is obese

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Obesity costs..

- BMI 30-40kg/m is associated with almost 50% and BMI over 40 is associated with 100% greater healthcare expenditures due to obesity comorbidities.
- BMI > 30 has been linked with increase in annual healthcare costs of approximately 37%

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Obesity trends...

- Regardless of ethnicity or socioeconomic status, from 1999-2018, obesity prevalence in the US increased from 30.5% to 42.4%
- 40% (20-39 y/o)
- 45% (40-59 y/o)
- 43% (over 60 y/o)

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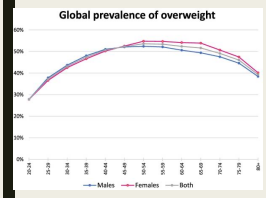

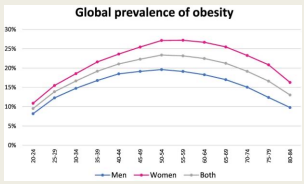

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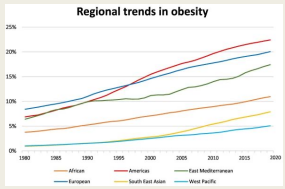

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OBESITY AND ORTHOPAEDICS

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Biomechanical Effects

- Obesity produces altered body mechanics
- A top risk factor for progression of OA in load bearing joints (knees>hips/ankles)
- Reduced muscles strength (volume of articular cartilage in the knee is positively correlated with local muscle mass around the knee)…interpretation = lower muscle mass = greater loss of articular cartilage in load bearing joints.

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Metabolic Effects

- OBESITY = CHRONIC, LOW-GRADE, PROINFLAMMATORY STATE
- Higher serum markers of inflammation (CRP, interleukin-6, and leptin)
- These cytokines are derived from adipose tisse
- Leptin – responsible for triggering an intra-articular, pro-inflammatory cycle → contributes to breakdown of collagen → worsens arthritis
- May explain why OA is also more prominent in non-weightbearing joints of obese patients (shoulder and hand)

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Complications

- Peri-operative Period:
  - *Lack of anatomical landmarks – surgical procedures more challenging and prone to unfavorable outcomes.*
- Increases the risk of post-op infections, delayed wound healing, non-unions, chronic pain, and failure of implants
- Additionally, comorbidities associated with obesity (T2DM, HTN, Dyslipidemia, CVD, Stroke, Sleep Apnea, Gout) increase potential for adverse anesthesia and surgical outcomes.

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Let's summarize

1. We are faced with a global epidemic of obesity that is worsening each and every day

2. Roughly 1/3 patients you encounter is going to be overweight or obese in most orthopaedic settings (projections to be ½ population by 2030)

3. Volume of patients in our clinic limits our ability to treat these patients effectively (limited amount of time with your patients)

4. Outcomes matter for our patients and our practices

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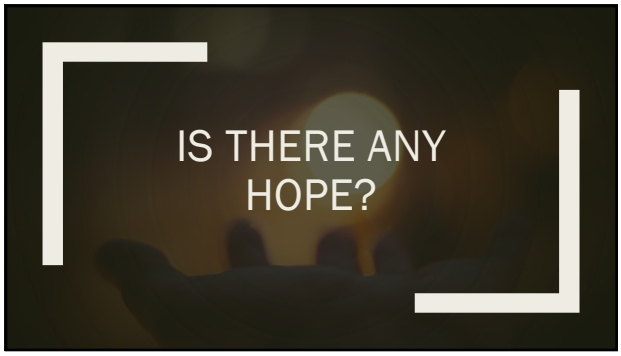

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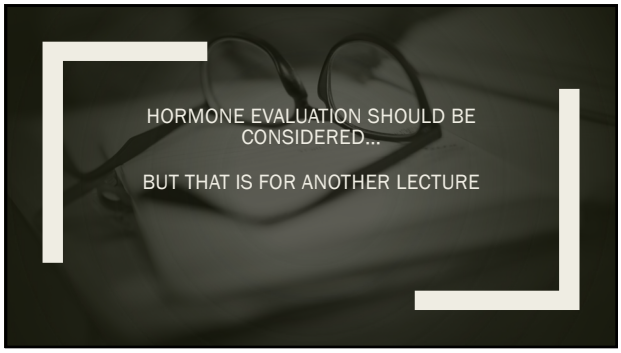

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GLP-1 Peptides

>GLP1 peptide is an incretin hormone

>Incretin Hormones are naturally released by our bodies when we eat

>incretin secreted by the distal intestinal ileum and colon L-cells following food intake<

>Directly acts on the Beta cells of the pancreas to secrete insulin

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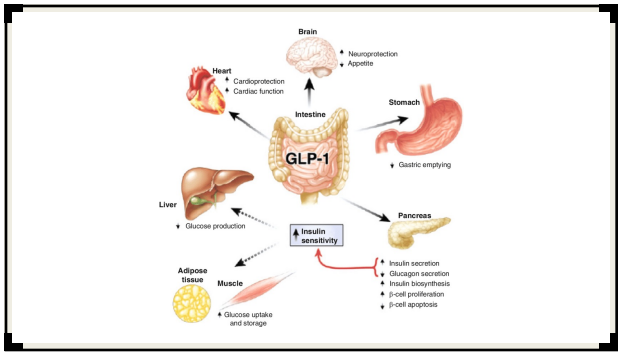

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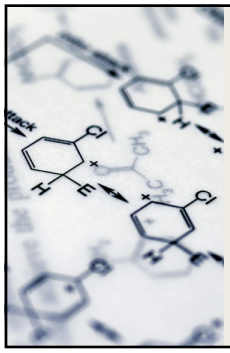

GLP-1 Peptides

>More circulating insulin> glucose is pushed into the cells removed from the blood stream> control glycaemic spikes

>Improving cellular uptake of insulin> allowing glucose to be burned as energy and not stored as fat

Yukon et al., 2010

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GLP-1 Receptor Agonist

>(GLP-1 RA) is a mimicking class of drug.

>works by mimicking the natural GLP-1 hormone that our bodies produce

- targets receptor sites within the body to elicit responses

- Yukon et al, 2010

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GLP-1 RA's

>GLP-1 RA mediate their effects via the GLP'1 receptor (GLP-1R) = brain, pancreas, GI tract, kidneys, heart, & Lungs

>We see the main effects of this class of drug from the involvement on brain and pancreas

>Benefits are seen in most major organs of the body

Yukon et al., 2010

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The History of GLP-1 Peptides

>GLP-1 research spans over 30 years. Earliest time frame being early 1970's-1980's timeframe

>GLP'1 ability to function as an incretin hormone one of the early studies was 1987

>Further proof of the insulinotropic activity published in 1993

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GLP-1 Receptor Agonists

>Byetta (Exenatide ,first fda approved in 2005 as a twice daily injectable approved for glycemic control in type2 DM

>Trulicity (Dulaglutide) (once weekly) available around 2014 for tx of T2dm

>Saxenda (Liraglutide) (once daily) was soon to follow with FDA approval for Chronic weight management in 2014

>Semaglutide clinical trials starting in 2015 in effort to create a longer acting GLP1 RA FDA approved for DM2 and weight management

>Tirzepatide : FDA approved for DM2 and weight management

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Weight Loss

>Saxenda
- 10% of total body weight loss

>Semaglutide 2.4mg dose
- 12-15% of total body weight loss

>Semaglutide 1mg dose
- 6-10% of total body weight loss

>Tirzepatide 5,10,15mg dose
- 15 to 22.5% of total body weight loss

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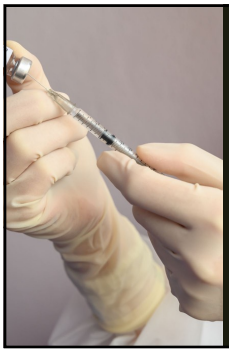

Ozempic/Semaglutide

>FDA approved use for Type 2 diabetes treatment
>Clinical trials began in 2015 with FDA approval in 2017

>What was seen in trials
1. Improved Glycemic control
2. Reduction of CV events
3. Body weight reduction

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Ozempic/Wegovy/Semaglutide

>FDA approval in 2021 for weight loss at a weekly dose of 2.4mg

1. BMI of 30 or more
2. Those with a BMI of 27 or more who are at risk of developing weight-related medical conditions like type 2 diabetes
3. Starting dose is 0.25mg increased every 4 weeks to a max dose of 2.4mg.
   0.25mg>0.5mg>1mg>1.7mg>2.4mg

>indicated for chronic weight management in adults and those who meet the BMI standards with as least one comorbid conditions, e.g.

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Zepbound/Mounjaro/Tirzepatide

- FDA approved for DM2 and weight management
- RCT late 22', N=2,500 adults who had obesity lost 15%-20% of their starting body weight after using Tirzep for 16 months.
- 2.5mg>5mg>7.5mg>10mg>12.5mg>15mg increasing every 4weeks

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GIP

>Glucagon Insulinotropic Polypeptide

- the 'neglected incretin',
- Is also an inhibitory hormone which stimulates insulin secretion secreted from the upper intestine unlike GLP-1
- The GIP RA has been studies since early 1980's.

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GIP's

>It wasn't until a Combo drug was formed that this reputation changed.

>Tirzepitide/Mounjaro/Zepbound

. a dual GIP/GLP-1 receptor agonist

>FDA approved in 2022 for tx of development for the treatment of type 2 diabetes

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GIP's

Tirzepatide/Mounjaro/Zepbound

shown superior efficacy in reducing plasma glucose and glycated haemoglobin (HbA_{1c}) in comparison to dulaglutide and semaglutide

Weight loss seen also superior when compared to max dosing

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Tirzepatide/Mounjaro/Zepbound

- Suggests that combing the GLP1 with GIP stimulation accelerates results. As they have similar effects.
- Reduces body weight and food intake, improvement in glucose tolerance, and insulin sensitivity

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GIP VS GLP's (Similar)

>Both GIP and GLP-1 exert their effects by binding to their specific receptors, the GIP receptor (GIPR), and the GLP-1 receptor (GLP-1R).

>enhance insulin secretion & insulin synthesis

> positive effect the cardiovascular system>>>> reduction CV risks.

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GIP VS GLP's (Similar)

>**Regulation of bone metabolism**>>improving bone health

.GIPS function by facilitating calcium deposits in the bone >>stimulates bone formation

.GLP1s TBA

>Improve **memory** and proactive from **neuronal diseases**

> both function in the brain to regulate appetite and satiety Though GLP's shown to be superior Yukon et al.,

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GIP VS GLP's (Contrast)

>GLP-1 greatly **slows down gastric** emptying

>GIP has been shown to have lesser effect on gastric emptying in humans

> GLP1s shown to **significantly improve cardiac performance** maybe more so then GIP's (unknown> as both have been shown to decrease CV risks and increase muscle perfusion)

(Nauck, et al, 1993) (Gasbjer et al 2020)

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GIP VS GLP's (Contrast)

>GLP1 slows gastric emptying while GIPs not as much

>slowed gastric emptying > cessation of fullness >not eating as much> Reduction of glucose> reduction in insulin secretion >lesser glycaemic events

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GIP VS GLP's

No longer a Floating hypothesis

>>effects on gastric emptying outweigh the direct insulinotropic effect of the GLP-1 RA >>result of lowering glucose concentrations

>>>> Giving the Leading role for GIP as a mediator of the incretin effect

Accepted theory to a combo drug being superior

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Ongoing Literature Tirzepatide Surmount-1

- Double blinded RCT -once weekly injection at 5mg/10mg/ 15mg once weekly for tx of obesity
- A 72 week trial
- Approx 2589 participants w/ BMI of 30 or more
- All doses shown to be clinically significant in weight reduction and body fat reduction
- Biggest side effect gastro issues
- Those taking tirzepatide at doses of 5, 10, or 15 mg lost an average of 15.0%, 19.5%, and 20.9%,

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Ongoing Literature Tirzepatide Surmount-2

- 72 week study
- Double Blinded RCT
- average weight loss after 72 weeks of treatment was 12.8% and 14.7% with tirzepatide 10mg and 15 mg, respectively, versus 3.2% with placebo.

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Surmount 3

- Double blinded RCT-evaluated the efficacy and safety of tirzepatide compared to placebo for 72 weeks
- *after 12 weeks of intensive lifestyle intervention, achieved an additional 21.1% mean weight loss with tirzepatide for a total mean weight loss of 26.6% from study entry over 84 weeks*
- The most commonly reported adverse event was gastro
- Utilized 10mg-15mg

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Surmount 4

- Double blinded RCT evaluated the efficacy and safety of tirzepatide compared to placebo for 52 weeks >>The trial had two periods: a 36-week period during which all participants took tirzepatide, followed by a 52-week double-blind treatment period during which participants were randomized to either continue on tirzepatide or switch to placebo.
- *mean weight loss of 26.0%*
- Utilized 10mg-15mg

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GLP1' s & Pancreatic Cancer (PC)

OBSERVATIONAL vs RANDOMIZED Trials

> OBS trials=INCREASED RISK OF PANCREATIC INFLAMMATION>>>> RISK OF PC (studies evaluated those with DM2 and those who were obese)—— already at risk

> RCT's disprove this theory that they DO increase risk

>As a result of **RCTs** trials have shown possible beneficial effects on cancer lines

Researchers still keep the PLAUSBILE floating theory of the risk

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GLP1s & Pancreatic CA

- meta-analysis of randomized controlled trials (RCTs), including 6 recently published large-scale cardiovascular outcome trials (CVOTs), to evaluate the risk of pancreatic cancer with incretin-based therapies in patients with type 2 diabetes (T2DM)

Treatment with incretin drugs was not associated with an increased risk of pancreatic cancer in people with T2DM

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Systemic/Meta Analyses looking GLP1s-PC

- Incretin-based agents in type 2 diabetic patients at cardiovascular risk: compared the effect of GLP-1 agonists and DPP-4 inhibitors on cardiovascular and pancreatic outcomes
- 6 prospective randomized controlled trials (EXAMINE, SAVOR-TIMI 53, TECOS, ELIXA, LEADER and SUSTAIN-6)-3 trials for DPP-4is and 3 trials for GLP-1 Ras

Incretin-based agents did not significantly affect PC;

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Cont. systemic Review

Glucagon-like peptide-1 receptor agonists and pancreatic cancer: a meta-analysis

>12 RCTs with GLP-1 RAs as an intervention,

GLP-1 RAs did not increase the risk for pancreatic cancer when compared to other treatments.;

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2020'

- Meta-analysis of cases of acute pancreatitis and PC as well as any malignant neoplasm reported in patients treated with GLP1's

Neither GLP-1 RAs nor DPP-4is were associated with a significantly elevated or reduced risk of PC.

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Cardiovascular Risks

- 23' Retrospective Cohort study evaluated CV Risks in those with already dx of CV and those with no risk factors of CV.

-those tx with GLP-1 RA had significantly greater weight loss and decreased CV Risk

patents who discontinuation of GLP-1 RA t was associated to a higher risk of major cardiovascular events, in both subjects with and without a history of CV events.

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CV Risks continued

longer duration of GLP-1 RA treatment associated with
>lower rate of non-fatal myocardial infarction
>lower rate of unstable angina
>decrease in non fatal strokes

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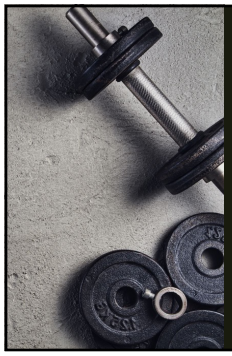

Effects on Muscle Mass

23' Retrospective longitudinal analysis

WHAT WE KNOW :Endogenous (GLP-1) facilitates postprandial glucose uptake as well as increasing muscle perfusion

WHAT WE THINK: hypothesized exogenous GLP-1 RAs would enhance muscle perfusion and positively affect glucose metabolism

- Muscle microvascular blood flow was assessed via contrast enhanced ultrasound.

Skeletal muscle microvascular blood flow significantly increased in response to GLP-1

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EATs my muscle

- Randomised, double-blind, placebo-controlled>12 weeks of treatment of semaglutide

Evaluated> once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity

A three-fold greater loss of mean fat over lean body mass was observed with semaglutide vs placebo

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Preservation of Bone Loss

- 22' A Randomized control study
- Investigating role of GLPs RA on bone formation and wt loss induced bone mass reduction
- Study population obese women BMI of 34, Pelvic, arm , and leg bone mineral content and bone markers were evaluated before GLP1 tx and after tx for 52 weeks.

Tx with long acting GLP-1 RA increased bone formation by 16% and prevented bone loss after weight loss

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Adverse Effects

>In studies reviewed

- <=2% of neoplasms
- Gastro events for the WIN with effecting over 50%=> of participants for both GLP-1 RAs and GIPs
- Gastroparesis
- Rates of fatal AEs, severe hypoglycemia, acute pancreatitis, cholelithiasis, and cholecystitis were extremely low (≤ 1%) across all doses of tirzepatide and semaglutide

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The perioperative patient

- "While there is currently a lack of scientific data on how GLP-1 receptor agonists affect patients having surgery and interact with anesthesia, we've received anecdotal reports that the delay in stomach emptying could be associated with an increased risk of regurgitation and aspiration of food into the airways and lungs during general anesthesia and deep sedation,"
- Michael Champeau, MD
- American Sociey of Anesthesiologist Opinion

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Prior to procedure

- Hold GLP-1 agonists on the day of the procedure/surgery for patients who take the medication daily.
- Hold GLP-1 agonists a week prior to the procedure/surgery for patients who take the medication weekly.

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Day of the procedure

- Consider delaying the procedure if the patient is experiencing GI and discuss concerns of regurgitation and aspiration with patient.
- If the patient has no GI symptoms, but the GLP-1 agonist medications were not held, use precautions based on the assumption the patient has a "full stomach" or consider using ultrasound to evaluate the stomach contents.

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So why should I care about this stuff???

- Ultimately…it is about the patient. Better patient outcomes
- We are often the first provider the patient sees in an orthopaedic practice.
- Our job as ortho PAs is often trying to look at what treatments has this patient attempted/failed prior to surgery and evaluation by the surgeon.
- You don't have much time with patients due to high volume most of the time so you have to be streamlined in your approach.
- Remember how I started this lecture

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Avoidable human misery is more often caused not so much by stupidity as by ignorance, particularly our ignorance about ourselves.

- Carl Sagan

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THANK YOU

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