METABOLIC OPTIMIZATION

AOD 9604 (ANTI OBESITY DRUG 9604):

Description: *(William Seeds, MD)*

AOD 9604 is a fragment of GH (growth hormone) polypeptide (amino acids 176-191) that has been shown to have lipid-reducing effects, similar to but more effective than GH on account of it not having adverse side effects of unmodified GH. AOD 9604 can regulate fat metabolism by stimulating *lipolysis* (the breakdown or destruction of fat) and inhibits *lipogenesis* (the transformation of nonfat food materials into body fat) both in laboratory testing; and in humans and animals. Recent studies also demonstrate that AOD 9604 possesses other regenerative properties associated with growth hormone. Currently, trials are underway to show the application of AOD 9604 in osteoarthritis, hypercholesterolemia, and bone and cartilage repair.

Properties:

- Sequence: Tyr-Leu-Arg-Ile-Val-Gly-Cys-Arg-Ser-Val-Glu-Gly-Ser-Cys-Gly-Phe

METABOLIC OPTIMIZATION

- MW = 1815.1

Benefits:

- Stimulates bone differentiation and mineralization in adipose-derived mesenchymal stem cells (MSC)
- Promotes myoblast differentiation
- Promotes chondrocyte production of collagen and proteoglycan
- Stimulates stem cell differentiation toward bone, muscle and cartilage repair

Applications:

- Inhibits lipoprotein lipase activity in adipose tissue, stimulating lipolysis and adipocytes
- Tyrosine (TYR) in AOD maintains stability of the amino acid sequence; this fragment holds the fat-reducing and tissue repair sequence and mimics the effect of HGH on lipid metabolism, without having growth-promoting or pro-diabetic effects.
- Unable to induce dimerization and thereby activation of the receptor (no competition with HGH).

Clinical Pearls:

- Consider adding AOD 9604 with the GLP-1s for patients that have 30 lbs or more of fat to lose or patient's that are not getting the expected results with the GLP-1s alone. When doing this we suggest a minimum of 3 months in a row. We have found that trying AOD 9604 only for one month at a time does not yield the desired results.
- We recommend combining AOD 9604 with either a GLP-1 agonist or other peptides as we have not found it to yield consistent results (for weight loss) as a stand-alone treatment.
- A good adjunct when a patient is **not** a good candidate for any of the GHRP's (growth hormone releasing peptides); Although AOD 9604 is a fragment of the human growth hormone chain it will not promote growth hormone release.
- Communicate expectations with your patients: In layman's terms, " adding AOD 9604 does not guarantee fast weight loss, but scientifically it is assisting with lipolysis (the breakdown of fat) and prevention of lipogenesis (the formation of new fat) helping your fat metabolism work more efficiently). Healthy weight loss is a journey, not a quick fix.

METABOLIC OPTIMIZATION

Dosage:

- Advitam dosing: 300 mcg SubQ 20 days on 10 days off
- 250 mcg BID for fat loss
- SubQ, Oral, topical
- Length of treatment varies; from 6 weeks to 3 months, up to 6 months

Possible side effects:

- No allergic Rxns
- GRAS in foods under the conditions of intended use of AOD 9604

BPC 157 (BODY PROTECTIVE COMPOUND 157)

Description: *(William Seeds, MD)*

BPC 157 is a penta-decapeptide composed of 15 amino acids. It is a partial sequence of the body protection compound (BPC) that was discovered in and isolated from human gastric juice. It has been shown to accelerate wound healing of muscle, tendon and ligaments. Additionally, BPC 157 has shown to protect organs and aids in the prevention of gastric ulcers. BPC-157 acts systemically in the digestive tract to combat leaky gut, IBS, gastro-intestinal cramps, and Crohn's disease. It demonstrates its effects on the gut-brain-axis. This peptide has been known to exhibit analgesic and anti-inflammatory characteristics, and counteracts negative effects of corticosteroids on muscle tissue. It positively modulates serotonergic and dopaminergic systems and offers neuroprotective characteristics including neurogenesis. It has been used with patients suffering from traumatic brain injuries (TBI). Research has shown its ability to help skin burns heal at a faster rate by increasing blood flow to damaged tissues. BPC-157 significantly accelerates reticulin and collagen formation as well as angiogenesis together with stimulation of macrophages and fibroblasts infiltration representing a potential therapeutic tool in wound healing management. BPC 157 shows great potential healing for a vast array of cell repair.

Properties:

- Pentadecapeptide (15-amino acid chain)
- MW = 1419
- Sequence: Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val

METABOLIC OPTIMIZATION

- Focuses on the gut-brain axis
- Human BPC is found in gastric juices (made in the lining of the stomach)

Clinical Applications / Benefits:

- Skin:
  - Used in deep skin burns, corneal injuries
  - Post-operative incisions

- Injury to muscle, tendon, ligament and bone

- Gastric protection:
  - It is an antinuclear peptidergic agent (GERD)
  - Cytoprotective
  - Improves nitric oxide (NO)
  - Helps improve GI Mucosal Integrity
  - Decreases gastric side effects of NSAID's and alcohol

- Helps heal tissues:
  - Reportedly improves cell survival under oxidative stress
  - Increases fibroblast migration and dispersal
  - Induces F-actin formation in fibroblasts
  - Improves angiogenesis
  - Enhances vascular expression of VEGFR2
  - Increases the extent of phosphorylation of paxillin and FAK proteins without affecting the amounts produced

- Neuroprotective:
  - Influences serotonergic, dopaminergic, opioid, and GABAergic systems
  - Improves nerve regeneration
  - Decreases neuroinflammation
  - May help with depression
  - Ameliorates alcohol withdrawal symptoms and opposes alcohol intoxication

- Cardioprotective:
  - May help regulate blood pressure
  - Rapidly and permanently counteracts the QTc prolongation induced by neuroleptics (such as haloperidol, fluphenazine, clozapine, olanzapine, quetiapine) and prokinetics

METABOLIC OPTIMIZATION

Clinical Pearls:

- Many clinicians that have experience with peptides would agree that, if they were trapped on an island and could only have one peptide- it would be BPC 157. Clinically we have seen overall improvement in many areas: orthopedic related issues, accelerated recovery times from exercise, pain, neurogenic pain, chronic pain, skin, post-surgical wounds/ bruising, cognition, vaginal tissue, GERD, stomach ulcers, IBS and more. Many believe this is because of its effect on the gut-brain axis. It continues to surprise us. BPC 157 like most peptides is pleiotropic which means it affects more than one phenotype. You end up correcting multiple cellular functions improving the overall human system.

Dosage:

- Half-life approximately 4 hours
- General use: SubQ injection = 400-600mcg/day total; Oral = 500-1,000mcg daily
- Injury specific, split dosing into 200-300 mcg SubQ BID, injected specifically around injury site

Possible Side effects:

- Injection site erythema
- Injection site pruritus
- Peripheral edema

EPITHALON (EPITHALON ACETATE TETRA-PEPTIDE)

Description: *(William Seeds, MD)*

Epithalon (also known as Epitalon or Epithalone) is a synthetic version of the polypeptide epithalamin, which is naturally produced in humans in the epithalamium-epiphyseal region of the brain. Epithalamin increases a person's resistance to emotional stress and also acts as an antioxidant. It is a bioregulator for the endocrine system, especially for the pineal gland, and has been shown to lengthen telomeres in human cells. It reduces lipid oxidation ROS (reactive oxygen species), and

normalizes T cell function, which assists with cell repair. It also demonstrates the ability to restore and normalize melatonin levels in older people who have lost some pineal function due to aging.

Properties:

- MM = 390.34588 g/mol
- Sequence: Alanine-Glutamate-Asparagine-Glycine
- Anti-aging
- Regulates cell cycle through telomerase activity upregulation

Benefits:

- Decelerates aging
- Suppresses tumor development
- Induces telomerase activity
- Induces telomere elongation
- Prevents chromosome fusion
- Decreases incidence of spontaneous radiation in carcinogenic tumors
- Normalizes reproductive system in senescent animals
- Improves antioxidant defense
- Normalizes melatonin levels
- Improves cortisol secretion consistent with circadian rhythms
- Improves insulin sensitivity

Clinical Pearls:

- Can be used as a starting therapy to help with DNA repair and upregulate antioxidants
- Can be given as a stand-alone therapy twice a year as it is valuable for cell protection, improving cell resistance, and stopping cell senescence from occurring
- Can be used intermittently with other peptide therapies

Dosage:

- IM injection
  - 100 mg total; 10 mg IM qd x 10 days every year x 2 years
  - 50 mg total (Ukraine Academy Medical Sciences); 10 mg IM every 3rd day, every 6 months x 3 years
- Troches
  - 3 mg sublingual x 30 d (minimum 2 month break in between cycles)

Possible side effects:

- Injection site erythema
- Injection site pruritus
- Peripheral edema

GHK-Cu (COPPER TRIPEPTIDE GHK-Cu)

Description: *(William Seeds, MD)*

A naturally occurring copper peptide occurs in human plasma. As people age they lose the capacity for production. GHK-Cu demonstrates the ability to activate wound healing, regulates immune response, acts as an anti-inflammatory and antioxidant, and stimulates collagen synthesis. Research suggests that GHK-Cu helps to modulate gene expression with anti-aging benefits.

Properties:

- MW = 403.9242 g/mol
- Naturally occurring copper complex of glycyl-L-histidyl-L-lysine peptide
- Has a high affinity for copper
- First isolated from human plasma; it is also found in saliva and urine
- We lose GHK as we age; at 20 y/o the plasma level of GHk-Cu is about 200 ng/mL. By age 60, it declines to 80 ng/mL.
- Decline in GHK coincides with noticeable decrease in the rejuvenative capacity of an organism

Benefits:

- Activates wound healing, including gastric
- Attracts immune cells
- Is an antioxidant
- Is an anti-inflammatory
- Stimulates collagen and glycosaminoglycan synthesis in skin and fibroblasts
- Modulates the activity of both metalloproteinases and their inhibitors
- Improves stem cells
- Defends against tumors
- Restores replicative vitality of fibroblasts after radiation therapy

- Helps regenerate skin; useful for diabetic skin ulcers
- In cosmetic products; GHK has been reported to
  - Stimulate hair growth
  - Tighten loose skin
  - Improve elasticity
  - Improve skin density and firmness
  - Reduce fine lines and wrinkles
  - Reduce photodamage and hyperpigmentation
  - Increase Keratinocyte proliferation
  - Stimulate nail growth

Clinical Pearls:

- Have noticed some mild hypersensitivity issues with some patients including pruritus, erythema local to the injection site. Have noticed moderate hypersensitivity, urticaria extending away from the injection site.
- I recommend splitting the dose in half; administering half in the morning and half later on in the day.
- Anything more than mild local injection site irritation; we discontinue the use of this peptide
- Ask patient if they know of having any copper sensitivities

Dosages:

- Inject 1,000- 2,000 mcg SubQ daily
- I recommend injecting 1,000 mcg SubQ BID
- No longer than 6 continuous weeks with at least 4 weeks off in between; Can utilize up to 3-4 times per year

Possible Side effects:

- Possibility of of copper toxicity; monitor carefully
- The lunula of the nail turns blue (corrects after 4-6 weeks)

GH (Growth Hormone)

Description: *(William Seeds MD)*

Growth hormone is significantly involved in cellular proliferation and efficiency as well as the production of IGF-1, which is also involved in cellular growth, repair and cell

survival. After the third decade of life, there is a progressive decline of GH secretion by approximately 15% for every decade of adult life. Integrated measurements of daily GH secretion demonstrate that secretion peaks at puberty at about 150 µg/kg/day, then decreases to approximately 25 µg/kg/day by age 55. We can postulate (based off of an abundance of research that growth hormone is involved in a multitude of physiologic processes) that restoring growth hormone levels in aging adults can improve overall cellular efficiency, decrease cellular senescence and have a positive downstream effect on all of the organ systems and functions in the human body.

- Secretion of GH is a process of the HPS axis (hypothalamic-pituitary-somatotropic-axis)
- GHRH (growth hormone releasing hormone- somatotropin) is released from the hypothalamus signaling the anterior pituitary gland to secrete GH. The GH is then received by various cells and organ tissues to go to work. When it is received by the liver it stimulates the production of IGF-1.
- The hypothalamus gland also secretes GHIH (Somatostatin) which when sensed by the anterior pituitary gland inhibits the release of GH.
- The HPS axis works on both positive and negative feedback

GHRPs (Growth Hormone Releasing Peptides)

One global way of stimulating senescent cells to re-enter the cell cycle is through GH (growth hormone) and IGF (insulin-like growth factor) pathways, giving the cell a chance to to benefit from improved autophagy (cellular cleaning/ checks and balances) and mitophagy (mitochondrial checks and balances). Growth hormone releasing peptides work in various ways to improve cell cycle functioning and proliferation to signal endogenous growth hormone. These hormones are also used to improve the landscape for improved DNA repair so the cell can confidently reenter the cell cycle.

The purpose of administering GHRPs is to elevate the physiologic release of endogenous GH, improve downstream transcription, and help with translation of hepatic and more importantly extrahepatic cellular IGF1. Keep in mind that using GHRH (growth hormone releasing hormone) by itself does not necessarily mean there will be an immediate endogenous growth hormone release. The machinery in the anterior pituitary secretagogue is set in motion to produce the pulse of growth hormone, but the hypothalamus still controls the release of GH, with somatostatin having a rate-limiting effect. In this way, though GH will be released once somatostatin inhibition is lifted. It's

for this reason that it's important to consider using a GHRP in combination to ensure endogenous growth hormone release within a desired 20-minute window.

It's important to understand how consumed nutritional substrates affect GHRH/GHRP peptides. Pure protein has no effect on release of GH; on the other hand carbohydrates and fatty acid consumption can blunt the release of GH. **Here is the rule: No food for up to 30 minutes after GHRH/GHRP use and no food 1 ½ hours prior to use.** These are the only peptides known to be affected by nutrition.

GHRH is pleiotropic simply put this means it is producing more than one desired effect, which is why we use it in combination with many of our protocols/programs. It has been discovered that there are GH receptors found in most of the tissues of the body:

- Pituitary gland
- Stem Cells
- Muscle
- Liver
- Fibroblasts
- Bone
- Fat
- Pancreatic Islet
- Immune-beta cells/monocytes (not T cells)
- Cardiac
- Adipose
- And others

When GHRH and GHRP are used effectively, they can upregulate endogenous GH and IGF to improve cell efficiency by:

- Upregulating beta oxidation
- Upregulating oxidative phosphorylation
- Upregulating PGC-1alpha
- Upregulating PPAR-gamma
- Improving mitochondrial efficiency
- Upregulating the SIRT gene
- Activating the FOXO gene
- Improving the stem cell stress response and maintaining the quiescent state
- Decreasing cellular senescence
- Improving cellular autophagy
- Improving cellular mitophagy
- Decreasing cellular apoptosis
- Improving intracellular cortisol production

METABOLIC OPTIMIZATION

- Improving immune function with a decreased TH17/TReg ratio
- Improving NAD+/NADH ratio (increased)
- Improving NADP+/NADPH ratio (decreased)

Types of GHRH (growth hormone releasing hormone)

- Sermorelin: First GHRH FDA-approved for short stature
- MOD GRF (1-29) known in the industry as CJC 1295 **without DAC** (drug affinity complex- increases the half life of the peptide)
- CJC 1295 (MOD GRF (1-29) **with DAC**)- *this is the one that has the increased half life*
- Tesamorelin: Was FDA approved for visceral adiposity in HIV patients

Types of GHRP (AKA ghrelin mimicking peptide) (these are the two that we use; there are others.

- Ipamorelin: (most commonly used) the mildest of the GHRP's.
  - Does not create prolactin or cortisol (this makes it safer)
  - Gives a large release of GH without causing desensitization, even at very large doses
- MK677 (Ibutamoren) GHRP mimetic
  - Strong GH and potential supraphysiologic IGF1 response

Ipamorelin (GHRP)

Properties / Benefits:

- Sequence: Aib-His-D-2-Nal-D-Phe-Lys-NH2
- MW = 711.85296 g/mol
- GHRP; third generation
- Increases GH release per somatotrope
- Selective agonist for ghrelin
- Stable form
- Suppresses somatostatin
- **Doesn't raise cortisol, aldosterone, or prolactin levels**
- At very large doses, was reported to give a large release of GH **without desensitization**
- **Doesn't promote hunger**
- Doesn't have ghrelin's lipogenic effects
- 2-hour half life

METABOLIC OPTIMIZATION

- **Increases bone growth**
- Improves GI recovery after bowel resection and it is a treatment for postoperative ileus

Clinical Pearls:

- When injecting: after the jab, introduce the medication **very slowly**; It is received by the pituitary gland very quickly activating it; this helps to reduce facial flushing, feeling warm, tachycardia (rare, usually short-lived 5 minutes), injection site pruritus.
- If a patient is sensitive to injection site pruritus, avoid the abdominal fat and instruct them to inject into the outer gluteal fat (seems to be less sensitive there).

Dosage:

- Some recommend 100 mcg or 1 mg/kg (and believe there is a saturation dose)
  - Industry standards however are quite different
  - Can be dosed alone or w/ GHRH's
- **Advitam Protocol**- Cre8 Pharmacy:
  - 9 mg vial
  - **Reconstitute w/ 4.5mL Bacteriostatic Water**
  - Roll between hands for 30 seconds and then **refrigerate** the mixture when not in use
  - Inject **20 units** (400mcg) subcutaneously (belly fat or gluteus fat) at **bedtime**, at least 90 minutes after last meal
  - **5 days on, 2 days off**

Possible side effects:

- Injection site erythema
- Injection site pruritus
- Peripheral edema

CJC 1295 (MOD GRF (1-29) WITH DAC (drug affinity complex)

Properties:

- MW = 3367.9 g/mol
- Sequence $C_{152}H_{252}N_{44}O_{42}$

- DAC increases the half life
- Measurable concentration after 6-8 days
- > 90% binding to serum Albumin
- Elevates GH and IGF1 for several days after a single administration

Clinical Pearls:

- Has the ability to bring IGF1 response above physiologic levels, which may be more advantageous in the short term- depending on your objectives
  - Used for burns or significant soft-tissue injury, post surgery

Dosage:

- Some recommend 100mcg SubQ BIW or
- 100mcg daily or
- 100mcg 2-3x daily

CJC 1295 / Ipamorelin (combination)

- **Advitam protocol**- Cre8 Pharmacy
  - **CJC1295/Ipamorelin: (4/4mg)**
    - **Reconstitute w/ 4mL Bacteriostatic Water**
    - Roll between hands for 30 seconds and then **refrigerate** the mixture when not in use
    - Inject **20 units** (200/200mcg) subcutaneously (belly fat or gluteus fat) at **bedtime**, at least 90 minutes after last meal
    - **5 days on, 2 days off**

  - **CJC1295/Ipamorelin: (5/9mg)**
    - **Reconstitute w/ 5mL Bacteriostatic Water**
    - Roll between hands for 30 seconds and then **refrigerate** the mixture when not in use
    - Inject **25 units** (250/450mcg) subcutaneously (belly fat or gluteus fat) at **bedtime**, at least 90 minutes after last meal
    - **5 days on, 2 days off**

MK-0677 (Ibutamoren)

Ibutamoren (MK-677) is a potent long-acting, orally administered, selective non-peptide agonist of the ghrelin receptor and a growth hormone secretagogue, mimicking the growth hormone (GH)-stimulating action of the endogenous hormone ghrelin. It has been shown to increase the secretion of several hormones including GH and insulin-like growth factor 1 (IGF-1) and produces sustained increases in the plasma levels of these hormones.

MK-677 is a nonpeptide, spiropiperidine sulfonamide reported functionally indistinguishable *in vitro* and *in vivo* from the peptide GH secretagogue GHRP-6. MK-677 also activates ghrelin receptors. MK-677 is active after oral administration in animals and humans. It is reported to increase the secretion of GH, insulin-like growth factor 1 (IGF-1) and IGFBP-3 levels in children with GH deficiency. It also produces sustained increases in the plasma levels of these hormones without affecting glucose, prolactin, triiodothyronine (T3), thyroxine (T4), and insulin levels. **Most** studies report no effects on cortisol, **but** there are human and laboratory animal studies that report MK-677 **can increase** cortisol (use w/ caution)

MK-677, by sustaining activation of the GH-IGF-1 axis, is reported in human studies to increase lean body mass with no change in total fat mass or visceral fat, and increases muscle mass and bone mineral density. As such MK-677 is under investigation as a potential treatment for reduced levels of GH and IGF-1, such as in children with growth hormone deficiency or elderly with frailty issues.

Properties:

- Oral form of GHRP
- MM = 528.7 g/mol
- Sequence: $C_{27}H_{36}N_4O_5S$
- Increase GH/IGF-1
- Non-pulsed ghrelin agonist
- Has a 24 hr ½ life

Benefits may include:

METABOLIC OPTIMIZATION

- Increase in muscle mass, and lean muscle mass
- Increased bone density
- Promotes lipolysis
- Improved sleep quality
- Improved energy
- Improved cellular repair
- Cognitive performance
- Increased endurance
- Increased IGF-1
- Supports joint health

Clinical Pearls:

- We use this w/ select patients that are in good health for short amounts of time for performance enhancement or sometimes for healing and repair after injury or surgery to help boost IGF-1 levels for healing purposes.
  - Our protocols are typically 4-6 wks with at least 4-6 wks off in-between
    - We stay well short of the recommendation not to use > 12 wks straight without a break
    - Prolonged use can cause desensitization and involution of the receptors in the pituitary gland
    - It may also increase IGF-1 levels w/ prolonged use; and we want to be cognizant of that; so check those levels periodically if you are using MK-677 throughout the year depending on how often you are using it.
- We have also used it for patients who are underweight, or cachectic and need appetite stimulation
- Excellent and safe to build muscle if following our guidelines
- Take on an empty stomach, wait at least 45 minutes before eating
  - We recommend taking before workouts (No sugar if using pre workout drink)
  - Taking in the evening may cause you to wake up and eat in the middle of the night- No good
  - It stimulates ghrelin which makes you very hungry; good for increasing your protein intake, but if you eat poorly, you may gain unwanted fat
- Can be used in combination with CJC 1295 / Ipamorelin for optimal results

Dosing:

- Males: Take 25 mg capsule PO qd x 4-6 wks (at least 4-6 wks off in between)
- Females: Take 12.5 mg capsule PO qd x 4 wks (at least 4 wks off in between)

Possible side effects:

- Increase in cortisol (by 2.3 times- have baseline and f/u labs)
- Increased appetite

IGF-1 LR3 (Insulin-like growth factor-1 long arginine 3)

IGF-1 - Insulin-like growth factor 1 (IGF-1) is a hormone that functions as the major mediator of growth hormone (GH)-stimulated somatic growth, as well as a mediator of GH-independent anabolic responses in many cells and tissues. IGF-1 is a small peptide (molecular weight 7647) that circulates in serum bound to high affinity binding proteins. IGF-1 is an unusual peptide in this regard since it is more than 99 percent protein-bound.

IGF-1 is synthesized by multiple mesenchymal cell types. As a result, there are two major mechanisms of IGF-1 regulation:

- IGF-1 that is synthesized in the liver and secreted into the blood is under the control of GH (growth hormone release stimulates the liver to produce IGF-1).
- Autocrine/paracrine IGF-1 is synthesized in peripheral tissues, such as bone. Its synthesis is controlled by GH and by factors that are secreted locally by the surrounding cell types. Some of the secreted autocrine/paracrine IGF-1 enters into the systemic circulation. Therefore, understanding the regulation of autocrine/paracrine synthesis of IGF-1 is necessary to interpret changes in serum IGF-1 concentrations.

IGF-1 exerts its effects via activation of the IGF-1 receptor [1]. This receptor is widely distributed, which enables blood-transported IGF-1 to coordinate balanced growth among multiple tissues and organs. In contrast, autocrine/paracrine IGF-1 can stimulate

local, unbalanced growth independently of systemic GH. Examples of this type of growth regulation are wound healing and growth of the contralateral kidney after unilateral nephrectomy.

IGF-1 LR3 - is a synthetic protein and lengthened analogue of human insulin-like growth factor 1 (IGF-1). It differs from native IGF-1 in that it possesses an arginine instead of a glutamic acid at the third position in its amino acid sequence ("arginine 3"), and also has an additional 13 amino acids, for a total of 83 amino acids (relative to the 70 of IGF-1). The results of these modifications are that IGF-1 LR3 retains the pharmacological activity of IGF-1 as an agonist of the IGF-1 receptor, has very low affinity for the insulin-like growth factor-binding proteins (IGFBPs), and has improved metabolic stability. As a result, it is approximately three times more potent than IGF-1, and possesses a significantly longer half-life of about 20–30 hours (relative to IGF-1's half-life of about 12–15 hours).

We have the highest levels of IGF-1 during the pubescent years and the lowest levels during old age (and infancy). When IGF-1 along with GH decreases w/ age it triggers increased cellular cortisol, sarcopenia and causes decreased glucose sensitivity.

Clinical Pearls:

- We air on the side of caution with IGF-1 LR3 as too much IGF-1 has been linked to many cancers. Not as the cause of the cancer. The concern is if IGF-1 increases proliferation of cells then we obviously do not want to exacerbate that in a patient who has cancer or a precancerous condition. Same goes for GH.
- Check IGF-1 levels during initial labs to get a baseline. If using IGF-1 LR3, or any growth hormone releasing peptides we suggest performing followup labs every 3-4 months if you feel the need.
- MK-677 also stimulates IGF-1 production
- Even though we are not aiming to hit supraphysiologic levels of GH production or IGF-1 production it is best to check patient's IGF-1 levels 3-4 times / year if they are taking growth hormone releasing peptides.
    - We have strategically designed the protocols to not be aggressive with these peptides, by not using them for prolonged periods without a break. Always exercise good clinical judgment.
- Be selective with which patient's you are using this with.

Customary Dosing:

- Inject 25-40mcg SubQ every other day (*not available at this time coming soon*)
- Current Advitam protocol:
    - Males: 75mcg sublingual troche every other day x 4 weeks

- ➢ Females: 50mcg sublingual troche every other day x 4 weeks

Glucagon Like Peptide 1 (GLP-1) Receptor Agonist - Semaglutide

Description:

GLP-1 - is produced from the proglucagon gene in L cells of the small intestine. It binds to a specific GLP-1 receptor, which is expressed in various tissues, including pancreatic beta cells, pancreatic ducts, gastric mucosa, kidney, lung, heart, skin, immune cells, and the hypothalamus. GLP-1 exerts its main effect by stimulating glucose-dependent insulin release from the pancreatic islets. It has also been shown to slow gastric emptying, inhibit inappropriate post-meal glucagon release, leading to a reduction in food intake. In patients with type 2 diabetes, there is an impaired insulin response to GLP-1, possibly related to a reduction in postprandial GLP-1 secretion or to other mechanisms.

Although GLP-1 has been shown to promote beta-cell replication and mass in animal models of prediabetes and diabetes, these findings have not been replicated in humans. GLP-1 exhibits a short half-life of one to two minutes due to N-terminal degradation by the enzyme dipeptidyl peptidase 4 (DPP-4). **Synthetic GLP-1 receptor agonists are variably resistant to degradation by the enzyme DPP-4, and therefore have a longer half-life, facilitating clinical use.** Longer-acting GLP-1 receptor agonists can be administered once daily or once weekly. Like native GLP-1, all synthetic GLP-1 receptor agonists bind to the GLP-1 receptor and stimulate glucose-dependent insulin release from the pancreatic islets as their primary effect.

Semaglutide is a selective glucagon-like peptide-1 (GLP-1) receptor agonist that increases glucose-dependent insulin secretion. GLP-1 also inhibits glucagon release and gastric emptying. It is a long acting GLP-1 and is administered by SubQ injection once weekly.

Benefits:

- ❖ Incretin-based therapies (IBT's) - reduce post meal blood sugar
- ❖ Glucose-lowering effects which are achieved without any increase in hypoglycemia (according to studies), **however use caution** as clinically we have seen some cases.

METABOLIC OPTIMIZATION

- Reduction in body weight
- Lipid reduction
- Blood pressure reduction
- Reduction in inflammatory markers
- Decrease in oxidative stress
- Decrease in endothelial dysfunction, and subclinical atherosclerosis
- Appetite suppression
- Enhance β-cell proliferation, have anti-apoptotic effects, inducing insulin biosynthesis
- Enhance glucose-dependent insulin secretion
- Suppress inappropriately elevated glucagon levels, both in fasting and postprandial states
- Promotes insulin secretion from pancreatic β-cells while decreasing glucagon secretion in the pancreatic α-cells
- Promotes satiety in the brain
- Demonstrates neuroprotective and neurotrophic actions
- Is in phase 3 trials for non-alcoholic liver disease (Semaglutide)
- Demonstrated Improved cognition in some preclinical studies and are under investigation in clinical studies for treatment of Alzheimer's disease (Semaglutide)
- Modifies the behavior of animals w/ alcohol, nicotine and cocaine dependence (Semaglutide)

Adverse effects:

- Nausea (most common)
- Constipation (more common)
- Vomiting, Diarrhea, flatulence (gas)
- Fatigue, dizziness
- Headache, vision changes (diabetic retinopathy)
- GERD/ belching/ indigestion
- Bloating/ abdominal distention
- Hypoglycemia-in patient's w/ Type 2 Diabetes (caution w/ all patients)
- Gastroenteritis

Serious side effects (Ozempic's website):

- Pancreatitis
- Vision changes
- Hypoglycemia- do not take with insulin or sulfonylurea medications
- Kidney failure/ kidney problems (**encourage good hydration**)

- ❖ Gallbladder problems
- ❖ Serious allergic Rxn's

Contraindications:

- ❖ PMH or FHx MTC (medullary thyroid cancer)
- ❖ PMH MEN 2 (multiple endocrine neoplasia type 2)
- ❖ Allergy to Semaglutide

Other considerations:

- ❖ PMH- pancreatic dz, kidney dz, diabetic retinopathy
- ❖ Pregnancy / breastfeeding- it is not known if Semaglutide will harm unborn babies or if it passes into breast milk. Recommendation is to stop Semaglutide 2 months before plans to become pregnant (Ozempic's website).

Clinical pearls:

- ❖ Re: **hypoglycemia**; studies indicate that GLP-1s do not cause hypoglycemia unless being used alongside with insulin or sulfonylurea medications; also that it is safe to use concomitantly w/ Metformin. My postulation is that most of our patient population is non-diabetic and therefore their blood glucose levels may be considerably lower than a type 2 diabetic's (which is likely the population that the studies were performed on; they have higher fasting glucose levels to work with). **We have had some patient's experience hypoglycemia**. If any of our non-diabetic patient's are on Metformin for weight loss or longevity, we require that they discontinue it prior to initiating Semaglutide or Tirzepatide as we have seen exacerbation of signs of low blood sugar- feeling fatigue, dizzy, lack of energy. When starting Semaglutide or Tirzepatide we instruct our patient's to:
  - ➢ Administer in the daytime hours (we don't want them to be asleep if their blood sugar drops)
  - ➢ Have a meal with carbohydrates within 30-60' of the injection
  - ➢ Eat healthy carbohydrates every day (NO LOW-CARB DIETS)
  - ➢ Caution w/ intermittent fasting (we use clinical judgment from patient to patient)
  - ➢ Follow our dosing protocols which are different from Ozempic, Wegovvy, & Mounjaro. We have a more gradual, customized approach
  - ➢ Ask the patient's the right questions during their followup visits
- ❖ Concerns of **pancreatitis**:
  - ➢ We do baseline pancreatic enzyme testing (Amylase/Lipase). Be aware that they increase fairly easily w/ alcohol use. Best to ask patient's to not

drink any alcohol 48-72 hours prior to lab testing, and encourage hydration.

- ➢ We have seen pancreas enzymes increase w/ the use of Semaglutide / Tirzepatide- usually not associated w/ any symptoms.
- ➢ For symptomatic patients ie. abdominal pain, vomiting, diarrhea, fever, irregular stool we:
  - ■ Instruct them to discontinue the GLP-1 / GIP until further notice, encourage hydration if they can tolerate
  - ■ call them back to the office (if it sounds urgent we would send them to the ER- has not happened)
  - ■ order labs with pancreas enzymes
  - ■ perform physical exam (attention to the abdominal quadrants)
  - ■ Determine the next best steps

❖ Patient's who struggle to get the most optimal results

- ➢ Check on their alcohol habits; daily drinkers (2-3 glasses wine/evening) have struggled
- ➢ Sedentary patients unwilling to exercise
- ➢ Patient's w/ gut inflammation (constipation, bloating, distended, poor diets)
  - ■ **For the best results they need to have a healthy gut; <u>address the microbiome</u>**
    - Enforce that they use a prebiotic (more important than a probiotic) every day; not just stop after 2 weeks
    - If you suspect prior to starting, also recommend Prolon for 5 days (fasting mimicking diet- great to do while they are waiting for their medication to arrive; as we don't think it is safe for them to do together-> hypoglycemia concerns
    - Hx of GERD: Alka Seltzer Gold- AM/ PM (amazing longevity hack)
    - Hx Barrett's Esophagus: Alka Seltzer Gold and Oral BPC 157 (very successful protection; heals ulcers, prevents new damage)

Semaglutide Dosage:

❖ **Advitam dosing** (see separate dosing schedule):

- ➢ Our pharmacy compounds Semaglutide w/ BPC 157 & Vit B6
- ➢ One of our other pharmacies compounds Semaglutide w/ L-Carnitine
- ➢ The vials come in different strengths and volumes
- ➢ Depending on the H&P, labs, body composition analysis, medications and goals of the patient, there are different options

- Some will use a microdose. Splitting the lowest dose in ½ and administering BIW
- For the typical patient, titrate:
    - Inject 0.25mg SubQ q 7d x 4 wks
    - Inject 0.5mg SubQ q7d x 4 wks **(at 7 week f/u determine if needs to increase or hold here)**
    - Inject 1.0mg SubQ q7d x 4 wks **(you may want to increase as indicated or stay at 1.0mg if pt trending appropriately- at next 7 week f/u determine if needs to increase or hold here)**
    - Follow that pattern; the additional adjustments we typically make are:
    - Inject 1.25mg SubQ q 7d
    - Inject 1.5mg SubQ q 7d
    - Inject 2.0mg SubQ q 7d

- Depending on the Strength compounded in the vial (which varies from pharmacy to pharmacy and sometimes within different strengths from the same pharmacy) will determine the volume to be administered in **units.** For example:
    - Pharmacy A: 10 units equals 0.25mg
    - Pharmacy B: 12 units equals 0.25mg
- Don't worry we have worked hard in trying to make it easy for you and we will teach you how to make adjustments if necessary.

❖ Typical dosing when using Ozempic:
- ➢ Inject 0.25mg SubQ q 7d, after 4 weeks increase to;
- ➢ Inject 0.5mg SubQ q 7d, determine if increase is needed;
- ➢ Inject 1.0mg SubQ q 7d, determine if increase is needed;
- ➢ Inject 2.0mg SubQ q 7d (Can increase up to 2.4mg q 7d)

Glucose-Dependent Insulinotropic Polypeptide (GIP Receptor Agonist)

Pharmacology:

GIP is produced in the K cells of the small intestine. It binds to a specific GIP receptor, which is expressed in various tissues, including pancreatic beta cells, pancreatic alpha cells, subcutaneous and visceral adipose tissue, bone, and heart. In the postprandial state, GIP is co-secreted with GLP-1, and they appear to interact in an additive fashion to potentiate glucose-induced insulin secretion. However, GIP exhibits different effects than GLP-1 on glucagon secretion. In the euglycemic or hypoglycemic states, GIP enhances glucagon activity.

Dual acting GLP-1 and GIP Receptor Agonist - Tirzepatide

A synthetic dual-acting GIP and GLP-1 receptor agonist (Tirzepatide) is available for the treatment of hyperglycemia in patients with type 2 diabetes]. The effect of Tirzepatide is largely mediated by its GIP component. Tirzepatide has a half-life of five days, allowing for once-weekly administration.

Tirzepatide: All of the information above re: GLP-1 receptor agonists applies to Tirzepatide as well as Semaglutide, as the risks, benefits and side effects are synonymous; but here are some specifics from Mounjaro's website.

Considerations:

- In both male/female rats causes dose dependent thyroid C-cell tumors
- Unknown whether Mounjaro causes thyroid C-cell tumors including medullary thyroid carcinoma (MTC) in humans
- Mounjaro is contraindicated in pt's w/ personal or family hx of MTC or in pt's w/ MEN 2 (multiple endocrine neoplasia type 2)
- Risk of Pancreatitis
  - Do baseline labs Lipase/Amylase
  - Repeat labs every 3 months
  - If symptoms of Pancreatitis DC Rx refer to PCP
  - If slightly elevated and asymptomatic evaluate and use clinical judgment
  - Exacerbated with alcohol use; discourage pt's from excessive drinking
- Risk of hypoglycemia w/ concomitant use of insulin secretagogues or insulin
- Hypersensitivity rxn's sometimes severe have been reported
- Acute kidney injury related to gastrointestinal conditions secondary to dehydration have been reported
- Associated w/ gastrointestinal adverse rxn's, sometimes severe
- Diabetic retinopathy complications in patients w/ Hx of diabetic retinopathy
  - The rapid improvement in glucose control has been associated with

temporary worsening of diabetic retinopathy

- Acute gallbladder disease reported by 0.6% users in a study
- Drug interactions- potential impact on medications as it delay's gastric emptying
- Pregnancy- Limited data. Based on animal studies there may be risks to the fetus; use only if potential benefit justifies the potential risk to the fetus

Clinical Pearls- Tirzepatide:

- Same as above for GLP-1 section
- We have seen Tirzepatide work better than Semaglutide for weight loss in some patients, as it should on paper; but there are some people who respond better to Semaglutide as well.
  - Generally we can tell by the first few doses (2.5mg, 3.5mg and 5mg)
  - For our patients that are looking to lose > 30lbs we encourage Tirzepatide (though we have had pt's lose > 30lbs w/ Semaglutide as well)
  - For the who only need to lose 10-15 lbs, we have found Tirzepatide to be too aggressive at times (they lose too much too fast, and don't feel so great)
  - For the patient's who need between 20-30 lbs weight loss, our decision is subjective based on all of our information (H&P, BCA, Labs, medications, lifestyle, financial consideration)
  - We have had very few pt's need to go up to 7.5mg, 10mg or above; we think this is because 1) efficacy of the medication working on 2 receptors, compared to just one (Semaglutide), 2) our combination proprietary protocols, and 3) our advisement and monitoring
  - Patient's who struggle to get the most optimal results
    - Check on their alcohol habits; daily drinkers (2-3 glasses wine/evening) have struggled
    - Sedentary patients unwilling to exercise
    - Patient's w/ gut inflammation (constipation, bloating, distended, poor diets)
      - **For the best results they need to have a healthy gut; <u>address the microbiome</u>**
        - <u>Enforce</u> that they use a <u>prebiotic</u> (more important than a probiotic) every day; not just stop after 2 weeks
        - If you suspect prior to starting, also recommend <u>Prolon</u> for 5 days (fasting mimicking diet- great to do while they are waiting for their medication to arrive; as we don't think it is safe for them to do together-> hypoglycemia concerns

- Hx of GERD: Alka Seltzer Gold- AM/ PM (amazing longevity hack)
- Hx Barrett's Esophagus: Alka Seltzer Gold and Oral BPC 157 (very successful protection; heals ulcers, prevents new damage)

Tirzepatide Dosage:

- Advitam dosing:
  - Our pharmacy compounds Tirzepatide w/ BPC 157 & Vit B6
  - One of our other pharmacies compounds Tirzepatide w/ Vit B12
  - The vials come in different strengths and volumes
  - Depending on the H&P, labs, body composition analysis, medications and goals of the patient, there are different options
    - For the typical patient, titrate:
      - Inject 2.5mg SubQ q 7d x 4 wks
      - Inject 3.5mg SubQ q 7d x 4 wks **(at 7 week f/u determine if needs to increase or hold here)**
      - Inject 5.0mg SubQ q 7d **(until further consultation- either by phone or office visit)**
  - Depending on the Strength compounded in the vial (which varies from pharmacy to pharmacy and sometimes within different strengths from the same pharmacy) will determine the volume to be administered in **units.** For example:
  - Pharmacy A: 10 units equals 0.25mg
  - Pharmacy B: 12 units equals 0.25mg
  - Don't worry we have worked hard in trying to make it easy for you and we will teach you how to make adjustments if necessary.

KPV (α-melanocyte-stimulating hormone)

Properties:

Peptide Sequence: Lys-Pro-Val
Molecular weight: 342.43 g/mol

METABOLIC OPTIMIZATION

Molecular Formula: $C_{16}H_{30}N_4O_4$

Description:

KPV is a tripeptide (Lys-Pro-Val) based on α-Melanocyte-stimulating hormone (α-MSH) molecule. KPV possesses anti-inflammatory properties, although it's mechanisms are still largely unmapped. α-MSH is an endogenous tridecapeptide cleavage product of proopiomelanocortin that has protective and anti-inflammatory effects. The anti-inflammatory activity of α-MSH is reported to be facilitated by three N-terminal amino acids, lysine-proline-valine, known as KPV.

Both α -MSH and KPV reduce cytokine release and leukocyte migration in the peritoneal cavity in a model of crystal-induced peritonitis. In a model of IL-1-induced cutaneous inflammation, administration of α -MSH as well as KPV ameliorated the inflammatory symptoms. In studies, KPV peptide was reported to exert a more potent anti-inflammatory effect than α-MSH itself. A study also reported that KPV can attenuate the inflammatory responses of colonic epithelial and immune cells and reduce the incidence of colitis in vivo upon oral administration. In glial cells KPV led to markedly decreased expression of TNF- α mRNA and reduced release of NO after stimulation with beta-amyloid or interferon-gamma.

It is important to note that the anti-inflammatory effects of KPV appear to be mediated through somewhat different mechanisms than those of α -MSH. Whereas α -MSH binds to specific melanocortin receptors, KPV does not. It seems KPV exerts its anti-inflammatory function inside cells, where it inactivates inflammatory pathways. Evidence of this comes from mouse studies in which blocking MC3/4 receptors, which mediate the antiinflammatory effects of α -MSH, has no impact on the anti-inflammatory effects of KPV. Specifically, blocking these receptors does not block the leukocyte migration effects induced by KPV.

The ability of KPV to be administered by various methods is also appealing over alpha-MSH, which is only injection. KPV can be used orally, transdermally, or injection without side effects. (*Description by IPS- International Peptide Society*)

Benefits:

- Anti-inflammatory, metaflammation
- Immune modulation
- Gastrointestinal repair- IBS, ulcerative colitis, intestinal damage, colon cancer

- Wound healing
- Injury healing
- Skin appearance (repairs skin barrier proteins)

Dosing:

- KPV 500 mcg capsules: Take one capsule PO BID
- KPV (2 mg/g) + D3 (1,000 iu/g) topical cream 30 mL topi-click

Side Effects:

- KPV peptide administered orally is reported safe and efficacious in recommended dosages.
- KPV is not reported to cause skin pigmentation, unlike alpha-MSH.
- No notable side effects

MOTS-c

Properties:

- MOTS-c is a 16-amino-acid peptide encoded in the mitochondrial genome.
- Sequence: Met-Arg-Trp-Gln-Glu-Met-Gly-Tyr-Leu-Phe-Tyr-Pro-Arg-Lys-Leu-Arg
- MW: 2288.6 g/mol
- Molecular formula: $C_{10}H_{152}N_{28}O_{22}S_2$

Description: (*Description by International Peptide Society*)

Mitochondrial-derived peptides (MDPs), encoded by mitochondrial DNA, play a cytoprotective role by helping preserve mitochondrial function and cell viability under stressful conditions. MDP's signal within the cell or are released to act as autocrine/paracrine/endocrine cytoprotective factors and play a key role in the cellular stress response.

The MDP family includes humanin and SHLPs encoded from the 16S rRNA region and have broad protective effects and MOTS-c which is encoded from the 12S rRNA region and has metabolic signaling activity with potent anti-obesity effects. MDPs have been

used clinically in various disease models and reported to play a role in many pathologies, including senolytic activity and delaying the progression of atherosclerosis, Alzheimer's and chemotherapy-induced side-effects, supporting glucose/insulin regulation, weight management and cardiovascular health, among other functions.

One of these MDPs, MOTS-c, holds great potential as a target to treat metabolic signaling issues by regulating muscle and fat physiology, and perhaps even extend a healthy lifespan.

MOTS-c is a 16-amino acid peptide encoded within the 12S rRNA region of mtDNA. It is measured in plasma and multiple tissues including muscle, brain, and liver. MOTS-c levels are correlated with insulin resistance in lean, not obese, individuals and circulating MOTS-c levels are reduced in obese male children and adolescents, but not in obese females. MOTS-c is also involved in lung, bone and cardiovascular disease.

Metabolic Signaling/ Insulin Sensitivity

MOTS-c bottom line is it helps turn available glucose into energy in the mitochondria. MOTS-c dramatically increases endogenous 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) levels and activates 5′ AMP-activated protein kinase (AMPK). MOTS-c increases glucose utilization, fatty acid oxidation, and alters mitochondrial function and nucleotide metabolism. MOTS-c has been reported to target the skeletal muscle and enhance glucose metabolism.

MOTS-c levels are correlated with markers of insulin resistance and obesity including BMI, waist circumference, waist-to-hip ratio, fasting insulin level, HOMA-IR, HbA1c. In addition, MOTS-c levels are correlated with endothelial function in humans. The effects of MOTS-c include:

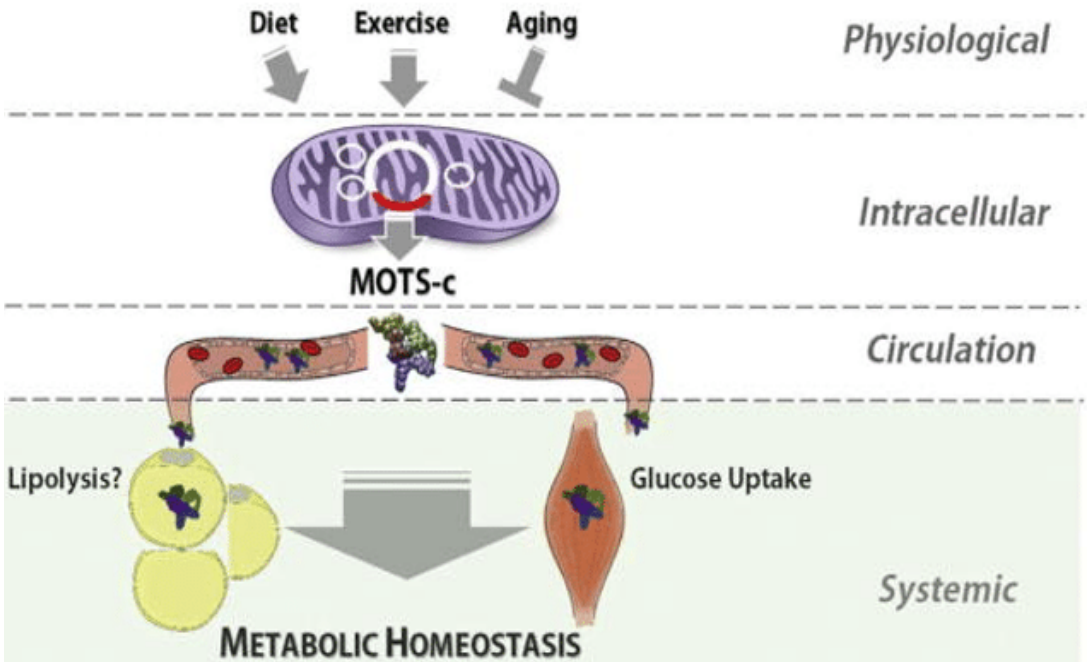
- Increased glucose utilization and fatty acid oxidation
- Decreased oxidative phosphorylation
- Increased endogenous AICAR levels
- AMPK activation
- Increased glucose uptake into muscle cells

In laboratory studies, MOTS-c administration in high-fat diet-fed mice decreases weight gain by increasing energy expenditure and significantly decreases the fat accumulation in the liver. The levels of insulin also were lower in MOTS-c–injected mice, suggesting that MOTS-c improves the insulin sensitivity in high-fat diet-induced mice.

METABOLIC OPTIMIZATION

MOTS-c is reported to increase adipose thermogenic activation to promote cold adaptation. MOTS-c is reported to dramatically upregulate brown adipose tissue (BAT) thermogenic gene expression and increase white fat “browning”, probably mediated by activated phosphorylation of the ERK signaling pathway by MOTS-c.

MOTS-c is reported as a potential biomarker for metabolic function. As discussed earlier, MOTS-c levels are inversely correlated with markers of insulin resistance and obesity.



Aging and Longevity:

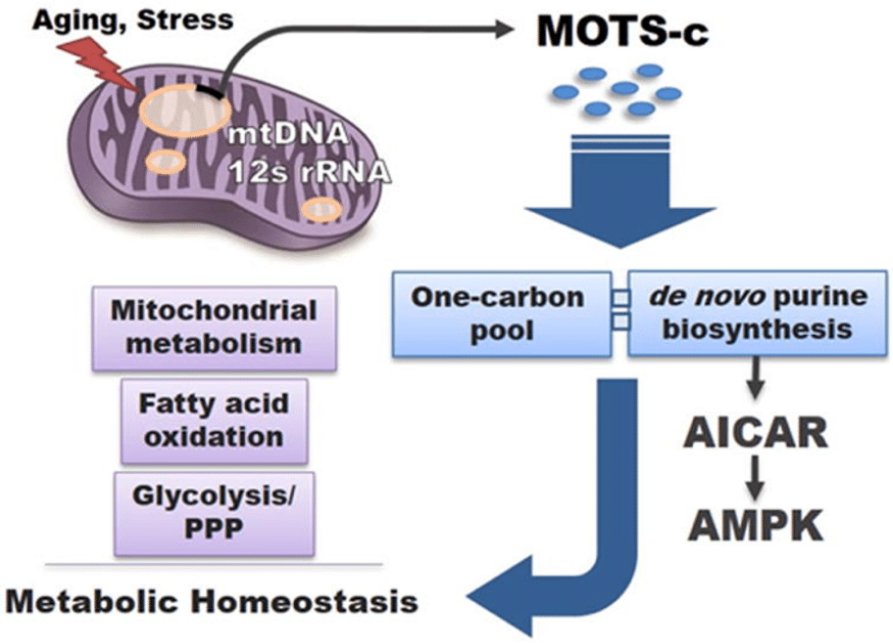
MOTS-c levels decline with age. Mitochondria are strongly implicated in aging and age-related diseases, and with the promising research and potential beneficial effects of MOTS-c in regulating metabolic homeostasis, the therapeutic implications in obesity and diabetes are evident.

There are metabolic links between known age-modifiers and MOTS-c. NAD^+ is a key metabolic coenzyme involved in redox reactions that declines with age, and restoring its levels can improve age-related disease conditions. Further, NAD^+ is a potent activator of sirtuins, which are conserved multifunctional regulators of aging and age-related diseases in various model organisms from yeast to mammals.

METABOLIC OPTIMIZATION

MOTS-c is reported to increase intracellular NAD^+ levels and MOTS-c-dependent glycolytic effects are mediated by sirtuin 1 (SIRT1).

In addition, MOTS-c restricts the folate/methionine cycle, causing a reduction in methionine metabolism. This leads to a depletion of intracellular 5MTHF, increased levels of AICAR, and activation of AMPK in the presence of ATP accumulation and decreased mitochondrial respiration. It also may lead to increased homocysteine levels and folate depletion. In rodents, methionine restriction can increase lifespan by about 45%, decrease age-related diseases (such as cancer and type 2 diabetes), delay lens deterioration, reduce visceral fat, and increase the major antioxidant glutathione (GSH). Note this regulation of the folate-AICAR-AMPK pathway is similar to the drug methotrexate.

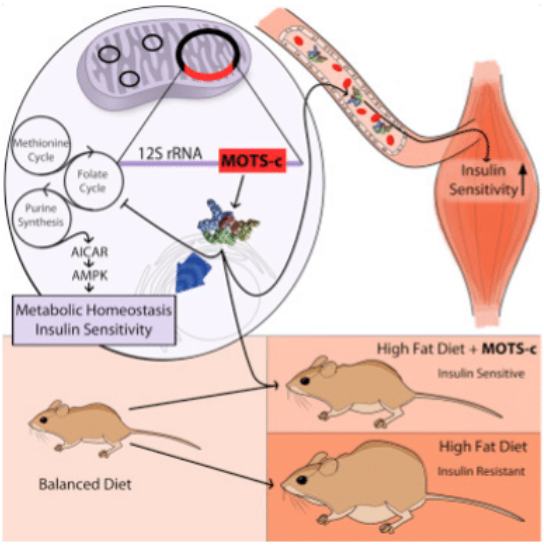


MOTS-c: Mitochondrial-encoded regulator of metabolic homeostasis

Exercise:

Mitochondria are key bioenergetics sources that fuel skeletal muscle during exercise, but they are also actively engaged in transmitting exercise-induced signals to other organs. Although the effect of exercise on regulating MOTS-c production and secretion is unknown, its beneficial effects on a high fat diet (HFD) is mirrored by MOTS-c. As discussed earlier, MOTS-c increases cellular levels of AICAR (an AMPK agonist) and activates AMPK, a well-described regulator of exercise. In laboratory studies, MOTS-c

injections were reported to activate mouse skeletal muscle AMPK and increase the level of the downstream glucose transporter GLUT4. MOTS-c may also act as a potential mitochondrial signal that mediates an exercise-induced mitohormesis response, thereby stimulating physiological adaptation and increased tolerance to exercise.



MOTS-c Promotes Metabolic Homeostasis

Cardiovascular Health

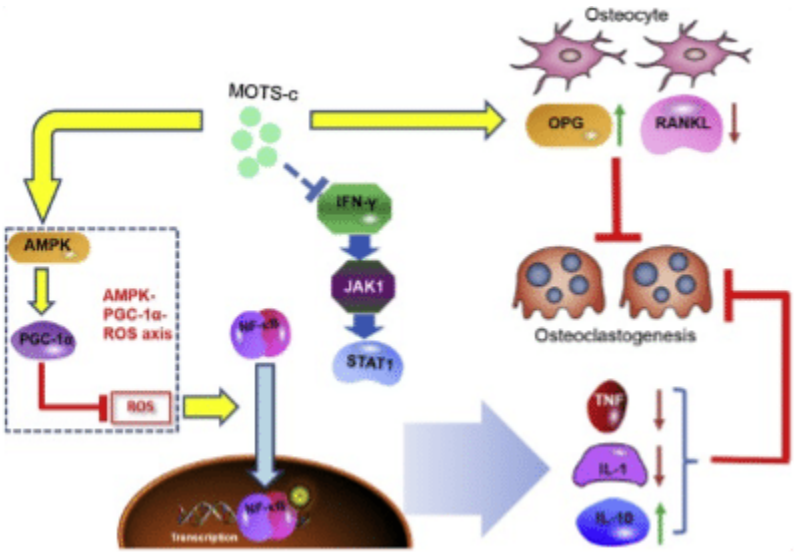
Aging, hyperlipidemia, insulin resistance, and atherosclerosis are all risk factors for cardiovascular diseases. MOTS-c is reported to protect against coronary endothelial dysfunction by the reduction of the release of pro-inflammatory cytokines and adhesion molecules, which results from the inhibition of NF-κB. MOTS-c is also involved in lipid metabolism. MOTS-c improves lipid utilization by stimulating carnitine shuttles to increase the level of β-oxidation. Moreover, MOTS-c can also reduce HFD-induced visceral fat accumulation and hepatic steatosis, but it is unclear whether this is due to the decreased lipogenesis or the increased lipolysis. In vitro, MOTS-c reduces triglyceride content, promotes AKT activity and reduces lipid droplet deposition through AMPK pathway in adipocytes. Although the genes associated with lipid oxidation did not change, the genes related to lipogenesis were significantly inhibited by MOTS-c treatment.

METABOLIC OPTIMIZATION

Studies also report MDPs play a protective role in myocardial ischemia-reperfusion injury. A laboratory study reported MOTS-c attenuated vascular calcification and secondary myocardial remodeling by activating the adenosine monophosphate-activated protein kinase signaling pathway (AMPK) and suppressing expression of the angiotensin II type 1 (AT-1) and endothelin B (ET-B) receptors.

Osteoporosis Prevention/Treatment

MOTS-c is reported to play a role in the synthesis of type 1 collagen by osteoblasts in bone tissue. MOTS-c is reported to suppress ovariectomy-induced osteoporosis via AMPK activation, and improve osteoporosis via the TGF-βeta/SMAD pathway. MOTS-c also inhibits osteolysis by affecting osteocyte-osteoclast crosstalk and inhibiting inflammation in laboratory studies.



MOTS-c Osteolysis Inhibition

Benefits:

- Assists in mitochondrial biogenesis
- Activates AMPK
- Restores homeostasis by initiating catabolic process for ATP production
- Decreases insulin resistance
- Increases GLUT4 uptake in muscle

- Improves athletic performance
- Improves weight loss

Clinical Pearls:

- This is an amazing peptide; an overall favorite
- The serum can be thick and sometimes there is some pruritus locally at the injection site for 5-15 minutes. We have our patients split the dose into two separate syringes; do ½ into one glute and ½ into the other to reduce the intensity of any local irritation.
- We follow a customary protocol of injecting once weekly for 4-6 weeks
- Always allow 2-3 months off in between uses

Dosing:

- Advitam Dosing: 10mg (split into two separate syringes) injected SubQ once weekly x 4-5 weeks
- Alternative dosing: 5mg injected SubQ 3x/wk x 4 wks

Safety / side effects:

- MOTS-c is reported safe in recommended dosages.
- Injection site pruritus.
- As with all injections, redness and pain at the site of injection may be present.
- As MOTS-c targets the folate cycle and de novo purine biosynthesis pathways, it is possible a depletion of intracellular 5-methyl tetrahydrofolate (5-MTHF) may occur when using MOTS-c protocols. It may be advised to supplement the diet with folate as folinic acid or 5-MTHF, up to 1,200 mcg daily, between injections in the protocol, especially in those prone to folate deficiencies or methylation issues.
- It is recommended to check homocysteine and folate levels in patients taking MOTS-c.

METABOLIC OPTIMIZATION

Tesofensine

Description:

Tesofensine (NS2330) is a serotonin–noradrenaline–dopamine reuptake inhibitor (SDNI) from the phenyltropane family of drugs, which is being developed for the treatment of obesity. It is also known as a triple reuptake inhibitor (TRI). Tesofensine was originally developed by a Danish biotechnology company, NeuroSearch, who transferred the rights to Saniona in 2014. As of 2019, tesofensine was discontinued for the treatment of Alzheimer's and Parkinson's disease, and was subsequently dropped from development for these applications after early trial results showed limited efficacy for treatment of these diseases. However, weight loss was consistently reported as an adverse event in the original studies, especially in overweight or obese patients. Therefore, it was decided to pursue development of tesofensine for the treatment of obesity. It is currently in phase III clinical trials for obesity. It acts as an appetite suppressant and also acts by increasing resting energy expenditure.

Properties:

- Tesofensine has a long half-life of about 9 days.
- Metabolized by P4503A4 (CYP3A4) to its desalkyl metabolite M1" NS2360.
- The NS2360 metabolite is detectable for 16 days.

Benefits:

- Indirectly potentiates cholinergic neurotransmission improving cognition, particularly in learning and memory.
- Sustained treatment with tesofensine has been shown to increase BDNF levels in the brain, and may possibly have an antidepressant effect.
- Weight loss
- Appetite suppression
- Increase in lean body mass
- Increased energy
- Promotes lipolysis
- Increases metabolism
- Improves sleep quality
- Decreased HA1C and insulin levels

METABOLIC OPTIMIZATION

- Decreased triglycerides and cholesterol

Dosing:

- 0.25mg capsule- Take one capsule PO qd
- 0.5mg capsule- Take one capsule PO qd
- 1.0mg capsule- Take one capsule PO qd

Side effects:

- Most common: dry mouth, headache, nausea, insomnia, diarrhea, constipation
- At the end of phase II trials Saniona concluded:
  - Low incidence of increased heart rate, no significant effect on blood pressure

METABOLIC OPTIMIZATION

METABOLIC OPTIMIZATION