Independent Research & Further Reading

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Contents

Amino Acids and Peptides: Structural Units of Biological Function

> *"peptides are a structural class of medications (...) The best way to think about peptides is that just like we have small molecules, which are drugs that are very small, taken in a pill and have a wide ranging effect throughout the body, peptides are derived from little pieces of amino acids, which think of them as the Legos that make up the human body, the Legos that make up proteins. These are little fragments of proteins that are designed to specifically target certain receptors and affect cells in a very targeted fashion (...) amino acids are the building blocks of life."*

Amino acids are small biomolecules characterised by the presence of both an amine group ($–NH_2$) and a carboxyl group (–COOH) attached to a central carbon, along with a variable side chain that determines their chemical properties. They function as the fundamental building blocks of peptides and proteins and also play broader roles in physiology, including serving as precursors for hormones, neurotransmitters, and other signalling molecules.

Peptides are short chains of amino acids linked by peptide (amide) bonds, typically consisting of between two and fifty amino acids, and represent an intermediate level of organisation between individual amino acids and larger proteins. In biological systems, amino acids combine to form peptides, which can further fold into proteins with specific structural and functional properties.

Both amino acids and peptides contribute to a wide range of physiological processes, including signalling, metabolism, and cellular regulation, and their proper synthesis, modification, and degradation are essential for maintaining normal biological function.

References 1-6.

Insulin and the Emergence of Peptide Therapeutics

> *"The first peptide that was actually isolated and used in medicine was insulin back in 1921"*

Historical evidence indicates that insulin was the first peptide hormone to be isolated, purified, and successfully used in medical treatment, marking a decisive turning point in modern medicine. Following its discovery in 1921–1922, insulin was rapidly introduced as a life-saving

therapy for diabetes, with early preparations derived from bovine and porcine pancreatic extracts administered to patients from 1922 onwards. It is widely regarded as the first hormone purified for human therapeutic use and is consistently identified in historical and scientific literature as the origin point of the peptide drug era. Its successful clinical application established both a conceptual and practical framework for the development of subsequent peptide-based medicines, thereby initiating a broader transformation in pharmaceutical science.

References 7-9.

BPC 157: Angiogenesis and Ulcerative Colitis

> *"BPC 157. This is probably one of the most popular peptides that we're talking about right now because BPC 157 is a synthetic version of a naturally found peptide in the gut body protection compound 157 is the name of this. But what this actually does is it enhances blood vessel growth in areas of injury (...) they have completely transected the Achilles tendon in rats and then they transected transected. So they've cut across the achilles tendon. So not just a small injury that you or I might experience in the gym where we pull it or strain it, but actually surgically cut the, Achilles tendon and then they administer it to rats and they are healing spontaneously with administration of BPC 157 (...)*
>
> *[BPC 157 is] particularly effective in ulcerative colitis."*

BPC 157: Angiogenesis in Injured Tissue

Preclinical research indicates that BPC 157 has been shown to enhance blood vessel growth, or angiogenesis (the formation of new blood vessels), in areas of tissue injury. Evidence from animal and in vitro studies demonstrates increased vessel density, improved blood flow recovery, and upregulation of angiogenic factors such as vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) in models of ischemic muscle, tendon damage, and skin injury. These effects are consistently associated with improved structural healing, including enhanced collagen formation, re-epithelialisation, and tissue regeneration. Mechanistically, BPC 157 appears to activate signalling pathways such as VEGFR2–Akt–eNOS and ERK1/2, which are known to promote endothelial cell function and vascular growth. Some findings further suggest that this angiogenic response is temporally regulated, with early enhancement followed by later normalisation, indicating a

controlled, injury-specific process rather than excessive or pathological vessel formation. However, all current evidence is derived from preclinical models, and its relevance to human injury and clinical outcomes remains unconfirmed.

BPC 157 and Ulcerative Colitis: Preclinical Promise and Limited Clinical Evidence

Research suggests that BPC 157 may have therapeutic potential for ulcerative colitis, but the strength of evidence remains largely preclinical and insufficient to establish clinical efficacy. In animal models, BPC 157 has consistently demonstrated protective and restorative effects in chemically induced and ischaemic forms of colitis, including improvements in mucosal integrity, reductions in ulceration, normalisation of oxidative stress markers (biochemical indicators of cellular damage caused by reactive oxygen species), and restoration of blood flow through collateral vessel recruitment. These findings extend to more complex conditions, such as colitis combined with short bowel syndrome and post-surgical intestinal repair, where structural and functional recovery has also been observed.

Early human data are referenced in the form of phase II trials, in which BPC 157 is described as safe and reportedly effective; however, these reports lack detailed methodological information, including study design, control conditions, and quantified outcomes. Moreover, much of the existing evidence originates from a limited number of research groups, with little independent replication. Although the safety profile appears favourable across both animal studies and early clinical observations, the absence of robust, large-scale, and independently verified randomised controlled trials means that its effectiveness as a treatment for ulcerative colitis in humans remains unproven.

References 10-20.

BRCA1 and BRCA2: Discovery, Commercialisation, and Cancer Risk

> *"Myriad Genetics (...) This was the company that actually patented the BRCA one and BRCA2 genes. They discovered the breast cancer, the genes that caused breast cancer. "*

Myriad Genetics played a central role in the cloning, sequencing, and commercial development of BRCA1 and BRCA2 genes. The initial identification of a breast cancer susceptibility locus, later named BRCA1, emerged from academic research using linkage analysis, with multiple groups contributing to this foundational work. A team led by Mark Skolnick, who later founded

Myriad Genetics, subsequently succeeded in cloning and sequencing BRCA1 in 1994, followed by BRCA2 in 1995. Myriad then focused on developing diagnostic tests and securing patents on these gene sequences and their applications, which later became the subject of significant legal and ethical debate, culminating in a ruling that naturally occurring human DNA cannot be patented.

Independently of this history, BRCA1 and BRCA2 are firmly established as major breast cancer susceptibility genes. Inherited mutations in these genes are strongly associated with an increased risk of breast and ovarian cancer and are among the most significant high-penetrance genetic risk factors identified. They account for a substantial proportion of hereditary breast cancer cases and are widely recognised as central to understanding genetic vulnerability, disease onset, and tumour characteristics in these cancers.

References 21-29.

MK-677 (Ibutamoren) and Appetite in Cachexia: Mechanistic Potential Without Direct Evidence

> *"MK 677, also known as Ibutamoren (...) It binds to this receptor called ghrelin and it actually stimulates the release of significant growth hormone. But what was really interesting is that it would actually stimulate hunger, a profound amount, and all of a sudden patients that were struggling with cachexia, okay, so being very, very thin, very malnourished, maybe they're going through cancer treatment (...) So they were able to stimulate the hunger response and patients were actually able to eat more to meet caloric goals. And so this was a medication that was fantastically effective at that."*

Current evidence does not demonstrate that Ibutamoren (MK 677) has been shown to stimulate hunger specifically in people with cachexia (a syndrome of severe weight loss and muscle wasting often seen in chronic illness). Mechanistically, ibutamoren is a ghrelin receptor (GHSR) agonist, meaning it mimics the action of ghrelin, an orexigenic hormone that stimulates appetite and food intake. This provides a clear biological basis for a potential hunger-enhancing effect.

However, while other ghrelin receptor agonists, such as Anamorelin, have been tested in clinical trials and shown to increase appetite and body weight in cachectic patients, equivalent clinical data for ibutamoren in this population are not reported in the available literature. Research in

cachexia consistently highlights appetite improvements with ghrelin mimetics as a class, but ibutamoren itself is not included in these trials or outcome data. As such, although ibutamoren has a plausible mechanism for stimulating hunger, there is no direct clinical evidence confirming this effect in individuals with cachexia.

References 30-35.

GHRP-2 and GHRP-6: Growth Hormone Stimulation and Physiological Outcomes

> *"GHRP2 and GHRP-6 were some of the ones we were using at that time. those are growth hormone releasing peptides that stimulate the release of your body's natural growth hormone, which can help with tissue repair, can also help with fat loss and with building muscle"*

GHRP-2 and GHRP-6 are well-established growth hormone–releasing peptides, functioning as potent growth hormone secretagogues that stimulate the release of growth hormone from the pituitary gland. They act via the ghrelin receptor (GHS-R1a), with effects observed across multiple administration routes and often in synergy with growth hormone–releasing hormone.

Preclinical research suggests that these peptides may exert cytoprotective effects, including reductions in oxidative stress (cellular damage caused by reactive oxygen species), inflammation, and fibrosis across various tissue types such as cardiac, neuronal, gastrointestinal, and hepatic systems. These findings imply a potential role in tissue protection and repair; however, this evidence is largely derived from animal and experimental models, with no direct clinical confirmation of generalised tissue repair in humans.

With respect to fat loss and muscle gain, GHRP-2 and GHRP-6 have been described as having anabolic (tissue-building) and anti-catabolic (preventing tissue breakdown) properties in experimental contexts. While this suggests a theoretical capacity to influence body composition, the available research does not provide controlled human data demonstrating clear or consistent effects on fat reduction or increases in muscle mass.

References 36-42.

Peptides for Weight Loss

“we have peptides that can help you lose weight. Like the GLP one drugs (...) Mounjaro is the brand name for Tirzepatide. Alright. Tirzepatide being the leading GLP one product right now (...) this produces more weight loss per milligram than any other product that we've got out right now (...)

the best peptides for that [Insulin resistance] right now are the GLP one drugs (...) Because what you're doing is you are slowing gastric emptying, and so you have a slower absorption of that bolus of food that you've eaten, so your glucose doesn't spike. Okay. And so as a result, that increases insulin sensitivity significantly (...)

I am concerned about is the rapid weight loss with GLP one medications. Because the problem is, is that when you go into such a radical caloric deficit, your body goes into catabolism, which is breaking down tissue and you wanna break down fat, right? But your body isn't that judicious. It's gonna break down muscle (...)

what happens when you stop (...) You actually regain the weight.”

Tirzepatide and Weight Loss Compared to Other GLP-1 Agonists

Current evidence indicates that tirzepatide (Mounjaro) generally produces greater weight loss than established GLP-1 receptor agonists such as semaglutide and liraglutide when used at standard therapeutic doses. Across multiple randomised controlled trials and meta-analyses, tirzepatide consistently demonstrates larger average reductions in body weight in individuals with obesity or type 2 diabetes.

In comparative analyses, weekly tirzepatide at doses of 10–15 mg is associated with greater weight loss than semaglutide 2.4 mg or liraglutide 3 mg, as well as a higher likelihood of achieving clinically significant weight loss thresholds, including reductions of 5–20% of body weight. Quantitatively, pooled data from trials of at least 20 weeks’ duration suggest that tirzepatide produces approximately 3–8 kg more weight loss than GLP-1 receptor agonists overall. In large obesity trials without diabetes, tirzepatide has been associated with weight reductions of approximately 17–21%, compared with around 14% for semaglutide and 6% for liraglutide.

Adverse effects, particularly gastrointestinal symptoms such as nausea, vomiting, and diarrhoea, are common across all agents and appear broadly similar at effective doses. Some

analyses note a higher risk of severe hypoglycaemia with tirzepatide in certain contexts, particularly when combined with other glucose-lowering therapies. While these findings support the superior weight-loss efficacy of tirzepatide relative to current GLP-1 agonists, some comparisons rely on indirect analyses rather than fully matched head-to-head trials, and this should be considered when interpreting the magnitude of difference.

GLP-1 Receptor Agonists and Insulin Resistance

GLP-1 receptor agonists are effective in improving markers of insulin resistance, although their effects arise through both direct and indirect mechanisms. These medications enhance glucose-dependent insulin secretion (insulin release in response to elevated blood glucose), suppress glucagon, and promote weight loss, all of which contribute to improved metabolic regulation. Improvements in insulin resistance are commonly assessed using measures such as HOMA-IR (a calculation based on fasting glucose and insulin levels), fasting insulin, and related biomarkers.

Clinical evidence, particularly in individuals with type 2 diabetes, shows that GLP-1 receptor agonists can significantly reduce HOMA-IR and improve β-cell function (the ability of pancreatic cells to produce insulin). Some agents, including newer formulations and dual agonists, demonstrate reductions in insulin resistance that are only partially explained by weight loss, suggesting additional direct effects on insulin sensitivity. Improvements have also been observed across diverse populations, including individuals with chronic kidney disease and other metabolic conditions.

In specific groups such as those with polycystic ovary syndrome, GLP-1 receptor agonists have been associated with reductions in both body weight and insulin resistance, in some cases exceeding the effects of standard treatments like metformin, although the quality of evidence is limited.

GLP-1 Receptor Agonists and Muscle Mass

GLP-1 receptor agonist medications have been shown to reduce lean body mass, which includes muscle, as part of overall weight loss. Across multiple studies and meta-analyses, reductions in lean mass typically account for approximately 20–40% of total weight lost, often corresponding to around 0.8–1.0 kg. This indicates that while these medications are effective for reducing body weight, some degree of muscle loss commonly occurs alongside fat loss.

However, this reduction in muscle mass appears to be broadly proportional to the degree of weight loss rather than an isolated or disproportionate effect on muscle tissue. In some studies,

relative lean mass (the proportion of muscle compared to total body weight) improves, and measures of muscle function, such as strength, may be maintained or even enhanced. Evidence also suggests that muscle quality, including reduced fat infiltration within muscle tissue, may improve despite decreases in absolute muscle volume.

Importantly, the extent of muscle loss can be influenced by behavioural factors. Adequate protein intake and resistance training (strength-based exercise) have been shown to mitigate or even prevent reductions in lean mass during treatment. While concerns remain for vulnerable populations, such as older or frail individuals at risk of sarcopenia (age-related muscle loss), current evidence indicates that GLP-1 receptor agonists do reduce muscle mass to some extent, but not necessarily in a way that leads to functional impairment when appropriately managed.

Weight Regain After Discontinuation of GLP-1 Agonists

Current evidence consistently shows that a substantial proportion of weight is regained after discontinuation of GLP-1 receptor agonist medications. Weight regain often begins within weeks to months of stopping treatment and can reverse a significant portion of the initial weight loss. This pattern reflects the chronic nature of obesity, with these medications functioning as ongoing treatments rather than permanent solutions.

The extent of weight regain is generally proportional to the amount of weight lost during treatment, meaning that individuals who experience greater initial reductions, particularly with more potent agents, tend to regain more weight after cessation. Although weight is often not fully restored to baseline levels, many individuals retain only a modest net benefit over time.

The trajectory of regain appears to follow a gradual deceleration, with estimates suggesting a slowing rate over several months. Behavioural factors can influence outcomes, as interventions such as structured exercise during treatment have been shown to reduce the degree of subsequent weight regain, although they do not fully prevent it. Overall, the evidence indicates that discontinuing GLP-1 agonist therapy is commonly associated with clinically meaningful weight regain.

References 43-77.

IGF-1 LR3, Peptides, and Testosterone in Muscle Mass Development

> *"IGF-1 LR3 is basically the longer lasting version of IGF-1, which is the downstream effect of growth hormone (...) It can help contribute to muscle mass (...) but truthfully, if you're trying to gain significant muscle mass, this is not the way to do it. And so, right now, one of the things that peptides can't do for you is independently put on significant amounts of lean mass (...)*
>
> *I have so many patients that think that they can just take testosterone and just put on muscle naturally, and it doesn't work that way. You might get a tiny little bit, but you still have to have stimulus. You still have to get in the gym."*

IGF-1 LR3 and Peptides in Muscle Mass Development

Insulin-like growth factor 1 (IGF-1) is strongly implicated in muscle growth, but there is no direct clinical evidence demonstrating that IGF-1 LR3 specifically increases muscle mass in humans. Mechanistically, IGF-1 promotes muscle hypertrophy through pathways such as PI3K/Akt/mTOR, which enhance muscle protein synthesis (the process of building new muscle proteins), reduce protein breakdown, and support satellite cell activation involved in muscle repair and regeneration. Animal studies show that increased local IGF-1 expression can lead to significant gains in muscle size and strength, particularly when combined with resistance training. However, studies involving systemic increases in IGF-1 in humans show increases in fat-free mass that do not consistently translate into true muscle hypertrophy, with some effects potentially reflecting fluid retention or non-muscle tissue changes.

More broadly, there is evidence that certain peptides can contribute to increases in muscle mass, but typically not as independent interventions. Nutritional peptides, such as collagen peptides, have been shown in randomised controlled trials to modestly increase fat-free mass and strength when combined with resistance training. Other experimental peptides, including those that influence IGF-1 signalling or inhibit myostatin (a regulator that limits muscle growth), demonstrate muscle-building effects in animal models, including increased muscle fibre size and improved regeneration. However, these effects are generally observed in controlled experimental conditions or in combination with exercise, and direct evidence for peptides independently increasing muscle mass in humans remains limited.

Testosterone, Muscle Mass, and the Role of Resistance Training

Testosterone has been shown to increase muscle mass independently, but its effects are generally enhanced when combined with resistance training. In clinical and experimental settings, testosterone therapy can increase lean body mass and, in some cases, muscle strength even without exercise, particularly in older individuals, those with low testosterone levels, or in certain disease states. However, these gains are often modest, and improvements in functional outcomes such as strength or aerobic capacity are not consistently observed when testosterone is used alone.

Resistance training independently produces reliable increases in muscle mass and strength across a wide range of populations. When testosterone is combined with resistance training, the effects are typically greater than either intervention alone, especially at higher or supraphysiological doses. This combined approach leads to more pronounced increases in muscle size and strength, indicating a synergistic effect.

References 78-94.

GHK-Cu, Age-Related Decline, and Effects on Skin

> *"GHK-Cu (...) this is a copper tripeptide that has been found to decrease in expression and concentration as we age. But when it is applied topically, it's highly effect topically (...) it's been found to be extremely beneficial in regenerating the quality of skin so complexion. Alright, increasing the amount of collagen and elastin, the things that we need to keep our faces taught and youthful."*

GHK-Cu levels have been shown to decline with age, with evidence indicating that concentrations in human plasma decrease substantially from early adulthood to later life. This reduction is consistently reported across studies, although the precise implications for disease processes remain under investigation.

Topical application of GHK-Cu has been demonstrated to produce beneficial effects on the skin in multiple placebo-controlled human trials. These studies report improvements in skin density, thickness, elasticity, and firmness, along with reductions in fine lines, wrinkles, and photodamage. In addition, increases in collagen production and overall skin quality have been observed over treatment periods ranging from several weeks to a few months. Comparative findings suggest that, in

some cases, these effects are equal to or greater than those seen with other commonly used topical agents.

Mechanistically, GHK-Cu is associated with stimulation of collagen and elastin synthesis, modulation of extracellular matrix remodelling, and antioxidant and anti-inflammatory effects. It also appears to support processes relevant to tissue repair, including angiogenesis and cellular regeneration. Taken together, the evidence supports that GHK-Cu declines with age and that its topical application can improve multiple markers of skin ageing in human studies.

References 95-106.

Semax and Cognitive Function, Stroke, and Traumatic Brain Injury

> *"intranasal Cmax. So this is a derivative of ACTH, which is adrenal corticotropin releasing hormone, which is a hormone that is important for just endocrine regulation in the body. And this was one that was originally studied actually in Russia many years ago. And what they found is that this seven amino acid peptide, when it was administered after a TBI, so a traumatic brain injury, alright, or acute injury, that patients tended to bounce back faster. Also, they saw evidence of it improving outcomes after stroke. And it also seems to upregulate the same sort of factors that help with cognition"*

Evidence for Nootropic Effects

Semax has been shown to exhibit pro-cognitive, or nootropic, effects across a range of experimental and limited human studies. It is associated with improvements in learning, memory, and attention, particularly in contexts involving neurological stress or injury rather than in healthy populations.

Mechanistically, semax influences several pathways relevant to cognition. It increases brain-derived neurotrophic factor (BDNF) signalling, which supports synaptic plasticity (the ability of neural connections to strengthen and adapt), and modulates neurotransmitter systems such as serotonin and dopamine, both of which play key roles in cognitive processes. It also affects AMPA receptor activity, which is involved in fast synaptic transmission and memory formation.

In animal studies, semax has consistently demonstrated cognitive benefits. These include restoration of learning and memory in models of chronic brain ischemia, reduction of memory impairment under stress, and protection against cognitive deficits induced by toxins or developmental disruptions. Improvements have been observed in both short-term and long-term memory, as well as in working memory.

Human evidence is more limited but suggests similar effects. Reports indicate that semax may enhance memory and attention in individuals exposed to extreme conditions and is used clinically in some settings for cognitive impairment following central nervous system disorders.

Semax and Traumatic Brain Injury (TBI): Limited Preclinical Evidence

Current evidence for semax in traumatic brain injury is very limited and confined to animal research. A single controlled study in a rat model of mechanical TBI suggests that semax may exert neuroprotective and immunoprotective effects. In this model, semax administration was associated with reduced body-weight loss, restoration of immune function (including natural killer cell activity and lymphocyte proliferation), and improvements in behavioural outcomes such as locomotor activity. These findings indicate potential benefits in the context of injury-related neurological and immune disruption. However, there are no human studies or broader replication of these findings, and the evidence base remains narrow. As such, while preliminary data are positive, there is no clinical evidence to support improved TBI outcomes in humans.

Semax and Stroke: Clinical and Experimental Evidence of Benefit

In contrast, semax has been more extensively studied in the context of ischemic stroke, with both clinical and experimental evidence suggesting beneficial effects. Clinical studies in patients with acute stroke report improved recovery of neurological function, particularly motor deficits, when semax is added to standard therapy. Additional findings include increased levels of brain-derived neurotrophic factor (BDNF), a protein associated with neuronal survival and plasticity, and improved functional outcomes such as performance on the Barthel Index (a measure of daily living ability). Immunological studies further suggest that semax may promote an anti-inflammatory profile following stroke.

Experimental models support these findings, showing that semax reduces inflammatory and cell-death signalling, preserves neuronal integrity, and decreases infarct size (the area of tissue damage caused by loss of blood supply). Improvements in cognitive and motor function have also been observed in animal models of both acute and chronic brain ischemia.

References 107-121.

Monoclonal Antibodies and Muscle Mass Preservation

> *"what we are gonna see come down the pipe very soon is kind of the older brother of peptides, the more complex form biologics called monoclonal antibodies that are specifically designed to inhibit the enzymes that break down muscle. So these are specifically called myostatin inhibitors. There are three that are coming down the pipeline. There is one called Bimagrumab (...) And then you have Garetosmab and Trevogrumab, which are two other compounds owned by a different pharmaceutical company that are all designed to maintain muscle, even in a significant caloric deficit."*

Monoclonal antibodies such as bimagrumab, trevogrumab, and garetosmab have been shown to increase or maintain muscle mass, particularly in experimental and early clinical settings. These agents act by inhibiting signalling pathways, such as myostatin and activin pathways, that normally suppress muscle growth, thereby promoting anabolic (muscle-building) effects.

Evidence from both animal and human studies supports their impact on lean body mass. Bimagrumab has been shown to increase muscle volume and fat-free mass in clinical populations, including individuals with low muscle mass, and to prevent muscle loss during weight reduction in experimental models. Similarly, early-phase human studies with trevogrumab, alone or in combination with garetosmab, demonstrate increases in muscle volume and overall lean mass alongside reductions in fat mass.

In the context of weight loss, particularly when combined with agents that promote fat reduction, these antibodies appear to help preserve or even increase lean mass. Preclinical studies and early translational research suggest that combining these therapies with weight-loss treatments may shift body composition towards greater fat loss while maintaining muscle.

However, while increases in muscle mass are consistently observed, improvements in functional outcomes, such as strength or physical performance, are less consistent. Overall, the evidence indicates that these monoclonal antibodies can maintain or increase muscle mass, although long-term clinical data and functional benefits remain to be fully established.

References 122-129.

Obesity Prevalence in the United States

> *“here in the United States (...) obesity rates are estimated to be 40 to 70%. Okay. Whether you, depending on what BMI cutoff you're using, okay. BMI is not perfect, but it is what it is.”*

Nationally representative data indicate that approximately 40% of adults in the United States meet the clinical definition of obesity, defined as a body mass index of 30 or higher. When overweight and obesity are combined, defined as a body mass index of 25 or higher, the proportion increases to approximately two-thirds to three-quarters of the adult population. Estimates based on alternative measures of body composition, such as body fat percentage, suggest that the prevalence of excess body fat may be higher than body mass index–based figures, with some analyses reporting substantially elevated rates, particularly among women.

References 130-135.

Tesamorelin and Visceral Fat Reduction

> *“Tesamorelin (...) a peptide that is commercially available right now (...) it'll help boost growth hormone and it happens to be uniquely good at stripping abdominal fat. Okay? Or visceral fat. But the thing is, is that you know, the moment you stop taking it for a brief period of time, well if you haven't changed anything about your lifestyle, you're gonna go right back to where you were.”*

Tesamorelin has been shown to significantly reduce visceral adipose tissue in individuals with HIV-associated abdominal fat accumulation. Randomised, placebo-controlled phase III trials demonstrate reductions in visceral fat of approximately 15–18% over a six-month period, with minimal change observed in placebo groups. These effects are sustained with continued treatment, with similar reductions maintained at twelve months in those who remain on therapy.

The reduction in visceral fat appears consistent across different patient subgroups, including those on varying antiretroviral regimens, and is largely specific to visceral fat, with little impact on subcutaneous fat. Discontinuation of treatment is associated with reaccumulation of visceral fat, indicating that the effect is dependent on ongoing use.

In addition to changes in body composition, reductions in visceral fat are associated with improvements in metabolic markers, including lipid profiles and adiponectin levels, without evidence of clinically meaningful long-term impairment in glucose regulation.

References 136-142.

Melanotan II and Skin Pigmentation with UV Exposure

> *"Melanotan II (...) you can administer this, alright, And it will actually end up giving you a deep tan in response to just a little bit of UV sun exposure (...)"*

Melanotan II has been shown to increase skin pigmentation through activation of melanocortin receptors, leading to increased eumelanin production. Clinical and observational evidence indicates that this effect can occur independently of sun exposure, with visible tanning reported following administration without deliberate ultraviolet exposure.

In contexts where ultraviolet exposure is present, reports describe pronounced overall skin darkening in individuals using melanotan II, suggesting that it may enhance pigmentation alongside sun exposure. However, this interaction has not been systematically quantified in controlled studies, and there is a lack of precise dose–response data examining its combined effects with ultraviolet radiation.

Available evidence therefore supports that melanotan II promotes skin pigmentation and may contribute to enhanced tanning in the presence of sun exposure, although this effect is not well characterised experimentally. Safety concerns are also noted in the literature, including changes in melanocytic lesions and potential risks associated with combined use and ultraviolet exposure, though these risks are not fully established.

References 143-149.

Retatrutide: Effects on Weight Loss and Liver Health

> *"the next blockbuster drug that Lily is going to come out with probably in the next couple of months is this guy called Retatrutide (...) by stimulating the glucagon receptor while simultaneously hitting GLP one and GIP, what we found is not only do patients lose an incredible amount of weight, but they also get the best improvements we've ever seen in their liver health"*

Retatrutide has been shown to produce substantial weight loss in clinical trials, with phase 2 studies reporting mean reductions of approximately 23–24% of body weight over 48 weeks at higher doses, compared with minimal changes in placebo groups. These findings are supported by multiple randomised controlled trials and meta-analyses, which demonstrate consistent, dose-dependent decreases in body weight, body mass index, and waist circumference, with a significant proportion of individuals achieving clinically meaningful weight loss.

In addition to its effects on body weight, retatrutide has been shown to markedly reduce liver fat in individuals with metabolic dysfunction–associated steatotic liver disease. In a phase 2 substudy, liver fat content decreased by up to approximately 82% over 24 weeks, with many participants achieving normalisation of liver fat levels. These improvements are closely associated with reductions in body weight, abdominal fat, and enhancements in metabolic markers such as insulin sensitivity and lipid regulation.

However, while reductions in liver fat are robust, there is currently no direct evidence demonstrating improvements in liver inflammation or fibrosis, as histological data are not yet available. Long-term outcomes and effects in more advanced liver disease remain uncertain, and ongoing studies are required to establish the durability and clinical significance of these findings.

References 150-158.

Epithalon: Telomerase Activity and Circadian Rhythm Regulation

> *"Epithalon (...) hope is that, you know, this is going to expand cell life. So Epithalon, the purpose of it is it works to enhance telomerase (...) we know that shorter telomeres are associated with aging, potentially worse health outcomes. Then there's an enzyme that can help heal or repair the telomere called telomeres. Epithalon helps encourage that and so some people are looking at that as being one of the fountain of youth compounds. I'm very skeptical as far as that goes, uh, but it does show some benefits when it comes to you know, healing parts of your brain that are, you know, associated with regulating your circadian rhythm."*

Epithalon has been shown to enhance telomerase activity in experimental settings, particularly in cell-based studies. Telomerase is an enzyme that helps maintain telomeres, which are protective caps at the ends of chromosomes that shorten as cells divide. In human somatic cells, such as fibroblasts (connective tissue cells), which typically do not express telomerase, epithalon has been found to increase production of the enzyme's catalytic subunit, activate telomerase, and promote telomere elongation.

These effects have also been associated with an extended capacity for cell division beyond the usual Hayflick limit, which refers to the normal number of times a cell can divide before it stops. Reviews of multiple studies report that epithalon can increase telomerase activity and lengthen telomeres in cultured human cells. However, these findings are limited to in vitro (laboratory-based) and ex vivo (outside the body) systems, and there is no robust evidence demonstrating similar effects in living humans.

Epithalon and Circadian Rhythm Regulation

Epithalon has been associated with markers of circadian rhythm regulation, primarily through its effects on melatonin and clock-related genes, although the evidence remains limited and largely experimental. In a human study, short-term administration of epithalon increased levels of 6-sulfatoxymelatonin, a metabolite of melatonin (a hormone that regulates sleep–wake cycles), indicating enhanced melatonin production by the pineal gland.

The same study reported changes in the expression of circadian genes, which are genes involved in maintaining the body's internal biological clock. Specifically, alterations were observed in genes such as Clock, Cry2, and Csnk1e in blood cells, suggesting that epithalon may influence the molecular mechanisms that regulate daily physiological rhythms.

Animal research provides further support for this association. In a rat model, epithalon restored normal daily fluctuations (diurnal rhythms) of dopamine, a neurotransmitter involved in hormonal regulation, within brain regions that control reproductive hormone release. These findings suggest a role in normalising circadian-related neuroendocrine signalling.

References 159-164.

Male Fertility Trends Over Time

> *"back in 1973, total modal sperm counts. So how many healthy swimming sperm do we have in each ejaculation is exponentially higher and more dense than what we're seeing today. And so what we're seeing is a progressive decline in male fertility over time (...)*
>
> *so the leading culprits are going to be yes, microplastics and environmental toxins. Okay. Things that are put in our environment that we have been exposed to that we can't help. But again, the biggest modifiable risk factor is insulin resistance and metabolic disease."*

Research provides mixed evidence regarding a progressive decline in male fertility over time, with findings varying depending on the measures used and the populations studied. Many large-scale analyses report substantial long-term declines in semen quality, particularly sperm concentration (the number of sperm per unit of semen) and total sperm count, with decreases of approximately 50–60% observed globally since the 1970s. However, trends are not uniform across regions, with some studies showing stable or even improving parameters in certain populations.

Age-related changes are more consistently observed. Increasing age in men is associated with declines in several aspects of semen quality, including motility (the ability of sperm to move effectively), morphology (sperm shape), and DNA integrity, although sperm concentration may remain relatively unchanged. Longitudinal data also indicate that, within individuals, semen quality can decline over time, potentially affecting reproductive potential.

At the population level, measures of fertility such as time to pregnancy and infertility rates show less consistent trends. Some data suggest a slight increase in global infertility prevalence, with projections indicating a rising contribution from male factors. However, large national studies have reported stable or even improved couple-level fertility outcomes over recent decades. Overall, while

there is strong evidence for declines in certain sperm parameters, a universal and consistent decline in male fertility is not definitively established.

Environmental and Metabolic Influences on Male Fertility

Research indicates that both environmental toxins and metabolic disease are associated with impaired male fertility, particularly through effects on semen quality and hormonal regulation. Exposure to environmental pollutants such as heavy metals, pesticides, endocrine-disrupting chemicals (substances that interfere with hormone systems), and air pollution has been linked to reductions in sperm count, motility, morphology, and increased DNA damage. These effects are often attributed to mechanisms such as oxidative stress, a process in which cellular damage is caused by reactive oxygen species, and disruption of endocrine signalling.

Metabolic conditions, including obesity, diabetes, and metabolic syndrome (a cluster of conditions involving insulin resistance, high blood pressure, and abnormal lipid levels), are also consistently associated with reduced semen quality and altered hormone levels, particularly lower testosterone. These conditions can impair fertility through multiple pathways, including inflammation, increased scrotal temperature, vascular damage, and further oxidative stress. Some evidence also links male obesity with reduced likelihood of achieving live birth.

While these factors are widely considered contributors to declining semen quality, their exact role in broader population-level declines in male fertility remains uncertain. The available evidence supports a significant association, but causality is difficult to establish definitively due to the complexity of interacting influences and limitations in long-term human studies

References 165-173.

Doping Prevalence in Olympic-Level Athletes

> *“well based off of the world, anti-doping agency's own data, potentially up to 40% of athletes that are competing at the Olympic level you have either are currently using or have used banned substances at some point in time.”*

Research on doping among elite and Olympic-level athletes shows that prevalence estimates vary widely depending on methodology, population, and definition of use. Direct self-report studies

typically produce lower estimates, with some surveys indicating that approximately 6–9% of elite athletes report using prohibited substances within a recent timeframe. However, these figures are generally considered underestimates due to reporting bias.

Indirect survey methods, designed to increase anonymity and reduce underreporting, often yield higher estimates. Some studies using these approaches report doping prevalence in the range of approximately 20–40% for current or recent use, with even higher figures for lifetime use in certain athlete populations. Broader systematic reviews highlight extreme variability, with reported prevalence ranging from near zero to over 70%, though most studies cluster at the lower end and are limited by methodological inconsistencies.

Overall, the evidence suggests that doping prevalence is likely higher than official testing data indicate, and estimates in the range of up to 40% are reported in some elite contexts. However, these figures are not consistent across studies and should be interpreted cautiously due to substantial variability and uncertainty in the underlying data.

References 174-177.

Estimated Prevalence of Erectile Dysfunction in the United States

> *"there are 30 million men with erectile dysfunction in the United States right now (...) And if you look at statistics, the oral medications are gonna fail in 15 to 40% of those men the first time they fail that."*

Erectile dysfunction is estimated to affect tens of millions of men in the United States, with commonly cited figures ranging from approximately 18 million to around 30 million men. Nationally representative survey data suggest that roughly 18–24% of adult men meet criteria for erectile dysfunction, depending on the definition and measurement used. Model-based estimates using more recent population data place the figure at approximately 30 million men, based on a median prevalence of around 27%. Overall, while estimates vary, the evidence consistently indicates that erectile dysfunction affects a substantial proportion of the male population in the United States.

Response Rates to First-Line Oral Treatments for Erectile Dysfunction

Approximately 30–35% of men with erectile dysfunction do not respond satisfactorily to first-line oral medications such as phosphodiesterase type 5 inhibitors (PDE5 inhibitors), which include drugs like sildenafil and tadalafil. These medications are effective in around 60–70% of cases, implying an initial nonresponse rate of roughly one-third of patients. Among those who do not respond initially, a proportion may improve with optimisation of treatment, including correct dosing, timing, and repeated attempts. However, even after such adjustments, a subset of men remain nonresponsive and may require alternative or combination therapies.

References 178-185.

TB-500 (Thymosin β4) and Blood Flow in Injured Tissue

> *"TB-500 (...) which is a modified fragment of Thymosin Beta-4. This improves blood flow to an injured area (...)*

Research indicates that thymosin β4, the peptide on which TB-500 is based, can enhance blood supply to injured tissue primarily through angiogenesis, the formation of new blood vessels. Experimental studies show that thymosin β4 promotes endothelial cell migration and vessel formation, and increases signalling pathways such as vascular endothelial growth factor (VEGF), which drives new blood vessel growth.

In animal models, this has been associated with increased blood perfusion (blood flow through tissue) at sites of injury. For example, imaging techniques have demonstrated greater perfusion in wound areas treated with thymosin β4-related compounds, alongside increased microvessel density in damaged tissue and improved tissue survival. Similar effects have been observed in cardiac injury models, where enhanced vessel formation supports improved local blood supply.

However, most of this evidence comes from preclinical studies, and human research is limited, focusing mainly on wound healing with indirect indicators of increased vascularisation rather than direct measurements of blood flow. Overall, the evidence supports that thymosin β4 can improve blood flow to injured areas in experimental settings, but confirmation in human clinical contexts remains limited.

References 186-194.

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