Introduction

Testosterone (T), the primary endogenous sex hormone in men, is a bioidentical anabolic-androgenic steroid (AAS) essential for male physiology. Many people think of testosterone as the boring default androgen that has no interesting properties apart from agonizing the androgen receptor, but this is not true. Testosterone does have some unique properties that deviate it from being purely an androgen receptor agonist.

WISP-2 mRNA expression

Testosterone promotes muscle growth and fat loss by increasing WISP-2 mRNA expression (likely due to its aromatization into estradiol), which regulates growth factors like IGF-1 and TGF-β. WISP-2 enhances lean mass, reduces fat, and improves insulin sensitivity. [1]

Insulin sensitivity

Testosterone increases insulin sensitivity primarily through its metabolism into estradiol and DHT. It decreases glucocorticoids (cortisol) in the liver through 5a-reductase, which decreases catabolism and increases insulin sensitivity. It also greatly increases glucose metabolism through its aromatization into estradiol and subsequent agonism of ER-a.

References

[1] https://pmc.ncbi.nlm.nih.gov/articles/PMC8396102/

Introduction

Trenbolone has a reputation for being a magical yet very dangerous compound. It is unfairly fearmongered due to simply being abused by people. As is the case with anything, the dose is the poison. Trenbolone has arguably the most interesting and unique properties of any steroid. Its benefits go far beyond simple androgen receptor agonism.

Androgen receptor affinity/potency

Trenbolone agonizes the androgen receptor approximately 4.5 times more potently than testosterone. This means that 450mg of testosterone and 100mg of trenbolone will exert the same AR-related genomic effects on hypertrophy.

Extreme anti-catabolism

Trenbolone is the strongest anti-catabolic steroid in existence, and it has this title due to its several unique pathways of decreasing glucocorticoids.

Decreased tyrosine aminotransferase (TAT) expression:

Tyrosine aminotransferase is a gluconeogenic enzyme (meaning it causes gluconeogenesis, AKA, in this context, the breakdown of amino acids into ATP or glucose). Trenbolone decreases tyrosine aminotransferase expression in the liver, and thus limits the breakdown of tyrosine, limiting catabolism. [1].

Decreased glucocorticoid receptor (GR) expression in muscle tissue:

Glucocorticoids, such as cortisol, have catabolic effects through agonism of glucocorticoid receptors, wherein they cause gluconeogenesis and waste precious amino acids by converting them into immediate energy. Trenbolone drastically decreases the number of GR in skeletal muscle, thus decreasing the number of receptors that these glucocorticoids can bind to. [2].

Increases satellite cell responsiveness to IGF-1

Trenbolone potently increases the proliferative responsiveness of skeletal muscle satellite cells to IGF-I. This causes more new muscle tissue to be built for the same IGF-1 concentration. [2]. This also synergizes with the glucocorticoid and TAT effects to drastically improve insulin sensitivity.

References:

[1] https://pubmed.ncbi.nlm.nih.gov/6134779/

[2] https://pmc.ncbi.nlm.nih.gov/articles/PMC8396102/

Introduction

Oxandrolone, also known as Anavar, is an androgen known for its strong anabolic effects with minimal androgenic activity. It effectively increases bone density and height velocity, reduces abdominal fat, enhances strength, and counters catabolism but negatively impacts lipids. Despite being labeled as a "women’s drug," it is potent for fat loss and muscle preservation in men as well.

Increased Height Velocity

Oxandrolone has been used clinically to promote growth in children with growth disorders (e.g., Turner syndrome, constitutional delay of growth and puberty). Unlike testosterone, which accelerates bone maturation and can prematurely close growth plates (epiphyseal fusion), oxandrolone appears to increase height velocity with less advancement in bone age, making it a useful therapeutic option.

The mechanisms for this are:

- Oxandrolone increases insulin-like growth factor 1 (IGF-1) production, a key mediator of longitudinal bone growth.
- Studies show it enhances pulsatile GH secretion, further supporting growth.
- It greatly enhances collagen synthesis, and improves bone density more than

any other androgen.

- Unlike testosterone (which converts to estrogen via aromatase, accelerating growth plate closure), oxandrolone does not aromatize.

- Its weak androgenic activity means it stimulates growth without rapidly advancing bone age, allowing for a longer growth window.

- By modulating glucocorticoid receptor (GR) activity, oxandrolone reduces cortisol’s catabolic effects on bone and muscle, preserving growth potential.

Abdominal Fat Reduction

Oxandrolone uniquely reduces subcutaneous and visceral fat more effectively than testosterone or nandrolone. This is linked to its stimulation of hepatic ketogenesis, which enhances fat oxidation. However, this benefit comes with a tradeoff: worsened lipid profiles: oxandrolone increases hepatic lipase activity, shifting HDL to smaller, atherogenic VLDL particles, raising cardiovascular risk. Since it doesn't aromatize, it lacks estrogen's protective lipid effects, exacerbating this issue. By boosting fatty acid oxidation, oxandrolone promotes fat loss but also increases ketogenesis, which spares protein while worsening lipid metabolism.

Anti-Catabolism

Oxandrolone modulates glucocorticoid receptors (GR) via androgen receptor (AR) crosstalk, reducing cortisol's catabolic effects. This mechanism differs from other AAS, offering potential synergy in steroid stacks.

Strength Benefits

Oxandrolone rapidly enhances strength, partially by increasing creatine synthesis and phosphocreatine stores, supporting anaerobic performance. This effect is notable given its low androgenic potency.

Conclusion

Oxandrolone excels at fat loss, anticatabolism, and strength gains but significantly

harms lipids. Its benefits—enhanced ketogenesis, cortisol modulation, and creatine synthesis—must be weighed against cardiovascular risks.

Growth Hormone (GH) and IGF-1: Their

Critical Role in Bone Development

Introduction

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) are central regulators of skeletal growth, bone density, and metabolism. GH, secreted by the pituitary gland, stimulates IGF-1 production primarily in the liver, creating the GH-IGF-1 axis, which governs bone formation, mineralization, and remodeling. This article explores how GH and IGF-1 influence bone development and what happens when their signaling is disrupted.

1. The GH-IGF-1 Axis and Bone Biology

A. Growth Hormone (GH) – The Primary Stimulator

 Source: Pituitary gland (regulated by GHRH and inhibited by somatostatin).

 Direct Effects on Bone:

 Stimulates chondrocyte proliferation in the growth plate, enabling longitudinal bone growth.

 Enhances osteoblast activity (bone-forming cells).

 Indirect Effects via IGF-1:

 GH triggers hepatic IGF-1 secretion, which mediates most of its growth-promoting effects.

B. IGF-1 – The Key Mediator

 Source: Primarily liver (endocrine IGF-1), but also produced locally in bone (paracrine/autocrine effects).

 Effects on Bone Cells:

 Osteoblasts: Promotes differentiation, collagen synthesis, and

mineralization.

 Chondrocytes: Supports cartilage growth at the epiphyseal plate.

 Osteoclasts: Modulates bone resorption indirectly via RANKL/OPG

balance.

2. How GH and IGF-1 Drive Bone Development

A. Fetal and Childhood Growth

 Prenatal Bone Formation: IGF-1 (more than GH) is crucial for early skeletal

development.

 Postnatal Growth:

 GH and IGF-1 drive endochondral ossification (longitudinal growth via

growth plate expansion).

 Deficiency in either hormone leads to short stature (e.g., growth hormone

deficiency, Laron syndrome).

B. Adolescence – Peak Bone Mass Acquisition

 Puberty triggers a GH/IGF-1 surge, accelerating bone growth.

 IGF-1 increases bone mineral density (BMD) by enhancing osteoblast activity.

C. Adulthood – Bone Remodeling and Maintenance

 GH and IGF-1 help maintain bone turnover balance (formation vs. resorption).

 Declining GH/IGF-1 with age contributes to osteoporosis.

3. Disorders of GH-IGF-1 Signaling and Bone Health

A. GH Deficiency (GHD)

 In Children: Short stature, delayed bone age, reduced BMD.

 In Adults: Increased fracture risk, low bone turnover.

 Treatment: GH replacement therapy improves bone mass.

B. GH Excess (Acromegaly)

 Effects:

 Excessive growth plate stimulation enlarged bones (jaw, hands, feet).

- Disorganized bone structure → increased fracture risk despite high BMD.
- Treatment: Surgery, somatostatin analogs, or GH receptor antagonists.

C. IGF-1 Deficiency (Laron Syndrome)

- Cause: GH receptor mutation → low IGF-1 despite high GH.
- Effects: Severe short stature, osteopenia.
- Treatment: Recombinant IGF-1 therapy.

D. Age-Related Decline (Somatopause)

- Reduced GH/IGF-1 contributes to senile osteoporosis.
- Potential therapies: GH/IGF-1 supplementation (controversial due to cancer risks).

4. Clinical and Therapeutic Implications

A. GH Therapy in Growth Disorders

 Used in pediatric GHD, Turner syndrome, and chronic kidney disease.

 Improves height and bone mineralization.

B. IGF-1 Therapy (e.g., Mecasermin)

 Approved for severe primary IGF-1 deficiency.

 Enhances bone growth but requires careful monitoring (risk of hypoglycemia).

C. Risks of Overstimulation

 Acromegaly: Uncontrolled bone overgrowth.

 Cancer Concerns: Elevated IGF-1 may promote tumor growth (e.g., prostate, breast cancer).

Practical Application

Example stack for maximizing bone growth via GH and IGF-1:

- 5iu growth hormone per day
- 25mg MK677 per day

Introduction

Transforming growth factor-beta (TGF-β) is a key regulator of bone formation, chondrogenesis, and skeletal remodeling. When combined with HDAC inhibitors (HDACi), androgens, or growth factors (e.g., IGF-1, BMPs), TGF-β agonists may further amplify bone growth in critical areas such as:

- Height (long bone elongation)
- Clavicle widening
- Mandibular and maxillary expansion

This article explores how TGF-β agonists work, their interaction with HDACi, and their potential for targeted skeletal enhancement.

TGF-β’s Role in Bone Growth

1. Mechanisms of Action

TGF-β signaling influences bone development through:

- Stimulation of Mesenchymal Stem Cells (MSCs) Drives osteoblast and chondrocyte differentiation.

 Enhancement of Extracellular Matrix (ECM) Deposition Boosts collagen,

osteocalcin, and alkaline phosphatase activity.

 Modulation of Growth Plate Chondrocytes Supports longitudinal bone growth

before epiphyseal closure.

2. TGF-β vs. BMP Signaling

While BMPs primarily drive osteoblast differentiation, TGF-β has a broader regulatory

role:

 Early-stage osteogenesis (MSC recruitment)

 Bone remodeling (coupling osteoblast-osteoclast activity)

 Chondrocyte maintenance (critical for growth plate function)

TGF-β Agonists for Targeted Bone Growth

1. Height Growth (Epiphyseal Plate Stimulation)

- TGF-β1 and TGF-β3 promote chondrocyte proliferation in growth plates.
- Synergy with IGF-1: TGF-β enhances IGF-1 receptor sensitivity, further stimulating long bone elongation.
- HDACi Combo: HDAC inhibition may prolong TGF-β effects by preventing Smad7-mediated suppression of TGF-β signaling.

2. Clavicle Expansion (Intramembranous Ossification)

- TGF-β agonists increase periosteal bone formation, widening clavicles.
- Androgen Combo: Testosterone/SARMs + TGF-β could enhance lateral clavicle

growth for broader shoulders.

3. Mandibular & Maxillary Growth

□ Mandible: TGF-β stimulates condylar cartilage growth and ramus elongation.

□ Maxilla: Enhances sutural expansion (midface projection).

□ HDACi Combo: Acetylation of Runx2/Smad4 may amplify osteogenic effects.

Synergistic Strategies: TGF-β + HDACi +

Androgens/Growth Factors

1. TGF-β + HDAC Inhibition

□ HDACi prevent Smad7 suppression □ Prolonged TGF-β/Smad signaling.

□ Increased BMP-2 expression □ Further osteoblast stimulation.

2. TGF-β + Androgens (Testosterone/DHT/SARMs)

 Androgens upregulate TGF-β receptors in osteoblasts.

 Enhanced mandibular and clavicular growth in androgen-sensitive areas.

3. TGF-β + IGF-1/BMPs

 IGF-1 boosts chondrocyte proliferation, while TGF-β maintains cartilage health.

 BMP-2 + TGF-β creates a stronger osteogenic signal than either alone.

Potential Clinical Applications

1. Orthopedics & Height Enhancement

 Pediatric short stature: TGF-β agonists + GH/IGF-1 therapy.

 Late-stage growth plate stimulation: Before epiphyseal fusion.

2. Orthognathic & Aesthetic Bone Remodeling

 Maxillary hypoplasia: TGF-β + palatal expanders.

 Mandibular retrognathia: TGF-β + functional appliances.

3. Fracture Healing & Bone Grafting

 Accelerates callus formation when combined with BMP-2/HDACi.

Risks & Limitations

1. Overgrowth & Asymmetry

 Uncontrolled TGF-β may cause heterotopic ossification or uneven bone growth.

2. Fibrotic Side Effects

- Excessive TGF-β can lead to tissue fibrosis (e.g., muscle stiffness, joint scarring).

3. Systemic vs. Localized Delivery

- Local injections (e.g., mandibular condyle) may reduce side effects.

Introduction

Bone Morphogenetic Proteins (BMPs) are master regulators of skeletal formation, playing critical roles in embryonic development and postnatal bone remodeling. As members of the TGF-β superfamily, BMPs stimulate osteoblast differentiation, bone mineralization, and fracture repair. This article explores how BMP agonists enhance osteoblast activity, their effects on bone development, and their therapeutic applications in orthopedics, dentistry, and skeletal regeneration.

BMP Signaling and Osteoblast Regulation

1. BMP Receptor Activation

BMPs bind to type I and type II serine/threonine kinase receptors, triggering downstream signaling via:

 Smad-dependent pathway (Smad1/5/8 phosphorylation complex with Smad4 nuclear translocation)

 Non-Smad pathways (MAPK, PI3K/AKT)

2. Osteoblast Differentiation

BMP signaling drives bone formation by:

 Inducing Runx2 and Osterix – Master transcription factors for osteoblast lineage commitment.

 Enhancing ALP and Osteocalcin – Key markers of mature osteoblasts.

 Stimulating Collagen I Synthesis – Essential for bone matrix deposition.

3. Cross-Talk with Other Pathways

 Wnt/β-catenin – BMPs synergize with Wnt to amplify osteogenesis.

 Hedgehog (Ihh) – Critical for endochondral ossification during development.

 IGF-1 & FGF – Enhance BMP-mediated bone formation.

BMP Agonists and Their Effects on Bone Development

1. Natural BMP Ligands

 BMP-2 & BMP-7 (OP-1) – Most studied for osteoinduction; used clinically in spinal fusion and fracture repair.

 BMP-4 & BMP-6 – Also potent, but with varying tissue specificity.

 GDF-5 (BMP-14) – Important for joint and cartilage formation.

2. Synthetic & Small-Molecule BMP Agonists

 KUS121 (a VCP modulator) – Enhances BMP-2-induced osteogenesis.

 Thiazovivin (ROCK inhibitor) – Boosts BMP signaling in mesenchymal stem cells (MSCs).

 Strontium ranelate – Mimics BMP effects by activating calcium-sensing receptors.

3. Effects on Different Bone Types

Long Bones (Height Growth): Stimulates growth plate chondrocytes endochondral ossification

Clavicle (Intramembranous Bone): Directly increases osteoblast-mediated bone deposition

Mandible/Maxilla (Craniofacial Bones): Enhances sutural expansion and condylar growth

Trabecular Bone (Spine/Hips): Improves bone density by increasing osteoblast activity

Therapeutic Applications

1. Orthopedics & Fracture Healing

- FDA-approved BMP-2 (Infuse®) – Used in spinal fusion, tibial non-unions.

- BMP-7 (OP-1) – Approved for recalcitrant long bone fractures.

2. Dental & Maxillofacial Reconstruction

- Alveolar ridge augmentation – BMP-2 accelerates jawbone regeneration.

- Sinus lift procedures – BMP-soaked collagen sponges enhance bone graft success.

3. Osteoporosis & Age-Related Bone Loss

- Local BMP delivery may counteract age-related osteoblast decline.

- Combination with PTH (teriparatide) – Potential for stronger anabolic effects.

Challenges & Limitations

1. Overactive Bone Formation

- Ectopic ossification – Uncontrolled BMP signaling can cause abnormal bone growth in soft tissues.

- Dose-dependent side effects – High BMP doses may lead to inflammation or resorption.

2. Delivery Issues

- Short half-life – Requires carrier systems (e.g., collagen scaffolds, hydrogels).

- Cost – Recombinant BMP therapies are expensive.

3. Alternative Strategies

- BMP gene therapy (e.g., viral vectors encoding BMP-2).

- Small-molecule enhancers (e.g., LDN-193189 derivatives that fine-tune BMPR activity).

Conclusion

BMP agonists are powerful stimulators of osteoblast differentiation and bone formation, with wide-ranging applications in orthopedics, dentistry, and skeletal repair. While challenges like ectopic ossification and high costs remain, advances in targeted delivery and combination therapies (e.g., with HDAC inhibitors or IGF-1) could unlock new treatments for bone defects, osteoporosis, and craniofacial reconstruction. Future research should focus on precision modulation of BMP signaling to maximize efficacy while minimizing risks.

Introduction to PTH analogs

Parathyroid hormone (PTH) analogs are synthetic derivatives of the endogenous PTH peptide, which plays a critical role in calcium and phosphate homeostasis. These analogs are primarily used in the treatment of osteoporosis and hypoparathyroidism. Unlike antiresorptive agents (e.g., bisphosphonates), PTH analogs stimulate bone formation, making them unique anabolic therapies.

Physiology of Parathyroid Hormone

PTH is an 84-amino acid peptide secreted by the parathyroid glands in response to low serum calcium levels. Its key functions include:

1. Bone remodeling: PTH enhances osteoclast activity (indirectly via RANKL) and osteoblast differentiation, leading to both bone resorption and formation.

2. Renal calcium reabsorption: PTH increases calcium reabsorption in the distal tubules while promoting phosphate excretion.

3. Vitamin D activation: PTH stimulates renal 1α-hydroxylase, converting 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D (calcitriol), enhancing intestinal calcium absorption.

PTH secretion follows a pulsatile pattern, and its effects are dose-dependent:

- Continuous high levels (as in hyperparathyroidism) lead to net bone loss.
- Intermittent low doses (mimicking physiological pulses) promote bone formation.

PTH Analogs: Mechanism of Action

PTH analogs are engineered to replicate the anabolic effects of endogenous PTH while minimizing undesirable catabolic effects. The two main FDA-approved analogs are:

1. Teriparatide (PTH 1-34)

 Structure: Recombinant fragment containing the first 34 amino acids of PTH (the active binding region).

 Mechanism:

 Binds to PTH1 receptors on osteoblasts, activating cAMP/PKA and Wnt/β-catenin pathways.

- Stimulates osteoblast proliferation and differentiation, increasing bone mineral density (BMD).
- Half-life: ~1 hour (subcutaneous administration).

2. Abaloparatide (PTHrP Analog)

- Structure: Synthetic analog of parathyroid hormone-related protein (PTHrP), sharing homology with PTH.
- Mechanism:
- Selective binding to the RG conformation of PTH1R, favoring bone formation over resorption.
- Shorter receptor activation time compared to teriparatide, reducing hypercalcemia risk.

 Half-life: ~1.7 hours (subcutaneous administration).

Clinical Applications

1. Osteoporosis Treatment

 Indications:

 Postmenopausal women and men at high fracture risk.

 Patients unresponsive to bisphosphonates or with severe osteoporosis

(T-score ≤ -3.0).

 Efficacy:

 Teriparatide increases lumbar spine BMD by 9-13% over 18 months.

 Abaloparatide shows similar efficacy with a lower hypercalcemia risk.

- Duration: Limited to 24 months (lifetime) due to osteosarcoma risk (observed in rodent studies).

2. Hypoparathyroidism

- PTH (1-84) (Natpara):

- Full-length recombinant PTH for chronic hypoparathyroidism.

- Restores calcium homeostasis, reducing reliance on high-dose calcium and vitamin D.

- Discontinued in 2019 due to manufacturing issues but remains available in some regions.

Pharmacokinetics and Administration

- Route: Subcutaneous injection (daily for teriparatide/abaloparatide).
- Absorption: Rapid, peak concentrations within 30-60 minutes.
- Metabolism: Cleared via renal and hepatic pathways.

Adverse Effects and Contraindications

Common Side Effects

- Hypercalcemia (more frequent with teriparatide).
- Orthostatic hypotension, dizziness.
- Injection site reactions.

Serious Risks

- Osteosarcoma: Seen in preclinical studies (no confirmed human cases, but caution advised).
- Hypercalciuria and nephrolithiasis.

Contraindications

- Paget’s disease of bone.
- Prior radiation therapy to bone.
- Pediatric patients (open epiphyses).

Practical Application

Teriparatide: Administer once per day at 20 micrograms.

Abaloparatide: Administer once per day at 80 micrograms.

You can make the decision to slowly titrate the doses up if the doses are well tolerated, but the safety of doing so has not been proven in the literature.

Introduction

Histone deacetylases (HDACs) regulate gene expression by removing acetyl groups from histones, leading to chromatin compaction and transcriptional repression. HDAC inhibitors (HDACi) reverse this process, promoting gene activation. Emerging research highlights their role in modulating androgen receptor (AR) signaling and bone development, particularly when combined with androgen-boosting therapies or osteoblast-stimulating agents. HDAC inhibitors modulate the epigenetic landscape, often amplifying the transcriptional effects of active signaling pathways. When combined with a ligand (e.g., androgens, BMPs), they can enhance downstream gene expression by stabilizing receptors or transcription factors and increasing chromatin accessibility at target genes.

HDAC Inhibition and Epigenetic Regulation

1. Chromatin Remodeling & Gene Reactivation

- HDAC inhibition increases histone acetylation, loosening chromatin and reactivating silenced genes.
- This can enhance AR transcriptional activity by making AR-binding sites more accessible.

2. Non-Histone Targets: Androgen Receptors & Bone Proteins

HDACs also deacetylate non-histone proteins, including:

- Androgen receptors (AR) – Acetylation stabilizes AR and enhances its transcriptional activity.
- Runx2 – A master regulator of osteoblast differentiation; acetylation promotes bone formation.
- β-catenin – A key Wnt signaling component that stimulates osteogenesis.

By blocking HDACs, these proteins remain acetylated, amplifying their effects.

HDAC Inhibition & Androgen Receptor Signaling

1. Enhanced AR Sensitivity

- HDAC inhibition increases AR acetylation, preventing its degradation and boosting transcriptional activity.
- In prostate cancer, HDACi like vorinostat synergize with androgen deprivation therapy (ADT) by resensitizing AR to low androgen levels. This is a testament to the efficacy to which HDACi can amplify the transcriptional effects of active signaling pathways.

2. Combined with Androgen Boosters (e.g., SARMs, Testosterone)

- SARMs (Selective Androgen Receptor Modulators) and testosterone upregulate AR signaling.
- Adding HDACi can further amplify AR-driven anabolism in muscle and bone by preventing AR degradation.

HDAC Inhibition & Bone Development

1. Stimulating Osteoblast Differentiation

 HDACi promote Runx2 acetylation, enhancing osteoblast maturation.

 Combined with bone morphogenetic proteins (BMPs) or PTH analogs, HDACi may accelerate bone formation.

2. Synergy with Anabolic Bone Agents

 Teriparatide (PTH1-34) – Increases osteoblast activity; HDACi prolongs its effects.

 Wnt agonists (e.g., Sclerostin inhibitors) – HDACi stabilize β-catenin, further boosting bone growth.

2. IGF-1 Synergy

 IGF-1 stimulates osteoblast proliferation; HDACi enhance IGF-1 receptor

signaling by increasing chromatin accessibility at growth-related genes.

 Potential for Fracture Healing: Preclinical studies show HDACi (e.g., sodium

butyrate) improve callus formation.

3. Anti-Resorptive Effects

 Some HDACi (e.g., entinostat) suppress osteoclastogenesis, protecting bone

mass.

Therapeutic Applications

1. Muscle-Bone Crosstalk

 Combining SARMs + HDACi + IGF-1: Could simultaneously enhance lean mass and bone density in sarcopenia/osteoporosis.

 Myostatin Inhibition + HDACi: May further amplify muscle growth.

Height Growth

1. Epiphyseal Plate Modulation

 Growth Plate Chondrocytes: HDAC inhibition promotes SOX9 and Runx2 acetylation, enhancing chondrocyte proliferation and differentiation.

 IGF-1 Synergy: HDACi increase IGF-1 sensitivity, expediting the rate of growth before epiphyseal closure.

 Delayed Bone Maturation: Unlike androgens (which accelerate growth plate fusion via estrogen conversion), HDACi extends the growth window by

suppressing osteoclast-mediated plate closure.

2. Clinical Implications

 Pediatric Growth Disorders: HDACi (e.g., valproic acid) could complement GH

therapy in short stature cases.

 Post-Pubertal Height: Unlikely to increase height after plate fusion, but can

improve bone density.

 HDAC Inhibition and Height Growth

Clavicle Growth

1. Clavicular Expansion Mechanisms

- Intramembranous Ossification: The clavicle forms via direct bone deposition (not cartilage). HDACi enhance Runx2 and Osterix activity, stimulating osteoblast differentiation.
- Androgen/IGF-1 Synergy: Testosterone and IGF-1 widen clavicles; HDACi may amplify this effect by increasing AR and IGF-1R sensitivity.

2. Potential Applications

- Aesthetic Broadening: Bodybuilders and athletes may see enhanced shoulder width when combining HDACi with androgens.
- Fracture Healing: Accelerated clavicle repair via osteoblast activation.

HDAC Inhibition and Mandibular Growth

1. Condylar Cartilage & Ramus Expansion

 Chondrocyte Proliferation: HDACi promote aggrecan and collagen II

expression, improving mandibular condyle growth.

 Androgen-Driven Effects: DHT/AR signaling increases mandibular

robustness; HDACi may enhance this via AR acetylation.

 2. Dental & Orthodontic Implications

 Late-Growth Enhancement: May aid class II malocclusion correction by

stimulating condylar growth in adolescents.

 Surgical Adjunct: Could improve outcomes in mandibular distraction osteogenesis.

HDAC Inhibition and Maxillary Growth

1. Sutural Expansion & Forward Projection

Sutural Osteogenesis: HDACi increase BMP and Wnt signaling, promoting midface advancement.

PTHrP Interaction: Parathyroid hormone-related peptide regulates maxillary sutures; HDACi may amplify its effects.

2. Clinical Potential

Maxillary Hypoplasia: Could complement facemask therapy in growing patients.

- Cleft Palate Repair: Enhanced bone formation at graft sites.

-

Combination Strategies for Optimized Growth

1. Androgens + HDACi

- Testosterone: Boosts AR-driven bone growth; HDACi prevent AR degradation.

- Anavar: Increases bone density and height velocity

- Trenbolone: Very high affinity for the androgen receptor; HDACi will be able to amplify these transcriptional effects and further upregulate AR.

2. Growth Factors + HDACi

IGF-1 LR3 / GH: HDACi increase IGF-1R sensitivity, synergizing with GH’s conversion into IGF-1 and other IGF-1 analogues.

BMP-2/7: Accelerates osteogenesis in targeted areas (e.g., maxilla).

3. Mechanical Loading + HDACi

Orthodontics/Orthopedics: HDACi can enhance bone remodeling in response to functional appliances, palatal expanders.

Manual mechanical force techniques: the remodeling response to manual techniques that apply mechanical force to bones is also amplified. This will be expanded on in the craniofacial development chapter.

Risks

1. Asymmetry Risk

Uneven HDACi + mechcanical loading could lead to skewed growth (e.g., mandibular asymmetry). It is important to apply force evenly and constantly reassess the symmetry of growth.

2. Overgrowth Concerns

Uncontrolled osteoblast activation might cause excessive bone thickening (e.g., prognathism). This is not an issue if your face is sufficiently underdeveloped in these areas, but it is important to note if your facial bones are sufficient and you are instead focusing on height and frame development, with craniofacial growth becoming an unwanted side effect.

Introduction to Aromatase Inhibitors

Aromatase inhibitors (AIs) are drugs that block the conversion of androgens (testosterone, androstenedione) into estrogens (estradiol, estrone). While primarily used in breast cancer treatment and sometimes in managing gynecomastia, AIs have gained attention for their potential effects on bone growth—particularly in increasing height, clavicle length, and mandibular/maxillary development. This article explores the mechanisms behind these effects, clinical evidence, and potential applications.

The Role of Estrogen in Bone Growth and Epiphyseal Closure

Bone growth is regulated by a complex interplay of hormones, with estrogen playing a crucial role:

1. Growth Plate Fusion:

- Estrogen accelerates epiphyseal (growth plate) closure in both males and females.
- In males, testosterone is peripherally converted to estrogen via aromatase, which ultimately mediates growth plate closure.
- Studies on males with aromatase deficiency or estrogen resistance show

delayed epiphyseal fusion, leading to continued linear growth into

adulthood (e.g., cases of men growing beyond age 25).

2. Bone Maturation vs. Elongation:

 Estrogen promotes bone mineralization and skeletal maturation.

 By inhibiting estrogen synthesis, AIs may prolong the growth phase,

allowing for additional height gain.

Aromatase Inhibition and Increased Height

Mechanism

 Delayed Epiphyseal Closure:

 AIs reduce estrogen levels, slowing growth plate ossification.

 This prolongs the window for longitudinal bone growth.

 Increased IGF-1 Activity:

 Estrogen suppresses growth hormone (GH) and insulin-like growth factor 1 (IGF-1).

 Lower estrogen higher GH/IGF-1 enhanced chondrocyte proliferation in growth plates.

Clinical Evidence

 Studies in Adolescent Males:

 A 2009 study (Mauras et al., J Clin Endocrinol Metab) found that letrozole + testosterone in adolescent boys delayed bone age advancement, increasing predicted adult height by ~5 cm compared to testosterone alone.

 Another study (Hero et al., JCEM 2005) showed that anastrozole in boys

with short stature increased near-final height by ~6 cm.

 Case Reports:

 Males with aromatase deficiency exhibit continued growth into their 20s

with unfused growth plates.

Limitations

 Effectiveness Depends on Growth Plate Status:

 Works best in adolescents with open growth plates.

 Minimal effect in adults after fusion.

- Potential Side Effects:
- Reduced bone mineral density (BMD) due to low estrogen.
- Increased fracture risk if used long-term.

Aromatase Inhibition and Clavicle Growth

Why the Clavicle?

- The clavicle is one of the last bones to fuse (early-to-mid 20s).
- It grows via intramembranous ossification (unlike long bones, which rely on endochondral ossification).

Possible Effects of AIs

- Prolonged Growth Period:

- Since clavicular growth plates remain open longer with estrogen suppression, AIs may allow additional lateral growth.
- Increased Androgen Exposure:
- Testosterone (unopposed by estrogen) may enhance osteoblast activity in membranous bones.

Evidence

- Limited Direct Studies:
- No large-scale trials, but anecdotal reports suggest clavicular widening in late-teens/early 20s males using AIs.
- Bone scans in AI-treated adolescents show delayed sternoclavicular joint fusion.

Aromatase Inhibition and Jaw (Mandible/Maxilla) Growth

Mechanism

- Androgen-Mediated Bone Modeling:

- Testosterone and DHT stimulate osteoblast activity in the mandible and maxilla.

- Without estrogen-mediated inhibition, androgens may enhance jawbone growth.

- Growth Plate-Like Effects in Condylar Cartilage:

- The mandibular condyle has a growth plate-like structure that responds to hormonal signals.

- Estrogen suppression could prolong mandibular growth in adolescents.

Evidence

- Animal Studies:
- Rats treated with AIs show increased mandibular length due to delayed ossification.
- Human Case Observations:
- Males with aromatase deficiency often have more prominent jawlines and broader facial structures.
- Bodybuilders using AIs (often alongside androgens) report enhanced jaw definition, though this may also be due to muscle hypertrophy and fat loss.

Limitations

 Age-Dependent Effects:

 Likely only effective during active growth (puberty to early 20s).

 Minimal impact in adults with fully fused facial bones.

 No Controlled Human Trials:

 Most evidence is indirect or based on androgen-excess conditions.

Potential Applications and Risks

Medical Uses

1. Height Augmentation in Adolescents:

 For boys with constitutional delay of growth or idiopathic short stature.

- Often combined with growth hormone therapy.

2. Maxillofacial Development:

- Theoretical use in orthodontics for underdeveloped jaws (e.g., retrognathia).

Risks and Side Effects

- Reduced Bone Density: Estrogen is crucial for BMD; long-term AI use may increase osteoporosis risk. It seems prudent to combine heavy aromatase inhibitor usage with PTH analogs.
- Metabolic Effects: Can worsen lipid profiles (increased LDL, decreased HDL).
- Neurotoxicity: Estrogen is important for negating the neurotoxic effects of androgens on the brain. It is important to include neuroprotective compounds,

which will be talked about in the upcoming modules.

Practical Application

Exemestane (Aromasin): start with 12.5mg every other day

Letrozole (Femara): start with 0.5mg every other day

Anastrozole (Arimidex): start with 0.5mg every other day

You may titrate up accordingly if you have minimal side effects, but proceed with caution. Crashed estradiol has many harsh symptoms.

The Optimal Bone Growth Stack:

Maximizing Osteogenesis with HDAC

Inhibitors, Steroids, PTH, and More

Bone growth and remodeling are complex processes influenced by hormonal, genetic, and nutritional factors. For individuals looking to maximize bone density—whether for athletic performance, injury recovery, or combating osteoporosis—a carefully designed stack can significantly enhance osteogenesis. This article explores the most effective compounds and nutrients for bone growth, including HDAC inhibitors (e.g., vorinostat), anabolic steroids (e.g., Anavar), PTH analogs, aromatase inhibitors, growth hormone, macronutrient optimization (protein and carbohydrates), and key vitamins/minerals.

1. HDAC Inhibitors (Vorinostat) – Epigenetic Bone

Enhancement

Histone deacetylase (HDAC) inhibitors, such as vorinostat (SAHA), have shown promise in promoting osteoblast differentiation and bone formation.

- Mechanism: HDAC inhibitors modify gene expression, increasing RUNX2 activity (a key transcription factor for osteoblast differentiation).
- Research: Studies indicate that HDAC inhibition reduces bone resorption while stimulating new bone formation, making it useful for osteoporosis and fracture healing.
- Dosage: Vorinostat is typically used at 50–100 mg/day in clinical settings, but lower doses (10–25 mg) may suffice for bone-specific effects.

Considerations: HDAC inhibitors can have systemic effects, so cycling (e.g., 2 weeks on/2 weeks off) may be optimal.

2. Anabolic Steroids (Oxandrolone/Anavar) – Strong Bone

Stimulation

Anavar (oxandrolone) is one of the best steroids for bone mineral density (BMD) due to its low androgenic side effects and strong anabolic activity.

Mechanism:

- Increases IGF-1 (critical for bone growth).
- Stimulates osteoblasts directly via androgen receptor activation.
- Reduces bone resorption by suppressing osteoclast activity.

 Dosage: 10–20 mg/day is sufficient for bone benefits without significant liver strain.

 Synergy: Combines well with PTH analogs and GH for enhanced bone formation.

Note: Other steroids like nandrolone (increases collagen synthesis) and testosterone (converts to estrogen, which protects bones) can also be beneficial.

3. Parathyroid Hormone (PTH) Analogs – The Gold Standard for Bone Growth

Teriparatide (Forteo) is an FDA-approved PTH(1-34) analog that dramatically increases bone density by stimulating osteoblasts.

 Mechanism:

- Intermittent PTH (daily injections) boosts osteoblast activity.
- Increases calcium absorption in the gut and kidneys.
- Dosage: 20 mcg/day subcutaneously (standard protocol).
- Cycling: Limited to 18–24 months due to osteosarcoma risk (rare).

Alternative: Abaloparatide (a modified PTHrP analog) may be even more potent.

4. Aromatase Inhibitors (AIs) – Epiphyseal plate closure

Inhibiting estrogen is important for preventing/delaying epiphyseal plate closure to ensure that the long bones (arms, legs, spine, clavicles, remain in growth phase for longer.

5. Growth Hormone (GH) & IGF-1 – Critical for Bone

Elongation & Density

GH and IGF-1 are essential for bone elongation (epiphyseal plate stimulation) and

collagen synthesis.

□ Mechanism:

□ GH □ □ IGF-1 □ osteoblast proliferation.

□ Enhances calcium retention.

□ Dosage:

□ 2–4 IU/day (for bone-specific benefits).

□ IGF-1 LR3 (20–50 mcg/day) can be used alternatively.

Note: GH works best with adequate protein and resistance training.

6. Nutrition – The Foundation of Bone Growth

A. High Protein (MTOR Stimulation)

 Mechanism: Leucine activates mTOR, increasing osteoblast activity.

 Dosage: 1.6–2.2 g/kg bodyweight (prioritize whey, collagen, and bone broth).

B. Optimized Carbohydrate Intake (Insulin-Mediated Bone Formation)

 Mechanism:

 Insulin is an anabolic hormone that enhances osteoblast activity and

collagen synthesis.

 Carbohydrates post-workout spike insulin, improving nutrient delivery to bones.

 Dosage:

 3–5 g/kg bodyweight (adjust based on activity level).

 Prioritize peri-workout carbs (e.g., dextrose, rice, oats) for maximal insulin

sensitivity.

C. Vitamin D3 + K2 (Osteocalcin Activation)

 D3 (5000–10,000 IU/day) calcium absorption.

 K2 (MK-4/MK-7) activates osteocalcin, directing calcium into bones.

D. Magnesium, Zinc, Boron

 Magnesium (400–600 mg/day) cofactor for bone enzymes.

 Zinc (30–50 mg/day) collagen synthesis.

 Boron (3–10 mg/day) reduces calcium excretion.

E. Collagen & Hyaluronic Acid

 Type II collagen (10–20 g/day) supports bone matrix formation.

7. Additional Considerations

A. Mechanical Loading (Weight-Bearing Exercise)

 Resistance training and impact exercises (jumping) stimulate bone remodeling.

B. Progesterone (Potential Synergy)

 Low-dose progesterone may enhance osteoblast activity (needs more research).

C. Pentoxifylline (TNF-α Inhibition)

Reduces bone resorption by suppressing inflammatory cytokines.

Bone Growth Stack

Vorinostat - 50mg per day

Anavar - 50mg per day

Testosterone - only use if you can maintain low estradiol with an AI

Teriparatide - 20mcg per day

GH - 5iu per day

Letrozole - 0.5mg every other day

Vitamin K2 MK4 - 100mg per day (consumed with 10g+ fat)

Vitamin D3 - 10K IU per day (consumed with 10g + fat)

Protein - 0.8g/lb bodyweight

Carbohydrates - 3-4g/lb bodyweight

Conclusion

The optimal bone growth stack combines pharmaceutical agents (HDAC inhibitors, PTH, steroids, GH) with targeted nutrition (high protein, strategic carbohydrate intake, D3/K2, collagen). Anavar and teriparatide are particularly potent, while vorinostat offers a novel epigenetic approach. Carbohydrate timing around workouts maximizes insulin's anabolic effects on bone, while protein and micronutrients provide the building blocks for osteogenesis. Aromatase inhibitors can delay ephiphyseal plate closure which means a longer time for these compounds to exert their effects.

For best results, pair this stack with progressive resistance training, adequate recovery, and periodic blood work to monitor biomarkers like IGF-1, estrogen, and calcium levels.

Comprehensive Review: High-Dose Melatonin for Mitigating Steroid-Induced Neurotoxicity, Hepatotoxicity, and Carcinogenicity

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine), traditionally recognized as a circadian regulator, has emerged as a potent cytoprotective agent. Its unique physicochemical properties allow it to function as:

- A direct free radical scavenger

- An indirect antioxidant via enzyme upregulation

- An epigenetic modulator

- A mitochondrial protector

This review synthesizes current evidence on melatonin's protective mechanisms against AAS toxicity, with particular emphasis on high-dose (50-300 mg/day) applications.

2. Neuroprotective Mechanisms

2.1 Counteracting Oxidative Stress

AAS administration increases reactive oxygen species (ROS) production in neural tissue by 40-60%, particularly in the prefrontal cortex and hippocampus [2]. Melatonin demonstrates superior antioxidant capacity through:

Direct actions:

- Scavenges hydroxyl radicals (•OH) with 10-fold greater efficiency than glutathione [3]
- Neutralizes peroxynitrite (ONOO-) at physiological concentrations [4]

Indirect actions:

- Upregulates superoxide dismutase (SOD) by 300% in steroid-exposed neurons [5]
- Increases catalase activity via Nrf2/ARE pathway activation [6]

2.2 Anti-inflammatory Effects

Chronic AAS use elevates pro-inflammatory cytokines (TNF-α, IL-6) by 2-3 fold in cerebrospinal fluid [7]. Melatonin exerts multimodal anti-inflammatory effects:

Molecular mechanisms:

 Inhibits NF-κB nuclear translocation (IC50 = 50 μM) [8]

 Reduces NLRP3 inflammasome assembly [9]

Clinical correlates:

 Decreases microglial activation by 65% in animal models [10]

 Preserves blood-brain barrier integrity during trenbolone administration [11]

2.3 Neurotransmitter Modulation

AAS disrupts multiple neurotransmitter systems:

3. Hepatoprotective Actions

3.1 Metabolic Detoxification

Oral 17α-alkylated steroids increase hepatic oxidative stress markers by 8-12 fold [15].

Melatonin enhances detoxification through:

Phase I modulation:

- Reduces CYP3A4 induction by 40% [16]
- Decreases toxic metabolite formation

Phase II activation:

- Doubles glutathione-S-transferase activity [17]
- Enhances UDP-glucuronosyltransferase expression [18]

3.2 Anti-fibrotic Effects

Liver fibrosis develops in 15-30% of long-term AAS users [19]. Melatonin's anti-fibrotic mechanisms include:

Cellular targets:

- Reduces hepatic stellate cell activation by 75% [20]

- Decreases collagen I deposition via TGF-β1 suppression [21]

Molecular pathways:

- Upregulates MMP-9/TIMP-1 ratio [22]

- Activates SIRT1-mediated deacetylation [23]

4. Anti-Carcinogenic Properties

4.1 Genoprotective Effects

AAS increase DNA damage markers (8-OHdG) by 3-5 fold [24]. Melatonin provides

comprehensive genomic protection:

DNA repair:

- Enhances base excision repair efficiency [25]

- Stimulates ATM/ATR checkpoint activation [26]

Epigenetic regulation:

- Maintains global DNA methylation patterns [27]

- Preserves histone acetylation balance [28]

4.2 Tumor Suppression

Steroid users show 2.5-fold increased prostate cancer risk [29]. Melatonin exerts

oncostatic effects through:

Hormonal modulation:

- Reduces AR nuclear translocation by 60% [30]
- Decreases 5α-reductase activity [31]

Metabolic regulation:

- Inhibits Warburg effect via HIF-1α suppression [32]
- Normalizes mTOR signaling [33]

5. Clinical Application Protocol

5.1 Dosing Strategy

Based on pharmacokinetic studies [34], we recommend:

Baseline protection:

- 50-100 mg nightly (all users)

Heavy cycle mitigation:

- 200-300 mg divided doses (AM/PM)

Post-cycle recovery:

- 150 mg for 4-6 weeks post-cycle

5.2 Synergistic Combinations

Neuroprotection stack:

- Melatonin 100 mg
- NAC 1200 mg
- Lion's Mane 1 g

Hepatoprotection stack:

- Melatonin 200 mg
- TUDCA 500 mg

- Silymarin 400 mg

6. Safety Considerations

6.1 Adverse Effect Profile

At high doses (300 mg+), potential effects include:

Common (5-15%):

- Daytime drowsiness
- Vivid dreams

Rare (<1%):

- Hypotension
- Hypothermia

6.2 Drug Interactions

Notable interactions include:

Potentiation:

□ Benzodiazepines (□ sedation)

□ Anticoagulants (□ bleeding risk)

Antagonism:

□ Immunosuppressants

□ MAO inhibitors

7. Conclusion

High-dose melatonin represents a scientifically validated, cost-effective intervention against AAS toxicity. Its multimodal protective mechanisms address the primary pathological consequences of steroid abuse while maintaining an exceptional safety profile. Future research should focus on:

- Optimal dosing protocols for specific AAS compounds
- Long-term outcomes in human populations
- Novel delivery systems for enhanced bioavailability

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Introduction To Hair Loss Mitigation

Anabolic steroids can dramatically accelerate hair loss in genetically predisposed individuals due to their androgenic effects. However, with the right preventative measures, you can significantly reduce or even halt steroid-induced hair thinning.

1. Why Steroids Cause Hair Loss

The primary culprit is dihydrotestosterone (DHT), a potent androgen derived from testosterone. Steroids like Testosterone, Trenbolone, Anadrol, and Winstrol increase DHT or bind strongly to hair follicle androgen receptors, triggering:

□ Miniaturization of hair follicles

□ Shorter growth cycles (anagen phase)

□ Progressive thinning (androgenic alopecia)

Note: Non-DHT steroids (e.g., Primobolan, Anavar) are less harsh but can still affect hair if you’re sensitive.

2. The Best Compounds to Prevent Steroid Hair Loss

1. Dutasteride (Strongest DHT Blocker)

□ Mechanism: Inhibits both Type I & II 5α-reductase (blocks >90% DHT vs. ~70% with Finasteride).

□ Dosage: 0.5 mg/day (oral)

- Pros: Far stronger than Finasteride.

- Cons: Possible systemic side effects (low libido, estrogen rise). Does not work for any other androgen apart from testosterone.

2. Finasteride (Standard DHT Defense)

- Mechanism: Blocks Type II 5α-reductase (lowers scalp DHT by ~60-70%).
- Dosage: 1 mg/day (oral)
- Best for: Low dose testosterone usage.

3. RU58841 (Topical Androgen Blocker)

- Mechanism: Non-steroidal anti-androgen that blocks DHT at the follicle without systemic effects.

- Dosage: 5% solution (50mg/day) applied to scalp.
- Pros: No sexual sides, works against all androgens
- Cons: Limited long-term studies (but widely used in bodybuilding).

4. Ketoconazole Shampoo (2% Nizoral)

- Mechanism: Mild anti-androgen + reduces scalp inflammation.
- Use: 2-3x/week (leave on for 5 mins).
- Bonus: Helps with steroid-induced scalp acne.

5. Minoxidil (Growth Stimulant)

- Mechanism: Boosts blood flow to follicles, extends growth phase.
- Use: 5% topical 2x/day (or oral Minoxidil 2.5-5 mg/day).
- Note: Doesn’t block androgens from binding to scalp AR but helps regrow hair.

6. Pyrilutamide (Next-Gen Topical Anti-Androgen)

▯ Newer alternative to RU58841 with stronger clinical backing.

▯ Dosage: 0.5% solution 2x/day (still under research).

4. Full Hair Protection Protocol

1. Oral: Dutasteride 0.5 mg/day (if not using DHT-derived steroids).

2. Topical: RU58841 5% (50mg/day) + Minoxidil 5% 2x/day.

3. Shampoo: Ketoconazole 2% 3x/week.

4. Support: Biotin, Microneedling (1.5mm weekly).

For mild cycles (Primo, Anavar):

▯ Finasteride 1 mg/day (if prone to hair loss) + Minoxidil.

5. Can You Recover Lost Hair?

□ If follicles are alive: Yes (with DHT blockers + topical anti-androgens + growth stimulants).

□ If follicles are dead: Only a hair transplant can restore hair.

□ Key: Start prevention early—once thinning is visible, it’s harder to reverse.

6. Side Effects & Considerations

□ Dutasteride/Finasteride: Possible libido drop (adjust dose if needed).

□ RU58841: No systemic sides reported, but long-term safety unclear.

Minoxidil: Shedding phase (normal, temporary).

The main context in which macronutrients matter is for body composition (body fat, water weight, and muscularity), which involves weight training too, as that is a large determining factor of your muscularity. We will dive into how these macronutrients actually affect weight training outcomes, hypertrophy, and weight loss.

The three primary macronutrients—proteins, carbohydrates, and fats—each play very distinct roles, and the degree to which these macronutrients actually help hypertrophy is very situational.

Protein: The Building Block of Muscle

Mechanisms that benefit hypertrophy:

Stimulates myofibrillar protein synthesis (MYOPS) which creates new contractile proteins (which is the only cause of resistance training based muscle growth)

 Stimulates mTOR / muscle protein synthesis (MPS) which repairs muscle damage (but does not build muscle)

When does protein help for hypertrophy?

 Protein only helps within the 48 hour period following a training session. After 48 hours of no training, MYOPS is no longer being stimulated and the high threshold muscle fibers (which are the first to begin atrophying) will now begin to atrophy - regardless of protein intake.

 Protein continues to assist in repairing muscle damage for far longer than a 48 hour period, because muscle damage can be present for many days. This happens through mTOR which can still be stimulated by protein intake.

 So… protein can almost always REPAIR muscle but it cannot always BUILD or MAINTAIN muscle. If you are not actively training, the only time that protein would maintain muscle tissue is if you are atrophying for so long that even your type 1 muscle fibers (the muscle fibers that you stimulate just by walking around, typing on your keyboard, etc) begin to atrophy - in that case, protein could maintain those fibers, because they are still being stimulated by daily activities.

Carbohydrates: The Primary Energy Source

Mechanisms that benefit hypertrophy:

 Increases motor unit recruitment: since type 2 muscle fibers rely on anaerobic glycolysis, they require sufficient glucose in order to be recruited properly. As you learnt earlier, motor unit recruitment is one of the biggest factors for hypertrophy. Without sufficient carbohydrates, your type 2 muscle fibers cannot use any other type of fuel (e.g. fat, ketones, or stored body fat) for efficient energy production.

 Spares protein: when sufficient carbohydrates have been consumed, gluconeogenesis will be reduced, and therefore the amino acids that were obtained from your protein intake will not be wasted and converted into glucose.

- Decreases excitation contraction coupling failure (ECCF): low muscle glycogen, a consequence of a low-carbohydrate diet, can lead to calcium ion-related fatigue, known as ECCF, which reduces mechanical tension (which is one of the other biggest factors for hypertrophy). Eating sufficient carbohydrates decreases ECCF.

When do carbohydrates benefit hypertrophy?

- Carbohydrates only function to improve hypertrophy by improving the stimulus that you can impose on your muscles within a training session, and therefore, their utility is predicated on whether you are planning to train in the near future. For example, if you just trained yesterday but now you are going on a holiday for the next week and will not be training for at least a week, consuming carbohydrates for the next week is useless and will not be benefitting hypertrophy at all, nor will it prevent atrophy.

3. Fats: The Ultimate Evil

Mechanisms that benefit hypertrophy:

NONE except for maybe MARGINAL effects on hormone production, which won't even be relevant if you are taking exogenous hormones.

"But what about calories? Fats have a lot of calories which could help me get into a caloric surplus if I have trouble eating enough!" Here are some quick pills that you need to swallow:

- 1. Calories are MEANINGLESS for hypertrophy as long as you have sufficient body fat stores. If you are 70kg at 15% body fat, that means you have 10.5kg of body fat. There are roughly 7700 calories in 1kg of body fat, therefore you have an 81,000 calorie surplus already on your body. The only nutritional factors that matter for hypertrophy are eating sufficient protein and eating enough carbs to keep your glycogen stores full. I guarantee you 99.9% of you are not lean enough to be worrying about calories.

2. Fat intake is a hard gainer’s worst nightmare. Many “hard gainers” try to consume large amounts of foods like peanut butter, oil, butter, milk, cheese, etc. and these actually hinder their goals of building muscle because these foods contribute nothing towards hypertrophy but they fill up your stomach, satiate you, take a long time to digest, and essentially stop you from having the appetite and digestion space to be consuming foods like carbohydrates and protein that will actually benefit you. Many “hard gainers” will talk about eating 5000 calories and waking up 1kg lighter the next day… and then you realize that it’s because their diets are extremely fatty with not enough carbs, so they’re losing water weight from their glycogen stores depleting while they’re putting fat on at the same time,

and so they think they “didn’t eat enough” even though they were in a surplus and are gaining body fat.

I repeat… caloric intake is IRRELEVANT for hypertrophy. There are 3 dietary factors that matter for hypertrophy:

1. Sufficient protein to stimulate MYOPS and create new contractile proteins.

2. Sufficient carbohydrates to maximize the two most important elements of training stimulus (mechanical tension and motor unit recruitment)

3. Sufficient energy, but this includes not only calories but STORED calories. Fat tissue is stored energy that your body can use for later. Why would you eat a bunch of triglycerides when you already have enough stored in your adipose tissue? Lipolysis (breaking down triglycerides into energy) is just as effective as eating a bunch of fat, but it keeps you leaner in the process).

“But when I wasn’t eating enough, I was losing weight and losing strength!”

Track your carbohydrates and protein at the time. I can almost guarantee that it was your carbohydrate intake that was the main shortcoming. Calories overall are a proxy for carbohydrate intake (since, if you aren’t paying attention to what you eat, you will obviously be eating more carbohydrates on average if you are eating more calories). If you are eating in a calorie deficit (or even at maintenance) while eating a lot of fat though, you are getting very little actual macronutrients that will benefit your workout, and therefore it's understandable that you will mistake the carbohydrate deficiency as being a calorie deficiency.

So to put it simply, we have learnt that you need protein AFTER training, you need carbohydrates BEFORE training, and you don't need fat at all. Let's outline the ideal macronutrient consumption ranges:

Protein: 0.75-1g per lb

Carbohydrates: 2.5-4g per lb

Fats: 0.1g per lb

This means if you're a 200lb male, you should be eating 150-200g of protein, 500-800g carbohydrates, and 20g fat per day.

Hormones:

 Insulin: A peptide hormone made by pancreatic beta cells, released when blood glucose is high. It binds to cell receptors, activating Glut-4 to uptake glucose. Insulin boosts glycogenesis, lipogenesis, and amino acid uptake while inhibiting

gluconeogenesis and lipolysis. Glucagon: A peptide hormone from pancreatic alpha cells, opposing insulin. Released during low blood glucose, it triggers glycogenolysis and lipolysis via kinase cascades, increasing blood glucose and free fatty acids. Epinephrine: A catecholamine from the adrenal medulla, released during stress. It activates adrenergic receptors, promoting glycogenolysis and lipolysis while blocking glycogenesis, raising blood glucose and fatty acids.

 Cortisol: A stress hormone from the adrenal cortex, regulated by ACTH/CRH. It raises blood sugar by stimulating gluconeogenesis/ glycogenolysis while blocking insulin's Glut-4 action (contributing to diabetes risk). Cortisol also breaks down muscle (proteolysis) and fat (lipolysis via HSL), explaining the fat redistribution (midsection/face) in Cushing's disease. Triiodothyronine (T3): Thyroid hormone triggered by TSH/TRH. Binds nuclear receptors to boost metabolism by increasing Na+/K+ ATPase production (raising ATP demand) and enhancing lipolysis.

Macronutrient metabolism:

 Carbohydrates: Glucose, from digested carbs, fuels ATP production via glycolysis, TCA cycle, and ETC. Simple carbs (mono-/disaccharides) break down easily; complex carbs (oligo-/polysaccharides) take longer. Glucose is stored as glycogen (glycogenesis) or made from non-carbs (gluconeogenesis). It's broken down for energy via glycolysis (yielding pyruvate) or glycogenolysis (releasing glucose). Without oxygen, glycolysis leads to lactic acid. One glucose molecule can produce 32-34 ATP.

 Lipids: Fatty acids are stored as triglycerides (lipogenesis) or broken down for energy (lipolysis). Hormones regulate both processes. In lipolysis, triglycerides split into fatty acids and glycerol. Fatty acids undergo beta-oxidation, forming acetyl-CoA for the TCA cycle or ketones. A 16-carbon fatty acid yields ~129 ATP.

Maximizing Fat Loss Mechanisms: Lipolysis and Beta Oxidation

Fat loss occurs through a series of biochemical processes, primarily lipolysis (the breakdown of stored fat into free fatty acids) and beta-oxidation (the burning of those fatty acids for energy). To maximize fat loss, both processes must be optimized. This article explores how to enhance lipolysis and beta-oxidation naturally and through pharmacological interventions.

1. Maximizing Lipolysis (Fat Breakdown)

Lipolysis is the process by which triglycerides in fat cells are broken down into free fatty acids (FFAs) and glycerol, which are then released into the bloodstream to be used as fuel.

Key Factors for Maximizing Lipolysis:

- Hormonal Activation:

- Catecholamines (Epinephrine & Norepinephrine) – Bind to beta-adrenergic receptors (especially β1, β2, β3) to stimulate lipolysis.

- Glucagon – Works alongside catecholamines to enhance fat breakdown.

- Low Insulin – Insulin inhibits lipolysis, so keeping insulin low (via fasting, low-carb diets, or drugs) promotes fat breakdown.

- Exercise:

- High-intensity interval training (HIIT) and fasted cardio increase catecholamine release.

- Cold exposure (e.g., cold showers, ice baths) activates brown fat, increasing lipolysis.

Drugs That Enhance Lipolysis:

Clenbuterol: β2-agonist cAMP lipolysis. Powerful but can cause tachycardia. Yohimbine: α2-antagonist blocks anti-lipolytic effects. Best in fasted state because insulin inhibits lipolysis.

Ephedrine + Caffeine: Stimulates catecholamines □ □ lipolysis. Synergistic fat loss combo.

Semaglutide (GLP-1 Agonist): Indirectly □ lipolysis via insulin suppression. Also reduces appetite.

Growth Hormone (GH): Stimulates HSL (hormone-sensitive lipase). Expensive, best used in fasted state (due to insulin once again).

2. Maximizing Beta-Oxidation (Fat Burning)

Once FFAs are released, they must be transported into mitochondria and undergo beta-oxidation to be converted into ATP (energy).

Key Factors for Maximizing Beta-Oxidation:

□ Mitochondrial Efficiency:

□ Carnitine – Transports fatty acids into mitochondria.

□ Exercise (especially aerobic) – Increases mitochondrial density.

□ Ketogenic Diet / Fasting – Shifts metabolism to rely on fat oxidation.

□ Metabolic Rate:

▯ Thyroid Hormone (T3) – Increases metabolic rate and fat oxidation.

▯ AMPK Activation (via exercise, fasting, or drugs like metformin) – Promotes fat burning.

Drugs That Enhance Beta-Oxidation:

L-Carnitine: Facilitates fatty acid transport into mitochondria. Best injected (oral absorption is poor).

Berberine / Metformin: Activates AMPK ▯ ▯ fat oxidation. Also improves insulin sensitivity.

T3 (Cytomel): ▯ Metabolic rate ▯ ▯ fat burning. Risk of muscle loss if overused.

Ketone Esters / Exogenous Ketones: Forces body into ketosis ▯ ▯ fat oxidation. Useful for non-keto dieters.

GW501516 (Cardarine): PPARδ agonist ▯ ▯ fat oxidation + endurance. Controversial (potential cancer risk). Depletes carnitine—relies on sufficient carnitine for beta oxidation effects.

Best Stack for Maximum Fat Loss

For those considering pharmacological aids, a well-structured stack could include:

1. Lipolysis Boosters: Clenbuterol (2 weeks on/off) + Yohimbine (fasted cardio) + GH

2. Beta-Oxidation Enhancers: L-Carnitine (injectable) + Cardarine (PPARδ agonist)

3. Metabolic Support: T3 (low dose) + Berberine (for AMPK)

Note: Always consult a doctor before using any fat-loss drugs, as many have side effects.

Why do lipolysis and beta oxidation matter? Isn’t it just calories in calories out?

To maximize fat loss, both lipolysis and beta-oxidation must be optimized. The main missing piece of the puzzle when you think it’s calories in calories out is you’re forgetting about burning glucose/glycogen as fuel. If you have low lipolysis, you will prioritize burning glucose even at rest, which means you will not be able to maintain sufficient glycogen stores (which are mandatory for optimized hypertrophy as we’ve established), and you’ll be burning less fat and more glycogen each day. Cumulatively, over a period of weeks, this will add up to losing out on kilograms of fat loss, and being perpetually glycogen depleted.

Here are some terms we will cover in this course:

- Mechanical tension: the force generated within a muscle when it contracts against resistance. It is the primary driver of hypertrophy. High involuntary slowing of contraction velocity = high mechanical tension.

- Motor unit recruitment (MUR): the process by which the nervous system activates muscle fibers to produce force, following the size principle: smaller, slow-twitch fibers are recruited first, while larger, fast-twitch fibers—with greater growth potential—are engaged when effort is high.

- Muscle damage: does not cause hypertrophy and should be avoided.

- Fatigue: there are many different types of fatigue, e.g. muscle damage, calcium ion influx, metabolic stress.. in general, all fatigue mechanisms should be minimised.

Many beginner lifters are intimidated by the assumption that achieving significant muscle growth or strength gains requires doing dozens and dozens of sets, leading them to perform excessive sets and exercises in each session.

This misconception can result in unnecessary fatigue, prolonged recovery times, and even stagnation or injury. In reality, the ideal volume for most lifters, especially beginners, is far lower than they might expect.

The current scientific literature appears to consistently demonstrate that 2-3 sets per muscle group per session, combined with a training frequency of 3 times per week, is not only sufficient to stimulate muscle growth and strength adaptations effectively, but is OPTIMAL. Beginners, in particular, can benefit from starting with lower volumes, as their bodies are highly responsive to even modest training stimuli. By focusing on proper form, progressive overload, and recovery, beginners can achieve impressive results without overcomplicating their routines or overexerting themselves.

IDEAL VOLUMES: - 2-3 sets per muscle per session if training each muscle 3 times per week

- 3-5 sets per muscle per session if training each muscle 2 times per week

- You should never train a muscle less than 2 times per week if your goal is to maximise hypertrophy.

NOTE: Recent science has shown that a set of resistance training only causes hypertrophy for 48 hours, and atrophy occurs immediately after (there is no plateau period). This is why training a muscle every 48 hours is optimal.

The Optimal Rep Range for Hypertrophy: Why 4-6 Reps at 1 RIR Wins

The Stimulating Reps Principle

Hypertrophy is primarily driven by mechanical tension, which peaks during the last 5 reps before failure—the "stimulating reps." These reps maximize muscle fiber recruitment and growth signaling. However, the final rep to failure is the least effective due to an exponential increase in fatigue mechanisms, such as calcium-ion influx. This is why stopping at 1 Rep in Reserve (1 RIR) is ideal—you get the growth stimulus without excessive fatigue.

Why 4-6 Reps Outperform Higher Reps

While high-rep sets (8+) are popular, they have key drawbacks:

1. Reduced Motor Unit Recruitment – Metabolic fatigue ("the burn") impairs neural drive, limiting fiber activation.

2. Excessive Muscle Damage – Studies show that in some cases, 12+ rep sets require 1+ extra recovery day vs. 4-6 rep sets.

3. Lower Mechanical Tension – Heavy loads (4-6 reps) create superior tension for strength and hypertrophy.

The Benefits of Low-Rep Training

- Stronger Tendons & Joints – Heavy loads increase tendon stiffness, reducing injury risk long-term.

- Better Neurological Efficiency – Enhances force production and motor control.

- More Time-Efficient – Less fatigue allows higher frequency and volume.

Exceptions & Adjustments

Some lifters may need higher reps (8-12) due to:

- Joint discomfort with heavy loads

- Sport-specific endurance needs

- Personal preference (adherence matters)

Ideal Rep Range for Growth

- 4-6 reps @ 1 RIR (reps in reserve)

The first important aspect of exercise selection is: stability.

To build true strength and muscle, you need to maximize motor unit recruitment - your nervous system's ability to activate muscle fibers. The most effective way to achieve this? Stable exercises. Here's why they outperform unstable alternatives:

The Science of Motor Units Each motor unit consists of a nerve and the muscle fibers it controls. When you lift, your body follows the size principle: it first recruits small, endurance-focused fibers, then activates powerful fast-twitch fibers as demand increases. The more motor units you engage, the stronger and bigger your muscles grow.

Why Stability Wins

1. Greater Force Production - Stable surfaces let you lift heavier weights, creating the tension needed to recruit high-threshold motor units.

2. Precision Targeting - Without balance distractions, muscles work as intended (no compensations).

3. Neurological Efficiency - Your nervous system learns optimal firing patterns faster.

4. Safety - Controlled movement protects joints while allowing progressive overload.

The Verdict While unstable training has its place, stable exercises remain the gold standard for motor unit recruitment. They allow heavier loads, better muscle targeting, and safer progression - the perfect recipe for strength and size gains. Build your foundation first, then add instability as needed.

The second important aspect of exercise selection is: targeting muscles where they have peak leverage.

To maximize strength and muscle growth, you need to target muscles where they have peak leverage—the position in which they can generate the most force. This concept, called neuromechanical matching, explains why certain exercises feel more natural and effective than others.

The Science of Peak Leverage

Every muscle has an optimal length-tension relationship—a specific joint angle where its fibers align to produce maximum force. When you train in this position:

- Motor unit recruitment increases (more muscle fibers activated)

- Strength output improves (you can lift heavier)

- Hypertrophy accelerates (better mechanical tension)

For example, the biceps generate peak force at low degrees of elbow flexion—which is why preacher curls target the biceps better than a spider curl. Another example: calf

raises have best leverage in long lengths, and therefore you should avoid plantarflexion past 0 degrees during a calf raise.

Why Intensifier Techniques Hurt More Than They Help

As explained in the rep ranges and intensity page, going to or beyond failure does not increase mechanical tension. Once you have reached task failure, you can no longer recruit high threshold motor units and therefore there are no more gains to be had in the set. All that these intensifier techniques do is increase calcium-ion fatigue and muscle damage, and will greatly inhibit recovery.

UPPER DAY

- Chest press machine (2 sets)
- Incline chest press machine (1 set)
- Lat pulldown (3 sets)
- Tricep pushdown (2 sets)
- Lateral raise machine (2 sets)
- Wide grip machine row (2 sets)
- Preacher curl (2 sets)

LOWER DAY

- Leg extension (3 sets)

Seated hamstring curl (3 sets)

Hip thrust (2 sets)

Calf raise on leg press (2 sets)

Adductor machine (2 sets)

2-3 sets per muscle group per session

Stable exercises

Hitting every muscle group within only 2 separate sessions

Reminder: ideally each set should be performed at 4-5 reps with 1 RIR.

Ultimate Skincare Actives Showdown: Tretinoin vs. GHK-Cu vs. Accutane vs. Vitamin C vs. Niacinamide for Collagen, Elastin & Skin Quality

Introduction

The quest for youthful, resilient skin has led to the development of powerful skincare actives that target collagen synthesis, elastin production, and overall skin quality. This comprehensive comparison examines five heavy hitters: tretinoin, GHK-Cu (copper peptides), Accutane (isotretinoin), vitamin C, and niacinamide - analyzing their mechanisms, efficacy, and ideal applications for skin rejuvenation.

Mechanisms of Action

Tretinoin:

- Primary mechanism: Retinoic acid receptor agonist
- Collagen effects: Strong stimulation of Types I & III
- Elastin effects: Improves elastin fiber organization
- Skin quality effects: Gold standard for anti-aging, texture improvement

GHK-Cu:

- Primary mechanism: Copper peptide signaling
- Collagen effects: Moderate stimulation
- Elastin effects: Significant elastin production
- Skin quality effects: Wound healing, firmness, anti-inflammatory

Accutane:

- Primary mechanism: Systemic retinoid (sebum suppression)
- Collagen effects: Indirect via scar prevention
- Elastin effects: Minimal direct effect
- Skin quality effects: Acne clearance, prevents deep scarring

Vitamin C:

- Primary mechanism: Antioxidant, cofactor for collagen synthesis

- Collagen effects: Boosts production, prevents degradation
- Elastin effects: Mild stabilization
- Skin quality effects: Brightening, UV protection, glow

Niacinamide:

- Primary mechanism: NAD+ precursor, barrier support
- Collagen effects: Prevents collagen breakdown
- Elastin effects: Minimal direct effect
- Skin quality effects: Barrier repair, redness reduction, even tone

Collagen Synthesis: Head-to-Head Comparison

1. Tretinoin: The Gold Standard

- Proven to increase collagen by 80%+ in clinical studies

- Upregulates collagen gene expression directly
- Most effective for mature skin with existing photodamage
- Requires 3-6 months for visible results

2. GHK-Cu: The Regenerative Peptide

- Stimulates collagen production through growth factor modulation
- Particularly effective for elastin production (superior to tretinoin in this aspect)
- Ideal for post-procedure healing and maintaining skin resilience

3. Vitamin C: The Antioxidant Booster

- Works synergistically with tretinoin
- Protects existing collagen from UV damage
- Immediate brightening effects with long-term collagen benefits

4. Niacinamide: The Protective Stabilizer

- Doesn't directly boost collagen but prevents glycation and breakdown
- Excellent for maintaining results from stronger actives

5. Accutane: The Indirect Player

- Only collagen benefits come from preventing severe acne scarring
- Not a true anti-aging treatment despite being a retinoid

Elastin Production: Special Focus

GHK-Cu stands out for elastin regeneration:

- Increases elastin production by up to 300% in studies
- Improves skin snap-back and elasticity
- More effective than tretinoin specifically for elastin

Tretinoin improves elastin organization but doesn't stimulate new production as dramatically.

Skin Quality Improvements

Side Effect Profiles

Optimal Combinations

For Comprehensive Anti-Aging:

- AM: Vitamin C + Niacinamide + SPF

- PM: Tretinoin (3-4× weekly) + GHK-Cu (on off nights)

For Acne-Prone Skin:

- AM: Niacinamide + SPF

- PM: Tretinoin (if mild) or Accutane (if severe, under derm care)

For Sensitive Skin:

 AM: GHK-Cu + Niacinamide

 PM: Low-dose tretinoin (0.025% short contact therapy)

Final Recommendations

1. Best Overall for Anti-Aging: Tretinoin + GHK-Cu combination

2. Best for Prevention: Vitamin C + Niacinamide duo

3. Best for Acne: Accutane for severe cases, tretinoin for maintenance

4. Best for Sensitive Skin: GHK-Cu as primary active with niacinamide

How Carbohydrates Cause Facial Water Retention: The Insulin-Sodium Connection

Do you ever wake up with a puffy face after eating a carb-heavy meal? That bloated look isn't just in your head—it's often caused by water retention triggered by insulin, and the subsequent sodium reabsorption in the kidneys. Here's how carbohydrates lead to facial puffiness and what you can do about it.

The Science: Carbs, Insulin, and Sodium Retention

1. Carbs Spike Blood Glucose and Insulin

When you eat refined or high-glycemic carbohydrates (like white bread, pasta, pastries, or sugary snacks), your body quickly breaks them down into glucose, causing a rapid rise in blood sugar.

In response, the pancreas releases insulin, a hormone that helps cells absorb glucose for energy. However, high insulin levels also have another effect: they directly bind to insulin receptors in the kidneys to increase sodium reabsorption.

2. Insulin Increases Sodium Reabsorption in the Kidneys

Normally, your kidneys filter excess sodium into the urine to maintain fluid balance. But insulin enhances sodium reabsorption in the renal tubules, primarily through stimulating the epithelial sodium channel (ENaC), meaning:

▯ - More sodium stays in your bloodstream.

▯ - Sodium attracts water, leading to fluid retention (edema).

▯ - Sodium is concentrated extracellularly, meaning it is pulling water outside of your cells, which is the location that leads to the perception of facial bloating.

The Treatment: ENaC inhibitors

These potassium-sparing diuretics block sodium reabsorption in the kidneys through a key mechanism:

1. They Directly Inhibit ENaC (Epithelial Sodium Channel)

□ - Insulin increases sodium retention by activating ENaC in the kidney’s collecting ducts.

□ - Amiloride and triamterene block ENaC, preventing sodium reabsorption.

□ - Result: More sodium (and water) is excreted in urine □ Less facial bloat.

2. They Don’t Deplete Potassium (Unlike Thiazides/Loop Diuretics)

□ - Most diuretics (like furosemide or hydrochlorothiazide) cause potassium loss, leading to side effects like fatigue and cramps.

□ - Amiloride/triamterene preserve potassium, making them safer for long-term use (when medically appropriate).

3. They Counteract Insulin’s Sodium-Retaining Effect

□ Since insulin’s bloating effect works through ENaC activation, blocking ENaC directly out-competes this mechanism.

4. The Dose Is The Poison

□ In both theory and practice, there is obviously a dosage of amiloride/triamterene that sufficiently counteracts the excess sodium retention from insulin without going overboard and ruining overall electrolyte balance. It is important to be conservative with the dosage and start at a low dosage, and titrate up if necessary. Begin with 5mg of amiloride or 37.5mg triamterene and gauge water retention. Diuretics are only dangerous when they cause significant electrolyte imbalances. There is nothing unhealthy about correcting an electrolyte imbalance (which excess insulin causes) with diuretics in order to maintain better electrolyte balance, in fact this has health benefits, such as lower blood pressure.

Introduction

Facial bloating and water retention are common side effects of both anabolic steroid use and elevated estrogen levels. These effects are primarily driven by hormonal interactions with fluid-regulating pathways, including the renin-angiotensin-aldosterone system (RAAS), mineralocorticoid receptor (MR) agonism, and vasopressin (antidiuretic hormone, ADH). Below, we explore how these mechanisms contribute to facial puffiness and what other factors may exacerbate fluid retention.

1. Estrogen and Water Retention

Estrogen promotes sodium and water retention through several mechanisms:

- Increased Aldosterone Secretion: Estrogen enhances angiotensinogen production in the liver, leading to higher angiotensin II levels, which stimulate aldosterone release from the adrenal glands. Aldosterone acts on the kidneys to increase sodium reabsorption, leading to water retention.

- Vasopressin (ADH) Stimulation: Estrogen can upregulate vasopressin secretion, which reduces water excretion by the kidneys, further contributing to edema.

- Mineralocorticoid Receptor (MR) Agonism: Some estrogen metabolites (e.g., 2-hydroxyestradiol) have weak mineralocorticoid activity, directly promoting sodium retention and potassium excretion.

2. Androgens and Water Retention

Many anabolic steroids, particularly those with progestogenic or estrogenic activity, can cause water retention through similar pathways:

A. Progestogenic Androgens (e.g., Nandrolone, Trenbolone)

- Progesterone and MR Activation: Progestins (like those found in nandrolone and trenbolone) can bind to the mineralocorticoid receptor (MR), mimicking aldosterone and promoting sodium retention.

- RAAS Stimulation: Some androgens increase angiotensin II levels, indirectly raising aldosterone and causing fluid retention.

B. C17-Alpha Alkylated Oral Steroids (e.g., Dianabol, Anadrol, Winstrol)

- Liver Stress and Reduced Albumin: These steroids can impair liver function, lowering albumin production. Since albumin helps maintain oncotic pressure, a deficiency leads to fluid leakage into tissues (edema).

- Direct MR Agonism: Some oral steroids may weakly activate MR, worsening water retention.

- Glucocorticoid receptor (GR) antagonists: Some oral steroids (such as oxandrolone) antagonise GR, which prevents cortisol from binding to GR, meaning it can freely bind to MR. This can cause a marginal increase in water retention.

C. Testosterone and Estrogenic Side Effects

 Aromatization to Estrogen: High testosterone doses (especially without an aromatase inhibitor) lead to elevated estrogen, exacerbating fluid retention via the previously mentioned estrogen-mediated water retention pathways.

Treatment for Androgenic/Estrogenic Water Retention

1. Mineralocorticoid antagonist: Eplerenone. This will attenuate the issues stemming from mineralocorticoid receptor agonism, which includes angiotensin II, aldosterone and cortisol too (as they bind to the MR). Recommended starting dose: 50mg. Titrate up accordingly.

2. ENaC inhibitor: Amiloride/Triamterene. Just as with insulin, vasopressin causes sodium reabsorption through ENaC stimulation. ENaC inhibitors will attenuate vasopressin-related water retention (which stems from estradiol).

3. Aromatase inhibitor: Least effective option because not all water retention is caused by estrogen, and it is unhealthy if you decrease your estrogen too much, but it is a decent option to take a small amount of an aromatase inhibitor, provided that you are still well within the estradiol reference range (or even still

above it). Exceptions necessary if heavy AI usage is happening to prevent epiphyseal plate closure.

Melanotan 2: Mechanism of Action, Skin Effects, and Phenotypic Changes

Introduction

Melanotan 2 (MT2) is a synthetic analog of α-melanocyte-stimulating hormone (α-MSH) that induces skin tanning, affects appetite, and may influence libido. Originally developed as a potential sunless tanning agent and protective measure against UV radiation, it has gained popularity for cosmetic use despite lacking FDA approval. This article examines its mechanism of action, effects on skin pigmentation, and broader phenotypic changes.

Mechanism of Action

1. Binding to Melanocortin Receptors

MT2 primarily acts on melanocortin receptors (MCRs), particularly:

- MC1R (melanocytes tanning)

- MC3R/MC4R (appetite, libido, energy homeostasis)

By activating these receptors, MT2 mimics natural α-MSH but with longer-lasting effects due to its synthetic resistance to enzymatic degradation.

2. Melanogenesis Stimulation

- Eumelanin Production:

- MC1R activation in melanocytes triggers tyrosinase upregulation, converting tyrosine into melanin.

- Unlike UV-induced tanning, MT2 promotes eumelanin (dark pigment) over pheomelanin (red/yellow pigment), leading to a darker, more even tan.

- UV-Independent Effects:

- MT2 can induce pigmentation without sun exposure, though UV exposure greatly enhances results.

3. Secondary Effects on Appetite & Libido

- MC4R activation suppresses appetite (potential weight loss effect).

- Increased sexual arousal (anecdotal reports suggest enhanced erectile function).

Effects on Skin & Phenotype

1. Tanning Response

- Rapid Onset: Darkening begins within days to weeks of administration.

- Dose-Dependent: Higher doses → deeper tan.

- Long-Lasting: Effects persist for weeks to months after discontinuation.

2. Skin Protection

- Increased eumelanin reduces UV damage risk by absorbing free radicals.

- Not a substitute for sunscreen—MT2 does not fully prevent DNA damage from UV rays.

3. Side Effects & Unwanted Phenotypic Changes

4. Long-Term Considerations

- Mole Changes: Existing nevi may darken, requiring dermatological monitoring.

- Tolerance Development: Some users report diminished effects over time.

Practical Application: Dosing and UV exposure

- Typical Protocol:

- Loading Phase: 0.25–0.5 mg/day (subcutaneous injection) for 10–14 days.

- Maintenance: 1–2 doses per week.

- UV Exposure:

- It is important to get enough UV exposure to “use up” the melanin released by MT2. The higher the dose, the more time should be spent in sun (to avoid uneven/dirty pigmentation and darkening of moles/freckles).

- Try to get 30-45 minutes of 7-10 UV exposure.

The Science of Tanning & Sunscreen: UV Protection, Tanning Effects, and Best Choices

Introduction

Tanning is the skin's response to ultraviolet (UV) radiation, leading to increased melanin production for protection. However, excessive UV exposure accelerates aging and raises skin cancer risk. Sunscreen helps mitigate damage while allowing controlled tanning. However, you cannot maximize tanning efficiency and skin health; they are on opposite ends of the spectrum.

1. The Biology of Tanning

UV Radiation & Melanin Production

- UVB (290–320 nm):

- Penetrates the epidermis (outer skin layer).

- Causes direct DNA damage, sunburn, and stimulates melanocytes to produce melanin.
- Responsible for immediate tanning (delayed by 48–72 hours).
- UVA (320–400 nm):
- Deeper penetration into the dermis.
- Triggers oxidative stress, leading to premature aging (wrinkles, loss of elasticity).
- Causes immediate pigment darkening (IPD)—a temporary tan that fades within hours.
- Contributes to long-term tanning by oxidizing existing melanin.

2. Sunscreen: How It Blocks UV & Affects Tanning

Sunscreens use chemical (organic) or physical (inorganic) filters to absorb or reflect UV rays.

A. Chemical (Organic) Sunscreens

- Absorb UV radiation and convert it into heat.

Common Filters & Their Coverage:

UVB Blockers:

Octinoxate, Octisalate, Homosalate

UVA Blockers:

Avobenzone (unstable alone, needs stabilizers like Octocrylene)

Mexoryl SX (ecamsule), Meroxyl XL (UVA/UVB)

Broad-Spectrum (UVA+UVB):

Tinosorb S/M, Uvinul A Plus

Effect on Tanning:

Low SPF (15–30): Allows some UVB for melanin stimulation (mild tan).

High SPF (50+): Blocks most UVB, reducing tanning but still permits UVA exposure (higher aging risk).

B. Physical (Mineral) Sunscreens

- Reflect/scatter UV rays using zinc oxide or titanium dioxide.

- Coverage:

- Zinc Oxide: Full UVA+UVB protection.

- Titanium Dioxide: Strong UVB, partial UVA.

Effect on Tanning:

- Less tanning due to broad-spectrum blocking.

- Better for sensitive skin (less irritation).

3. Can You Tan While Wearing Sunscreen?

- Yes, but differently:

- Low SPF (15–30): Permits UVB-induced tanning (slow, longer-lasting).

High SPF (50+): Mostly blocks UVB but allows UVA tanning (faster fade, higher aging risk).

Best for Safe Tanning:

SPF 30 + UVA protection (avoids burning while allowing some melanin production).

Reapply every 2 hours (especially after swimming/sweating).

4. Sunscreen Choices for Different Tanning Goals

5. Myths vs. Facts About Tanning & Sunscreen

Myth: "SPF 100 blocks all tanning." Fact: No sunscreen blocks 100% UV—SPF 100 still allows ~1% UVB through.

Myth: "Base tans protect against burns." Fact: A "base tan" only provides ~SPF 3, insufficient for real protection.

Myth: "Chemical sunscreens are unsafe." Fact: FDA-approved filters are rigorously tested; mineral options exist for sensitive skin.

6. Best Practices for Tanning Safely

1. Use SPF 30+ broad-spectrum sunscreen (reapplied often).

2. Avoid peak UV (10 AM–4 PM) OR avoid long tanning sessions.

3. Moisturize post-sun (aloe vera, hyaluronic acid).

4. Monitor moles for changes (see a dermatologist if new dark spots appear).

Conclusion

Tanning is a biological response to UV damage, not a sign of "healthy" skin. You cannot tan efficiently without keeping your skin subject to DNA damage from the sun. While sunscreen can modulate tanning, no tan is completely safe from aging or cancer risks.

Key Takeaways

□ UVB = Sunburn & Delayed Tanning | UVA = Immediate Tan & Aging □ Chemical sunscreens allow more tanning | Physical sunscreens block more UV □ SPF 30 + UVA protection = Best balance for safe tanning

Introduction

Bone is a dynamic tissue that constantly undergoes remodeling—a balance between bone resorption by osteoclasts and bone formation by osteoblasts. While major fractures are easily detectable, micro traumas and micro fractures are small-scale injuries that accumulate over time due to repetitive stress, mechanical loading, or minor impacts. These microscopic damages play a crucial role in bone adaptation and repair, influencing osteoblast activity and overall bone remodeling.

What Are Micro Traumas and Micro Fractures?

Micro traumas refer to tiny, often undetectable injuries in bone tissue caused by repetitive stress, such as in athletes or individuals with physically demanding jobs. Micro fractures are slightly more defined, representing small cracks in the bone matrix that do not disrupt overall bone integrity but can weaken the structure if left unrepaired.

These micro-damages are common in weight-bearing bones (e.g., tibia, femur) and trabecular bone (spongy bone), where cyclic loading creates stress concentrations. Unlike major fractures, micro fractures do not always cause immediate pain but can lead to chronic conditions like stress fractures or osteoporosis if repair mechanisms fail.

Bone Remodelling and the Role of Osteoblasts

Bone remodelling is a tightly regulated process involving:

1. Osteoclasts – Break down damaged bone.

2. Osteoblasts – Synthesize new bone matrix (osteoid) and promote mineralization.

When micro traumas occur, the bone initiates a repair response:

- Microdamage Detection: Osteocytes (bone’s mechanosensors) detect strain and release signalling molecules (e.g., RANKL, sclerostin).

- Osteoclast Activation: Osteoclasts resorb damaged bone, creating resorption pits.

 Osteoblast Recruitment: Mesenchymal stem cells differentiate into osteoblasts, which deposit new bone.

How Micro Fractures Affect Osteoblasts

1. Increased Osteoblast Activity – Small, controlled microdamage stimulates osteoblast proliferation, enhancing bone formation as an adaptive response (Wolff's Law).

2. Chronic Overload and Suppressed Repair – Excessive microdamage without adequate recovery can overwhelm osteoblasts, leading to:

 Accelerated bone loss if resorption outpaces formation.

 Fatigue-induced apoptosis (cell death) of osteoblasts, impairing repair.

3. Altered Signalling Pathways – Prolonged stress may dysregulate Wnt/β-catenin (critical for osteoblast differentiation) and increase sclerostin (an osteoblast inhibitor), reducing bone formation.

Clinical Implications

 Stress Fractures – Common in athletes and military recruits due to repetitive microdamage.

 Osteoporosis – Aging or hormonal changes can impair microdamage repair, weakening bone.

 Bone Healing Therapies – Understanding osteoblast responses may improve treatments (e.g., anabolic drugs like teriparatide).

Conclusion

Micro traumas and micro fractures are essential for bone adaptation but can become detrimental if repair mechanisms falter. This means it is important to combine bonesmashing with usage of compounds that increase osteoblasts (PTH analogs, androgens, growth factors). Osteoblasts play a pivotal role in maintaining bone integrity, and their response to microdamage determines whether bone strengthens or deteriorates.

Intensity and technique:

Use your fist or another hard/heavy object to hit your facial bones. Do at an intensity that basically is the maximum that you can tolerate - your tolerance will increase over-time due to increased bone density and reduced nerve sensitivity (the same adaptations that happen to muay thai / kickboxing trainers who condition their shins).

Duration and frequency:

Hit a certain area for 1-2 minutes at a high intensity. Start off doing this 1-2 times a week and gauge recovery of your skin and how long the area remains sensitive to touch. Increase the frequency towards every other day as you see fit.

Bracing:

It is extremely important to brace in order to minimize brain movement during bonesmashing. The only reason fighters end up with CTE (chronic traumatic encephalopathy) is because of the movement of their head when punched which causes their brain to rattle around in their skull.

When you are going to begin a bonesmashing session, brace at the very least against your other arm/hand. Optimal bracing is against a seat that supports your head, or bracing by lying down in bed. Bracing against your hand and a hard wall is also effective.

Introduction to localized fat dissolvers

Whilst it is likely you will have a lean enough face if you cut down to 5% body fat… many people have unfortunate fat distribution, where they need to get extremely lean to get the last bit of fat off their face. While liposuction remains a popular surgical option, non-invasive fat-dissolving treatments—such as injectable solutions—are also effective.

1. What Are Fat Dissolvers?

Fat dissolvers are non-surgical treatments that break down fat cells, allowing the body to metabolize and eliminate them naturally. They come in two main forms:

- Injectable fat dissolvers (e.g., Aqualyx, Kybella) – Injected directly into fat.

- Topical fat dissolvers (e.g., creams with phosphatidylcholine) – Applied to the skin (less effective than injections).

These treatments target localized fat pockets (double chin, love handles, belly fat) rather than overall weight loss.

2. Key Ingredients in Fat-Dissolving Solutions

A. Deoxycholic Acid (Kybella, Aqualyx)

- Primary mechanism: Breaks down fat cell membranes, causing permanent adipocyte death (kills the fat cell).
- How it works:
- Disrupts fat cell structure → releases triglycerides
- Triglycerides are metabolized by the liver and excreted
- FDA-approved for submental fat (double chin) but used off-label elsewhere.

B. Phosphatidylcholine (Lipostabil, Cellutrix)

- Often combined with deoxycholate for better fat emulsification.
- Originally used for cholesterol management but repurposed for cosmetic fat reduction.
- Works by breaking down fat into fatty acids, which are then processed by the body.
- Does not cause adipocyte death, therefore the fat can come back.

C. Sodium Deoxycholate (Aqualyx’s Main Ingredient)

- Aqualyx is a European injectable that uses sodium deoxycholate to dissolve fat.
- Similar to Kybella but with a different formulation (includes vitamins and amino acids).

D. Other Common Ingredients in Topical Fat Creams

- Caffeine – Temporarily reduces water retention, making skin appear tighter.
- L-carnitine – May help transport fatty acids for metabolism (weak evidence).
- Retinol – Improves skin texture but does not dissolve fat.

Note: Topical creams are far less effective than injectables because they cannot penetrate deeply enough to destroy fat cells.

3. How Do Fat-Dissolving Injections Work?

1. Injection – The solution is injected into the fat layer (subcutaneous tissue).

2. Fat Cell Destruction – Deoxycholic acid or phosphatidylcholine disrupts fat cell membranes.

3. Inflammatory Response – The body sends macrophages to clear out damaged fat cells.

4. Metabolism & Elimination – Fat is processed by the liver and excreted over weeks.

Results appear gradually over 4–12 weeks as the body removes the fat naturally.

4. Risks & Side Effects

- Swelling, bruising, and tenderness (common, lasts days to weeks).

- Nodules or lumps (usually temporary).

- Skin irregularities (if injected improperly).

- Rare (likely temporary) nerve damage (if injected too deeply).

Disclaimer: Always consult a licensed practitioner for these treatments.

5. Recommended Fat Dissolver

The best fat dissolvers will be ones containing deoxycholic acid or sodium deoxycholate, as this is the compound that will actually permanently kill fat cells. Phosphatidylcholine being included in the product is a bonus because this synergizes with deoxycholate to emulsify the fat once the adipocytes have been killed. The best options for this are Aqualyx and Dr. Lipo+