MUSCLE AS THE CURRENCY OF AGING

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MEDMASTERS 2024

DISCLOSURES

I am part-owner of Vitali Skincare, GHK-Cu-containing peptide skincare line

OBJECTIVES

Review the physiology of muscle contraction

Review unique needs and evaluation of endurance, bodybuilding, strength and weekend warrior athletes

Peptide Stacks for maintenance

Peptide Stacks for competition

INVALUABLES

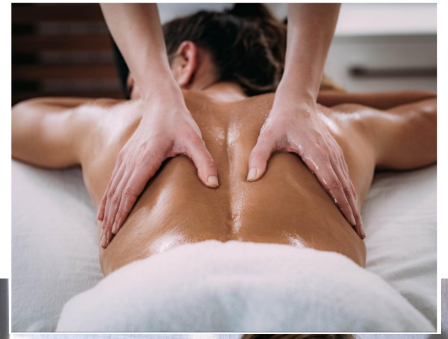


Table 1

Human equivalent dose calculation based on body surface area

Journal of Basic and Clinical Pharmacy JBCP Official Publication of Global Scientific Research Forum
Home Current issue Instructions Submit article

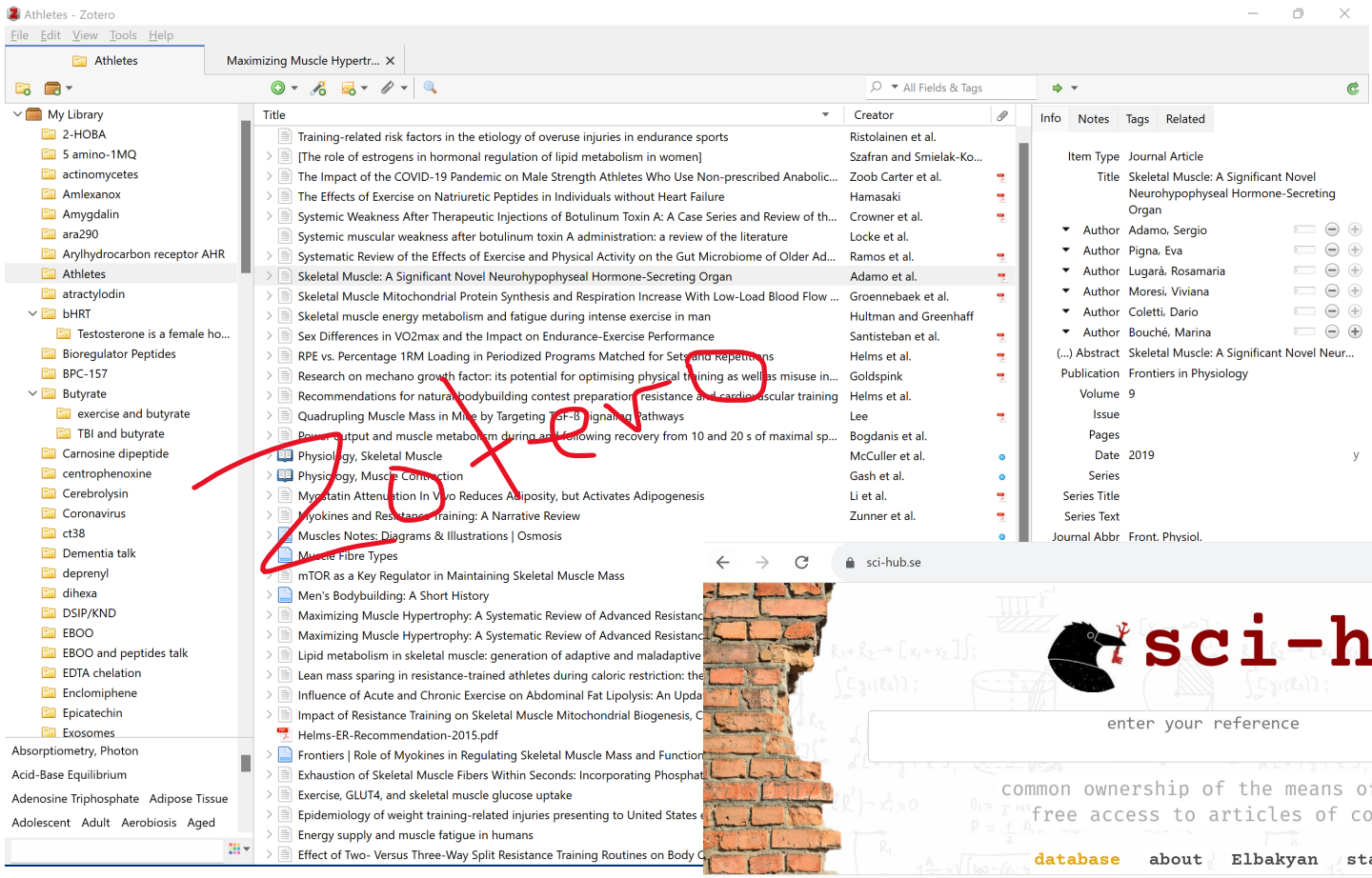
J Basic Clin Pharm. March 2016-May 2016; 7(2): 27–31.
doi: 10.4103/0976-0105.177703
PMCID: PMC4804402
PMID: 27057123

A simple practice guide for dose conversion between animals and human

Anroop B. Nair and Shery Jacob[1]

Species	Reference body weight (kg)	Working weight range (kg)	Body surface area (m^2)	To convert dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED in mg/kg, either	
					Divide animal dose by	Multiply animal dose by
Human	60	-	1.62	37	-	-
Mouse	0.02	0.011-0.034	0.007	3	12.3	0.081
Hamster	0.08	0.047-0.157	0.016	5	7.4	0.135
Rat	0.15	0.08-0.27	0.025	6	6.2	0.162
Ferret	0.30	0.16-0.54	0.043	7	5.3	0.189
Guinea pig	0.40	0.208-0.700	0.05	8	4.6	0.216
Rabbit	1.8	0.90-3.0	0.15	12	3.1	0.324
Dog	10	5-17	0.50	20	1.8	0.541
Monkeys (rhesus)	3	1.4-4.9	0.25	12	3.1	0.324
Marmoset	0.35	0.14-0.72	0.06	6	6.2	0.162
Squirrel monkey	0.60	0.29-0.97	0.08	7	5.3	0.189
Baboon	12	7-23	0.60	20	1.8	0.541
Micro pig	20	10-33	0.74	27	1.4	0.730
Mini pig	40	25-64	1.14	35	1.1	0.946

*Data obtained from FDA draft guidelines.[7] FDA: Food and Drug Administration, HED: Human equivalent dose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Epicatechin
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Acid-Base Equilibrium
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Training-related risk factors in the etiology of overuse injuries in endurance sports
Ristolainen et al.
[The role of estrogens in hormonal regulation of lipid metabolism in women]
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Skeletal muscle energy metabolism and fatigue during intense exercise in man
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Santisteban et al.
RPE vs. Percentage 1RM Loading in Periodized Programs Matched for Sets and Repetitions
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Recommendations for natural bodybuilding contest preparation: resistance and cardiovascular training
Helms et al.
Quadrupling Muscle Mass in Mice by Targeting TGF-β Signaling Pathways
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Power output and muscle metabolism during and following recovery from 10 and 20 s of maximal sp...
Bogdanis et al.
Physiology, Skeletal Muscle
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Li et al.
Myokines and Resistance Training: A Narrative Review
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mTOR as a Key Regulator in Maintaining Skeletal Muscle Mass
Men's Bodybuilding: A Short History
Maximizing Muscle Hypertrophy: A Systematic Review of Advanced Resistanc
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Impact of Resistance Training on Skeletal Muscle Mitochondrial Biogenesis, C
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Exhaustion of Skeletal Muscle Fibers Within Seconds: Incorporating Phosphat
Exercise, GLUT4, and skeletal muscle glucose uptake
Epidemiology of weight training-related injuries presenting to United States
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Author Adamo, Sergio
Author Pigna, Eva
Author Lugarà, Rosamaria
Author Moresi, Viviana
Author Coletti, Dario
Author Bouché, Marina
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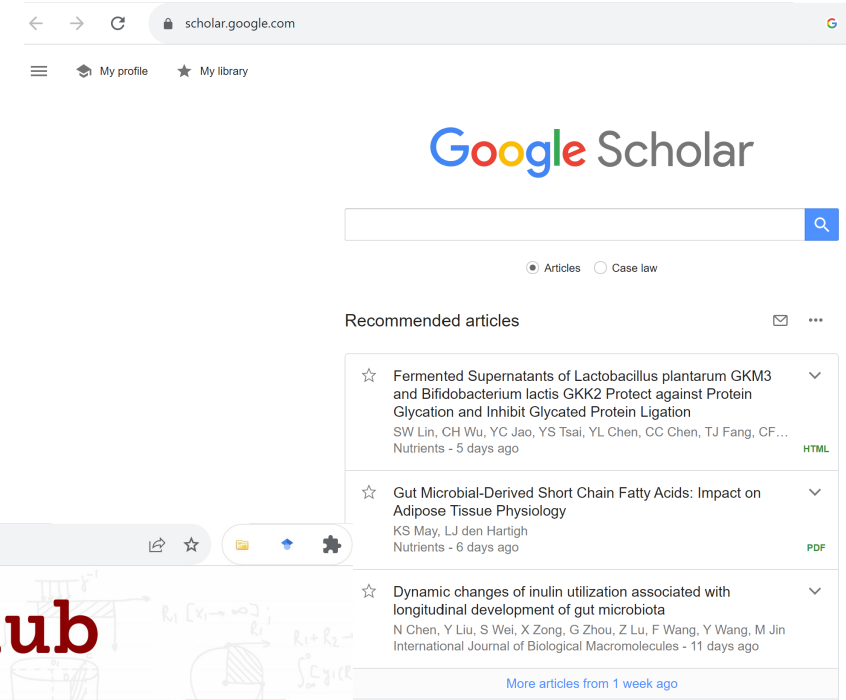
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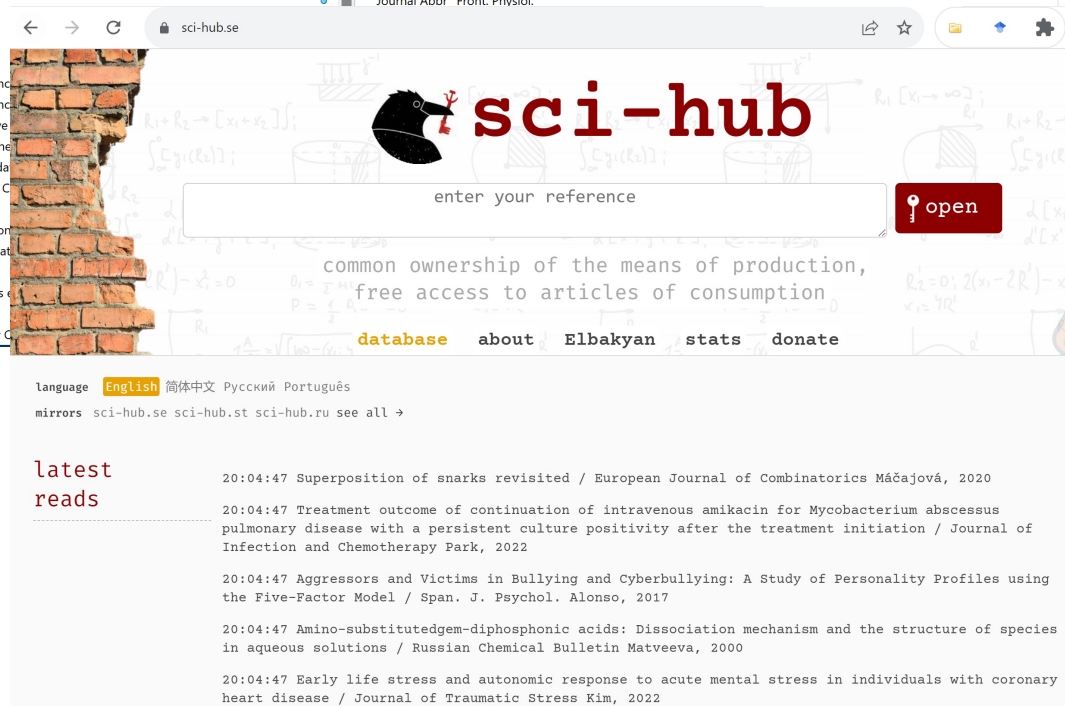
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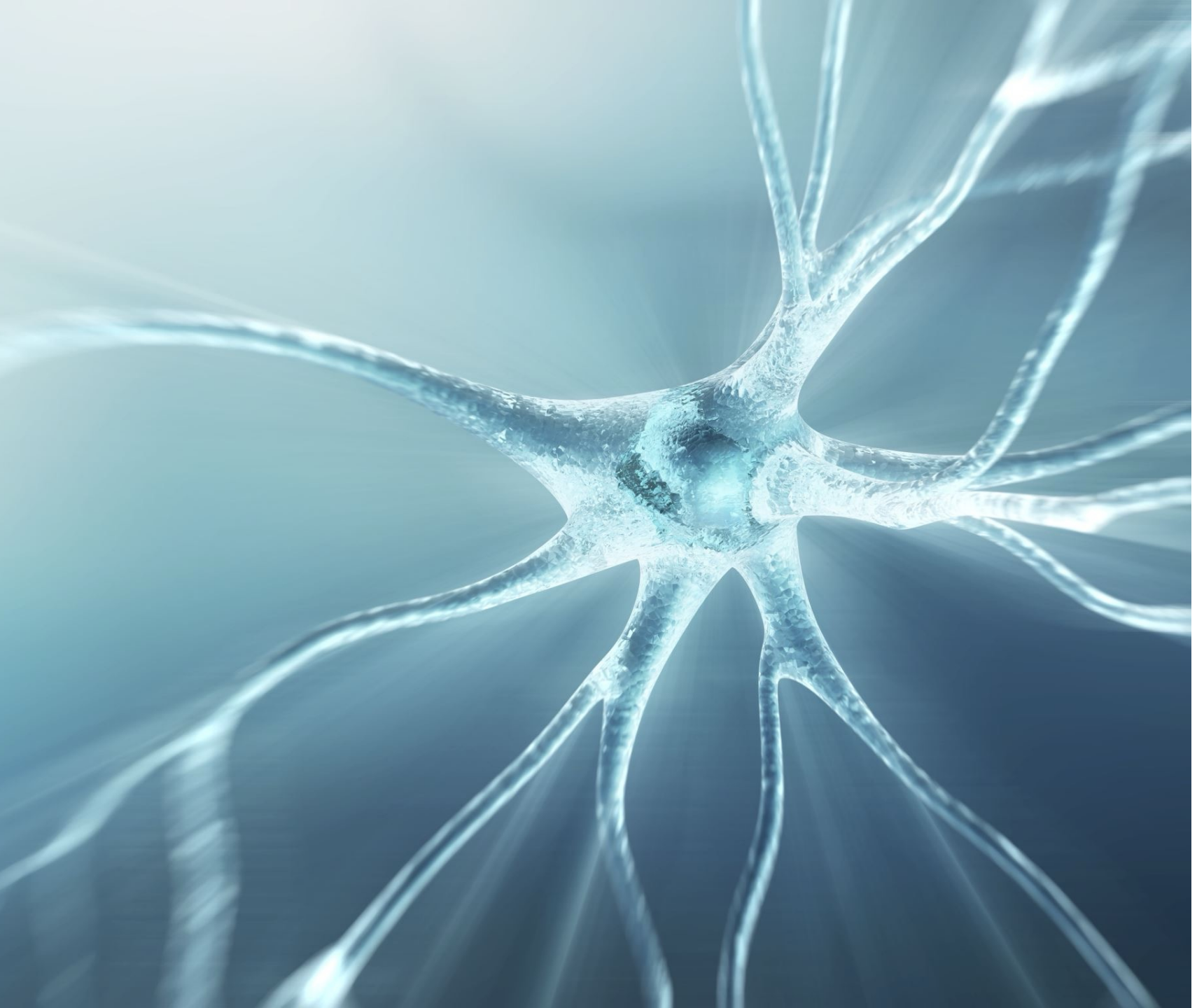


SOME PHYSIOLOGY

CONTRACTION GENERATION

The concentration of ATP in human quadriceps muscles is ~8 mM

During moderate knee extension exercise the average rate of ATP turnover in the quadriceps muscles is ~24 mM min−1

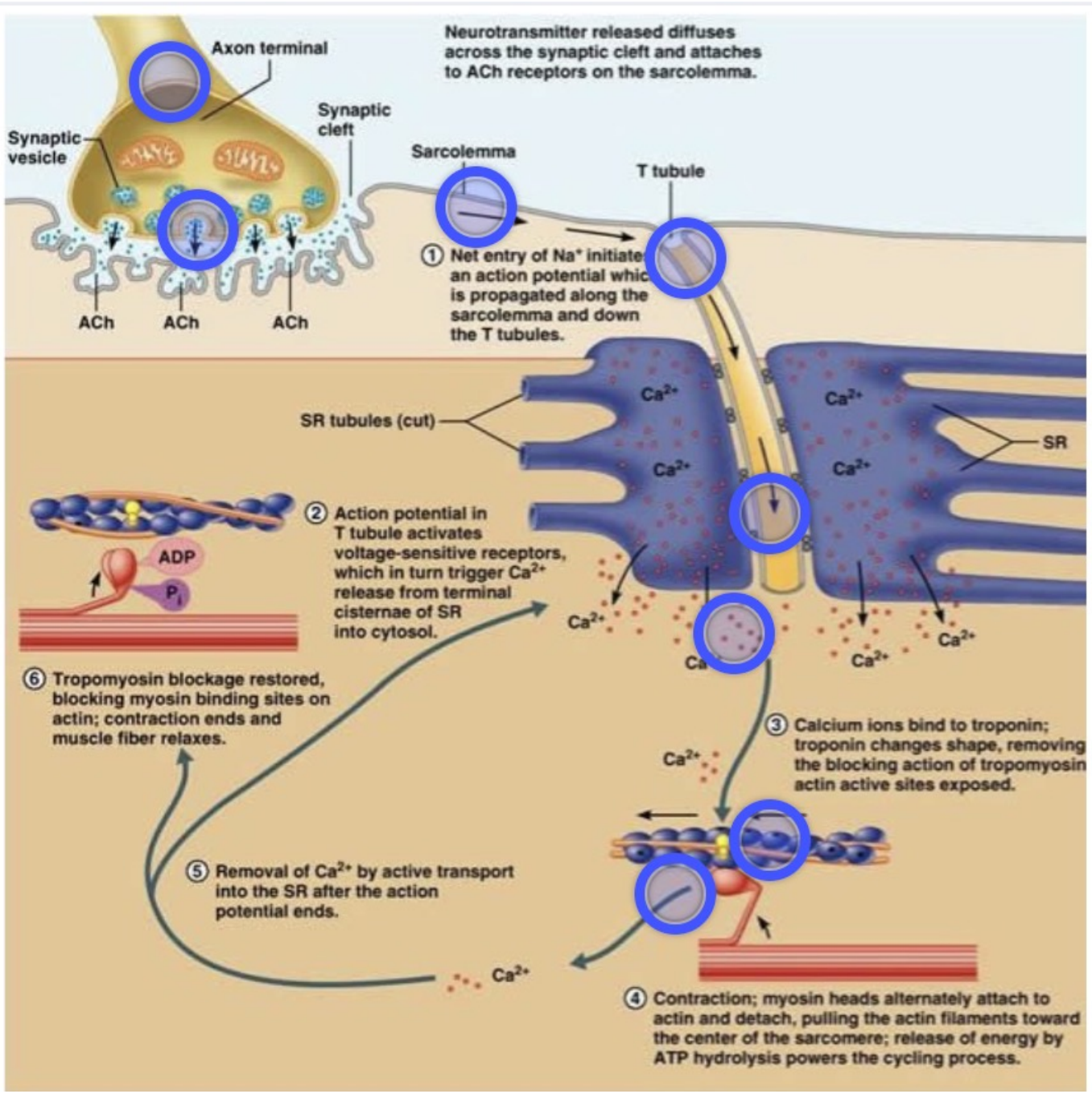
In the absence of any regeneration, ATP could only support 8/24=0.33 min or 20 s of such activity.

Consequently, a key aspect of the ability of muscles to perform for sustained periods, even at moderate levels, is the capacity to continually regenerate ATP.

Barclay, C. J. “Energy Demand and Supply in Human Skeletal Muscle.” *Journal of Muscle Research and Cell Motility* 38, no. 2 (April 2017): 143–55.

SKELETAL MUSCLE CONTRACTION

1. An action potential (AP) travels along a motor nerve to its endings on muscle fibers.
2. At each motor nerve ending, the nerve secretes **acetylcholine** (ACh)
3. ACh acts locally on the muscle fiber membrane to open ACh-gated cation channels
4. The opening of ACh-gated channels allows large quantities of **sodium (Na)** ions to diffuse to the interior of the muscle fiber membrane.
5. This depolarizes the muscle membrane, causing the sarcoplasmic reticulum (SR) to release large quantities of **calcium (Ca)** ions that have been stored within the SR.
6. The Ca ions change the conformation of **troponin**, releasing **tropomyosin** from **actin binding sites** for **myosin**
7. After a fraction of a second, the Ca ions are pumped back into the SR by a Ca-membrane pump and remain stored in the SR until a new muscle AP comes along.
8. The removal of Ca ions from the myofibrils causes muscle contraction to cease. (Gash 2022)


Axon terminal
Synaptic vesicle
Synaptic cleft
Neurotransmitter released diffuses across the synaptic cleft and attaches to ACh receptors on the sarcolemma.
Sarcolemma
T tubule
ACh
ACh
ACh
① Net entry of Na+ initiates an action potential which is propagated along the sarcolemma and down the T tubules.
SR tubules (cut)
SR
Ca2+
② Action potential in T tubule activates voltage-sensitive receptors, which in turn trigger Ca2+ release from terminal cisternae of SR into cytosol.
ADP
Pi
③ Calcium ions bind to troponin; troponin changes shape, removing the blocking action of tropomyosin actin active sites exposed.
④ Contraction; myosin heads alternately attach to actin and detach, pulling the actin filaments toward the center of the sarcomere; release of energy by ATP hydrolysis powers the cycling process.
⑤ Removal of Ca2+ by active transport into the SR after the action potential ends.
⑥ Tropomyosin blockage restored, blocking myosin binding sites on actin; contraction ends and muscle fiber relaxes.

BOTOX

Botulinum toxin, produced by *C. botulinum*, **inhibits ACh release from the presynaptic neuron at the NMJ**, preventing skeletal muscle excitation and causing flaccid paralysis.

Systemic weakness may occur, primarily in **younger women** using **higher doses** such as for detrusor instability or spasticity

Crowner, B. Racette. “Systemic Weakness After Therapeutic Injections of Botulinum Toxin A: A Case Series and Review of the Literature.” *Clinical Neuropharmacology* 33, no. 5 (2010): 243–47.

Locke, J. “Systemic Muscular Weakness after Botulinum Toxin A Administration: A Review of the Literature.” *Drugs & Therapy Perspectives* 37, no. 7 (July 1, 2021): 315–27.

GLUT4

Gene SLC2A4

Glucose transporter which translocates from intracellular storage depots to the plasma membrane and T-tubules upon muscle contraction

Expressed most abundantly in skeletal muscle (and adipose and cardiac muscle)

Skeletal muscle GLUT4 level correlates with the capacity for glucose uptake during very intense exercise

Exercise training is the most potent stimulus to increase skeletal muscle GLUT4 expression

GLUT4 levels are generally associated with a higher muscle oxidative capacity

Increased skeletal muscle GLUT4 expression would also facilitate postexercise glucose uptake and glycogen storage

MUSCLE CONTRACTION AND GLUT-4

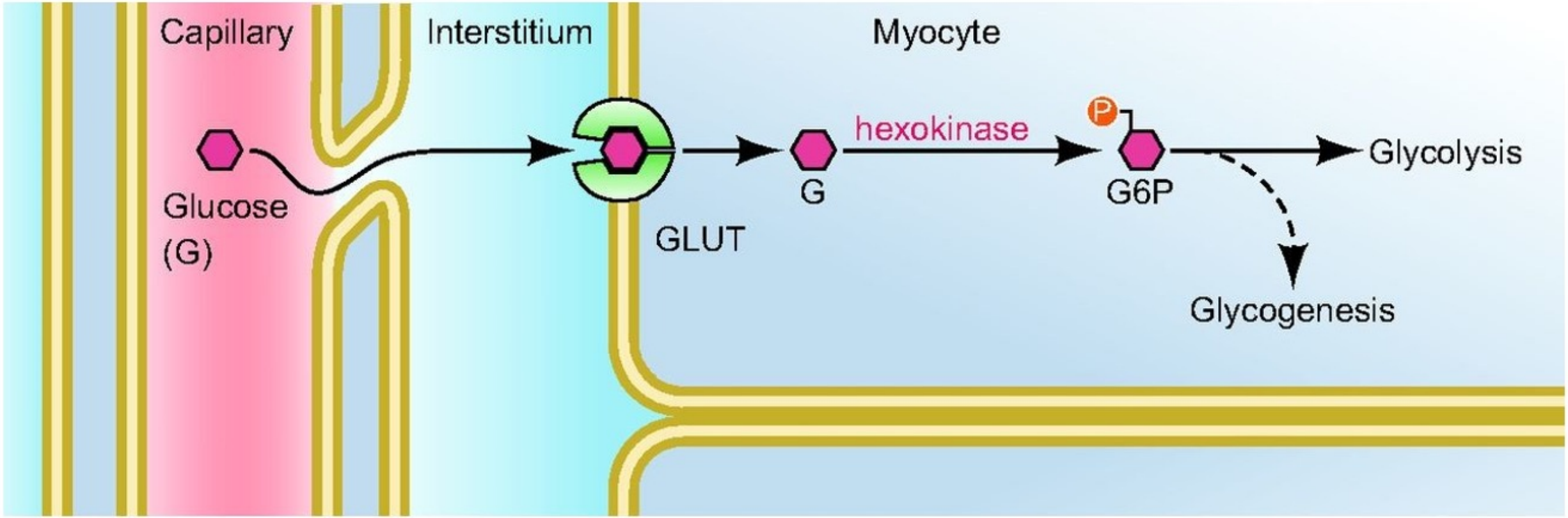
Glucose uptake by contracting skeletal muscle **depends on the presence of GLUT4 in the surface membrane** (sarcolemma and t tubules) and an inward diffusion gradient for glucose.

The vast majority of muscle **GLUT4 resides within intracellular storage** sites, so at **rest, glucose transport is rate-limiting**.

With **exercise, glucose phosphorylation becomes rate- limiting**, especially at high exercise intensities

Increased **blood flow** (20%), recruitment of capillaries increases the surface area of glucose uptake

With prolonged exercise, as the liver becomes depleted of glycogen and gluconeogenesis is unable to fully compensate, liver glucose output is reduced, and hypoglycemia can limit muscle glucose uptake (Richter 2013)



SUPPLY
- Perfusion
- Blood glucose concentration

TRANSPORT
- Surface membrane GLUT abundance
- Glucose gradient
- GLUT activity

METABOLISM
- Hexokinase activity
- Substrate flux

GLUT4 UPREGULATED

Magnesium (Solaimani 2014)

Vanadium (Sharfalddin 2022)

Berberine (Mi 2019)

GH/IGF-1/GHS (Sertie 2014)

MOTS-c (Bhullar 2022)

Oleanolic acid and other triterpines (Dev 2017)

Fenbendazole inhibits (Dogra 2018)

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Sharfalddin, A. “Therapeutic Properties of Vanadium Complexes.” *Inorganics* 10, no. 12 (December 2022): 244.

Solaimani, Ha. “Modulation of GLUT4 Expression by Oral Administration of Mg2+ to Control Sugar Levels in STZ-Induced Diabetic Rats.” *Canadian Journal of Physiology and Pharmacology* 92, no. 6 (June 2014): 438–44.

CREATINE PHOSPHATE AND MUSCLE CONTRACTION

Muscle fatigue: the decline in generable force level over time is 80% due to inability of muscle to provide energy through metabolic activity and the accumulation of inorganic phosphates (P, ADP)

First mechanism for ATP generation within the muscle is the transfer of a phosphate group from **creatine phosphate to ADP**

After 2 minute rest, muscle pH does not change, but creatine phosphate is resynthesized 80%

Rockenfeller, R. “Exhaustion of Skeletal Muscle Fibers Within Seconds: Incorporating Phosphate Kinetics Into a Hill-Type Model.” *Frontiers in Physiology* 11 (2020).

Bogdanis, G. “Power Output and Muscle Metabolism during and Following Recovery from 10 and 20 s of Maximal Sprint Exercise in Humans.” *Acta Physiologica Scandinavica* 163, no. 3 (July 1998): 261–72

LIPID METABOLISM AND MUSCLE CONTRACTION

Low to moderate intensity exercise, ranging from 25 to 65% of maximal oxygen consumption (VO_2max), is associated with a 5 to 10-fold increase in whole-body lipid oxidation compared to rest (Laurens 2020)

Long-chain fatty acids are derived primarily from **adipocyte lipolysis**

These fatty acids are taken up into muscle by passive diffusion and by protein-mediated transport (**CD36**)

Low **de novo lipogenesis** in skeletal muscle and slow **lipogenic rate** when compared with liver and adipose tissue

Lipid droplets are located near the endoplasmic reticulum (ER) and mitochondria

LIPID METABOLISM AND MUSCLE CONTRACTION

Carnitine palmitoyltransferase I (CPT I) is the critical regulator of **mitochondrial** fatty acid transport

Hormone sensitive lipase (HSL) is main lipolytic enzyme, increased during exercise, but decreased by AMPK after prolonged exercise (>90 minutes) (Watt 2012)

HSL triggered by contraction, beta adrenergic stimulation, estrogen, GH, glucagon and counteracted by insulin (Althaher 2022)

Atrial Naturetic Peptide (ANP) is particularly high after running a marathon, activating white adipose tissue (WAT) lipolysis (Hamasaki 2016)

Post-exercise lipolysis 24-48h due to preference of CHO use to replenish muscle glycogen

LIPID METABOLISM AND ENDURANCE ATHLETE

Increased skeletal muscle **TAG content** is associated with **insulin resistance**

But, **endurance-trained athletes** have increased skeletal muscle TAG despite being highly insulin sensitive- Paradox?

Training-induced **mitochondrial biogenesis**

Increased **oxidative disposal** of fatty acids

Reduction in **toxic lipid metabolite** levels (DAG)

Removal of inhibitory signals on **insulin signaling** (Laurens 2020)

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Althaher, Arwa R. “An Overview of Hormone-Sensitive Lipase (HSL).” *The Scientific World Journal* 2022 (December 8, 2022): 1964684.

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SLOW AND FAST TWITCH FIBERS

Type 1 or slow oxidative

Aerobic respiration for metabolizing glucose

Smaller, weaker contractions

Increased blood vessels, increased myoglobin, increased mitochondria

Red color

Generates lots of ATP, **but uses little, decreased glycogen storage**

Able to sustain muscle ability for long periods **(posture)**

General makeup is predominantly **genetic**

Possible through sprint training to increase power from slow twitch

Possible through endurance training to increase endurance of fast twitch

Never better than the genetics

FAST TWITCH FIBERS

Type IIa or **intermediate/fast oxidative**

Aerobic respiration for metabolizing glucose

Larger, producing stronger contractions

Increased blood vessels, increased myoglobin, increased mitochondria

Red color

Generates lots of ATP quickly, uses more ATP

Increased glycogen storage

Not explosive, more tension, more fatigue resistance

Type IIb/x or fast glycolytic fibers

Anaerobic respiration for metabolizing glucose

Largest fibers, stronger, quicker contractions

Decreased blood vessels, decreased myoglobin, decreased mitochondria

White color

Generate little ATP, use lots of ATP, high glycogen storage

Fastest fatigue (extraocular muscles)

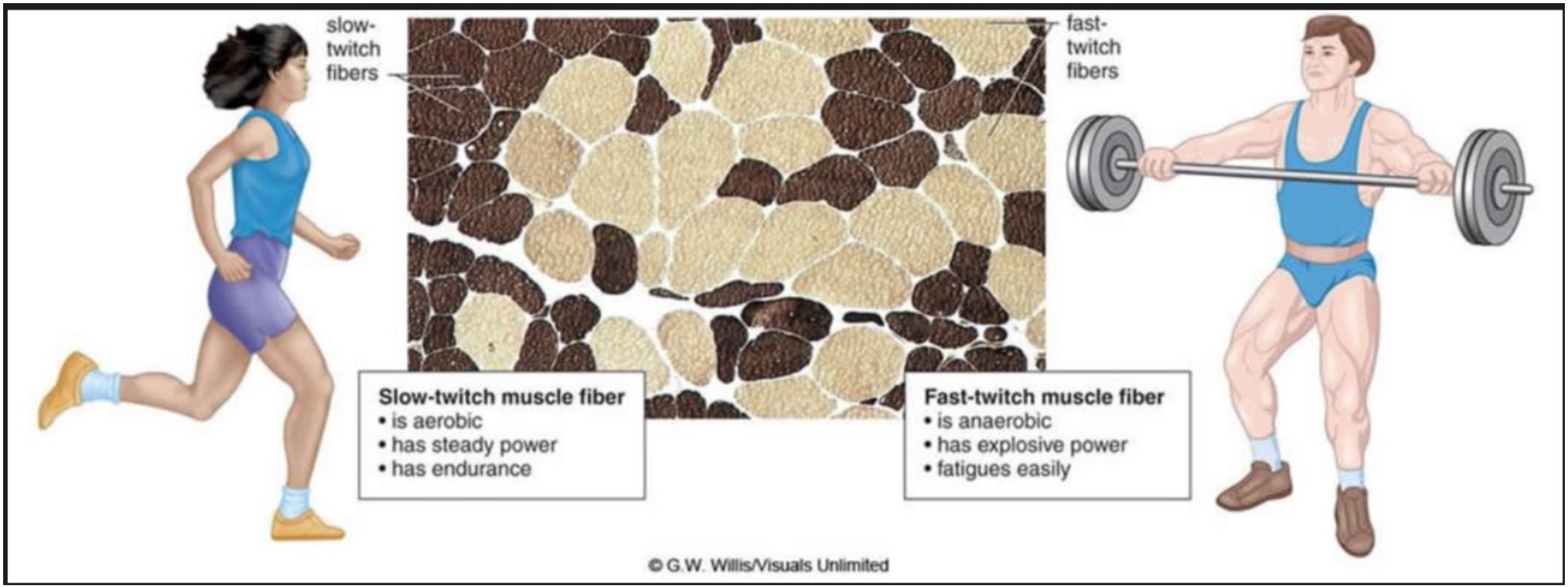
SLOW VS FAST TWITCH FIBERS

In humans, mean peak power occurred in a ratio of 10:5:1 for the Type IIb, IIa, and I fibers.

Peak power output is substantially greater in subjects possessing a predominance of fast fibers. The mechanical properties of slow and fast muscles do adapt to programs of regular exercise via increase in ATPase.

Endurance exercise training has been shown to increase the Vo of the slow soleus by 20%.

Regular endurance exercise training had no effect on fiber size, but with prolonged durations of daily training it **depressed Po and peak power**. When the training is maintained over prolonged periods, it may even induce **atrophy of the slow Type I and fast Type IIa fibers**


slow-twitch fibers
fast-twitch fibers
Slow-twitch muscle fiber
• is aerobic
• has steady power
• has endurance
Fast-twitch muscle fiber
• is anaerobic
• has explosive power
• fatigues easily
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MTOR AND MUSCLE MASS

mTOR deficiency reduces the transcription of **dystrophin**, resulting in a decrease in the content of the dystrophin-glycoprotein complex (DGC), which connects the cytoskeleton of a muscle fiber to its surrounding extracellular matrix; the disruption of DGC results in **muscular dystrophy**

mTOR knockout muscle also undergoes **metabolic changes**, resulting in **glycogen accumulation** due to increased glycogen synthesis and glucose uptake together with reduced glycogen breakdown through glycogenolysis and the glycolytic and oxidative pathways.

mTORC1 deficiency in muscle significantly reduces the expression of genes in **mitochondrial biogenesis**, such as proliferator-activated receptor γ coactivator-1 alpha (PGC1α), myoglobin, PPARγ, and cytochrome C oxidase IV (COXIV).

does not affect either intramuscular ATP level or whole body glucose homeostasis. (Yoon 2017)

MTOR AND MUSCLE MASS

IGF-1and insulin are upstream stimulator of mTOR in skeletal muscle

Mechanical stretch releases phosphatidic acids (PA), binding to mTOR at the rapamycin binding domain and activates mTOR (independent of IGF-1)

Promotes protein synthesis, skeletal myofiber hypertrophy

Yoon, Mee-Sup. “MTOR as a Key Regulator in Maintaining Skeletal Muscle Mass.” *Frontiers in Physiology* 8 (2017).

MYOSTATIN AND MUSCLE MASS

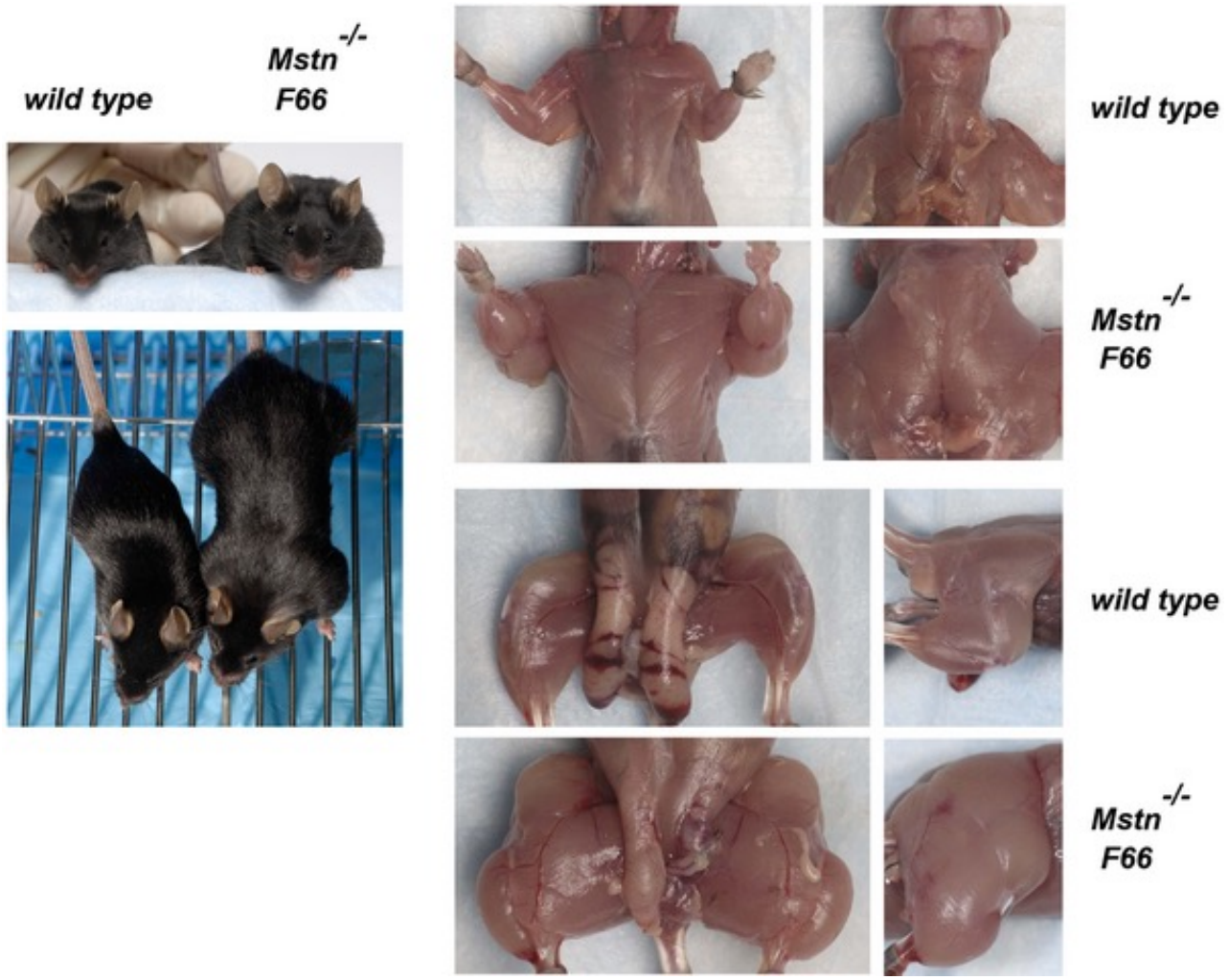
a transforming growth factor-ß (TGF-ß) family member that plays a critical role in **inhibiting the growth of muscle mass** and muscle cell differentiation.

regulate the number of muscle fibers that are formed during development and regulates **growth of muscle fibers postnatally**

Follistatin downregulates myostatin activity, and food deprivation and **glucocorticoids enhance** it

offspring with identical *Mstn* genotypes have **higher muscle weights** if the **mother** has fewer functional *Mstn* alleles

Figure 3. Comparison of wild type and F66/Mstn−/− mice.



Lee SJ (2007) Quadrupling Muscle Mass in Mice by Targeting TGF-ß Signaling Pathways. PLOS ONE 2(8): e789. https://doi.org/10.1371/journal.pone.0000789

MYOKINES AND MUSCLE MASS

Irisin: myokine that has been described to increase WAT lipolysis, mitochondrial biogenesis, stimulates muscle growth-related genes, better glycemic control and bone health

Growth and differentiation factor 15 (GDF15) enhances adipocyte lipolysis, is secreted following high and moderate-intensity exercise and recombinant GDF15 activated lipolysis in subcutaneous explants (Laurens 2020)

IGF-1 controls muscle growth, strength gain, maintains neuromuscular system (Zebrowska 2020)

SPARC calcium-binding protein involved in extracellular matrix reorganization, cell adhesion, and proliferation. Involved in wound healing, tissue response to injury, angiogenesis and its absence leads to intramuscular adipose tissue accumulation in aged muscle (Mathes 2022)

MEN VS WOMEN

Higher increase post-exercise FA consumption

Lower “Fatmax”

~10% higher VO2max

Larger lung size**

Continued left ventricular hypertrophy (VO2max) in response to endurance training up to 9 months

Less likely to underfuel and lose body fat

12% higher hemoglobin

Higher subcutaneous fat content

Greater lipid oxidation at given exercise intensity (Laurens 2020)

Better Running Economy (oxygen cost/speed or distance)

High % Type I skeletal muscle

Increased mitochondrial volume

Greater capacity for oxidative metabolism and fatigue resistance in single muscle activity

8x iron deficiency

Decreased heat dissipation and increased vasodilation

Santisteban, K. “Sex Differences in VO2max and the Impact on Endurance-Exercise Performance.” *International Journal of Environmental Research and Public Health* 19, no. 9 (April 19, 2022): 4946.

SARCOPENIA

Overall **decreases in size and number** of skeletal muscle fibers, mostly the type 2 or fast-twitch muscle fibers, and a **marked infiltration of fibrous and adipose** tissue into the skeletal muscle

Slower contraction and relaxation time

Loss of alpha motor neurons and reinnervation of abandoned muscle fibers by adjacent motor units of a different type

Reduced circulatory IGF-I and IGF-I mRNA levels and subsequently the activity of Akt/mTOR/p70S6K1 are decreased

Hyperactivation of mTOR in aged muscles **does not induce protein synthesis** and in leads to muscle atrophy mainly due to **inability to induce autophagy**

Resistance to anabolic stimuli in aged muscle (Yoon 2017)

BODYBUILDING

Fitness

Physique

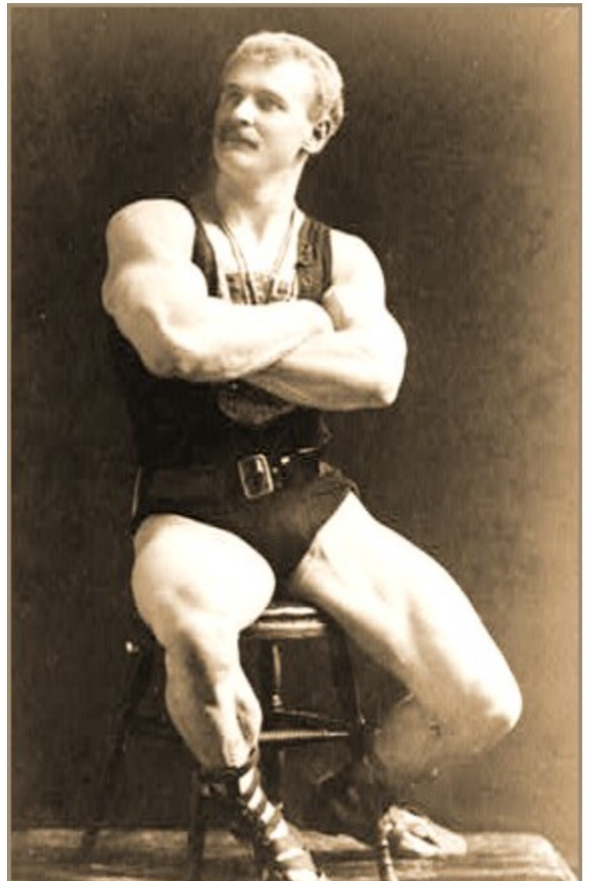
Bodybuilding

BODYBUILDING

The use of **progressive resistance exercise** to control and develop one's muscles (muscle building) by **muscle hypertrophy** for **aesthetic** purposes

Bodybuilding's origins in Europe in the late nineteenth century coincided with the **advent of photography**, which distributed striking images of muscular men to a worldwide audience. The first famous bodybuilder, **Eugen Sandow** (born Friedrich Müller in 1867), got his start under the employ of Oscard Attila (born Louis Durlacher in 1844), who had converted his music-hall act into a career as a professional strongman.

“Men’s Bodybuilding: A Short History.” Accessed December 11, 2022. http://www.bodybuildingreviews.net/Bodybuilding.html.



Sandow

BODY BUILDING PRINCIPLES

Muscle groups are trained 2+x/week

6-12 reps using 70-80% 1 rep max

40-70 reps per muscle group per session

Rest intervals of 1-3 minutes

1-2 sec concentric, 2-3sec eccentric tempo

Proper form and use of entire length of muscle (Helms 2015)

Lowest frequency and duration of **cardiovascular exercise** needed to induce fat loss

Severe caloric restriction over 3-6 months to achieve fat loss

In this situation, recovery **is impaired**

Helms, E. R., P. J. Fitschen, A. A. Aragon, J. Cronin, and B. J. Schoenfeld. “Recommendations for Natural Bodybuilding Contest Preparation: Resistance and Cardiovascular Training.” *The Journal of Sports Medicine and Physical Fitness* 55, no. 3 (March 2015): 164–78.

Hill, Jordan J. “Ernestine Shepherd at 85: A Day In The Life Of World’s Oldest Female Bodybuilder - BlackDoctor.Org - Where Wellness & Culture Connect.” *BlackDoctor.Org* (blog), June 15, 2021.

MUSCLE HYPERTROPHY TECHNIQUES

Agonist–antagonist, upper–lower body **supersets**, **drop and cluster sets**, sarcoplasma stimulating training, employment of fast, but controlled duration of **eccentric contractions** (~2s), and high-load RT supplemented with low-load RT under **blood flow restriction**

Krzysztofik, M. "Maximizing Muscle Hypertrophy: A Systematic Review of Advanced Resistance Training Techniques and Methods." *International Journal of Environmental Research and Public Health* 16, no. 24 (December 2019): 4897.

BFR Bands. "Blood Flow Restriction Bands | Occlusion Training Bands." Accessed January 11, 2023.

STRENGTH

Resistance training: to **add strength and muscle mass** for **health and fitness**. More specifically, this training is used to either **improve performance or prevent injury** in a particular sport

Using free weights (*e.g.*, dumbbells and barbells), machines, bodyweight exercises, or resistance bands to approximate the motion that the athlete is trying to improve in their particular sport.

For example, the shot put requires explosive strength of the shoulder, pectorals, triceps, legs, and hips, as well as stabilization of each of the various joints

Power lifting (SBD)

Style-dependent strength sports (e.g., strongman competitions, Highland games, field events such as shot put, discus, hammer throw, and javelin)

Olympic-style weightlifting (clean and jerk, snatch).

STRENGTH

sprains/strains account for approximately 46% of injuries, and the most common mechanism is **dropping of a weight** (65%) (Kerr 2010)

Power lifters more commonly injure their **shoulders**

Olympic weightlifters more commonly injure their **elbows and knees**.

Both power lifters and Olympic weightlifters experience **low-back muscular strains** at a higher rate than bodybuilders.

Ligament ruptures seem to be most associated with **inappropriate movement** of a joint (*e.g.*, misplacement of foot in squat causing lateral ankle sprain or in the bottom of the snatch causing a medial collateral ligament [MCL] injury to the knee). (Lavallee 2010)

Rate of 1-4/1000 training hours

TENDON RUPTURES

Tendon ruptures occur more frequently in those using certain muscle-enhancing products (*e.g.*, **creatine monohydrate, anabolic steroids, or human growth hormone** [HGH]), those recently having used **fluoroquinolones**, or those **over 40 yr old**.

Achilles ruptures in basketball players, Olympic weightlifters

Triceps tendon rupture in powerlifters

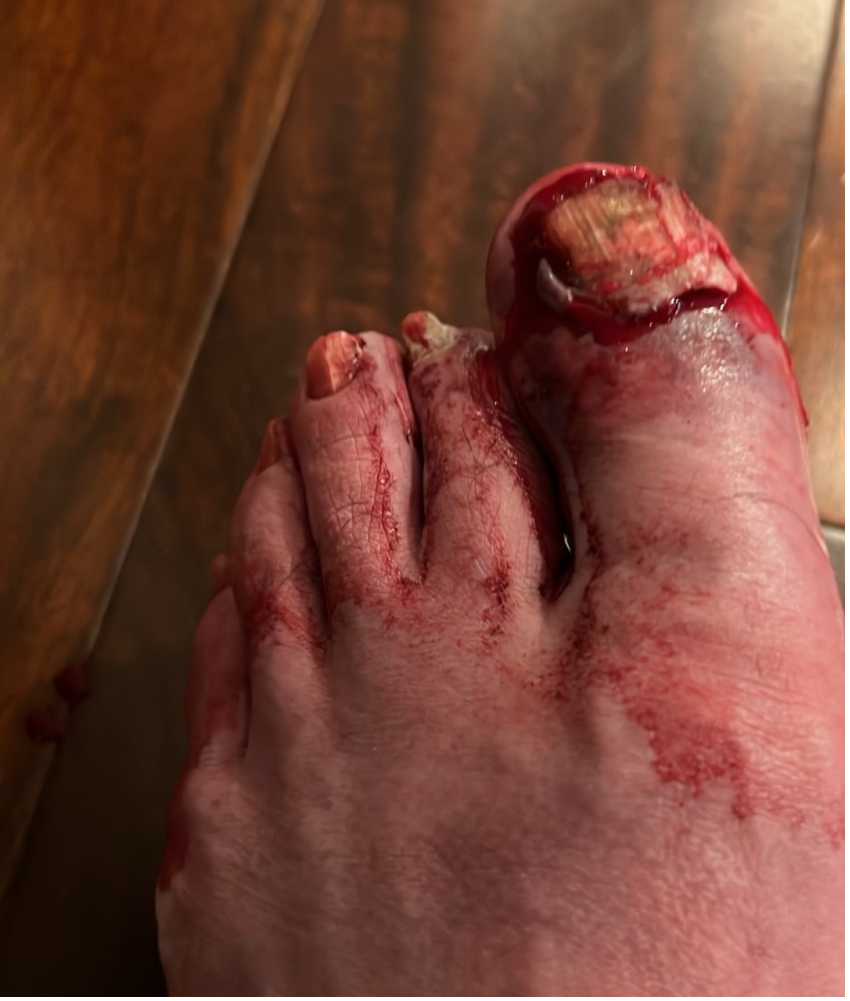
Bicep tendon rupture in Olympic weightlifters and bodybuilders

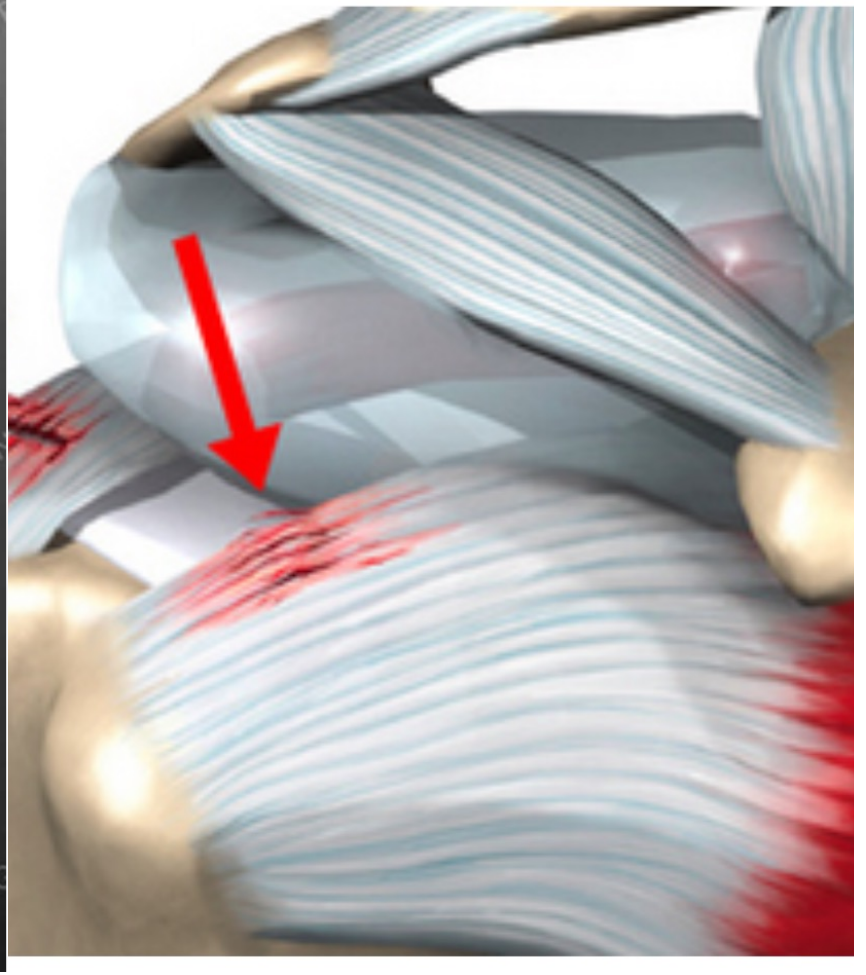
Pectoralis rupture in powerlifters (bench) and body builders (anabolic steroid use, corticosteroid use for previous injuries) (Lavallee 2010)

STRESS FRACTURES

in the long bones in endurance athletes

in the spine (spondylolysis) due to repeated excessive loads in powerlifters and Olympic weightlifters





HOSPITAL FOR SPECIAL SURGERY. "STRESS FRACTURES - ORTHOPEDIC TRAUMA SERVICE." ACCESSED JANUARY 26, 2023. HTTPS://WWW.HSS.EDU/ORTHOPEDIC-TRAUMA-CASE39-LEG-STRESS-FRACTURES.ASP.

SHOULDER SURGEON IN SEATTLE. "SHOULDER TENDINITIS AND BURSITIS AKA SWELLING (INFLAMMATION) WITHIN THE SHOULDER." ACCESSED JANUARY 26, 2023. HTTPS://SEATTLESHOULDERDOC.COM/SHOULDER-TENDINITIS-AND-BURSITIS/.

REFERENCES INJURIES

Kerr, Z. “Epidemiology of Weight Training-Related Injuries Presenting to United States Emergency Departments, 1990 to 2007.” *The American Journal of Sports Medicine* 38, no. 4 (April 2010): 765–71.

Lavallee,. “An Overview of Strength Training Injuries: Acute and Chronic.” *Current Sports Medicine Reports* 9, no. 5 (October 2010): 307.

ENDURANCE

Cross country skiing, running, swimming, basketball (2-5 miles), soccer (7-9 miles)

Less than 2 days **rest** per week had 5x risk of an overuse injury

Age increase by 2 years increased risk of tendon injury (Ristolainen 2014)

Patellofemoral symptoms from tendon injuries or chondral problems

“Ultramarathoner’s ankle” peritendinitis of the extensor tendons at the extensor retinaculum of the anterior ankle

Also medial tibial stress syndrome and chronic exercise-induced compartment syndrome (Almekinders 2019)

ENDURANCE

Prolonged bouts of **endurance exercise** (i.e., >2 h) result in considerable oxidation of amino acids, **specifically leucine**

Intense or prolonged bouts of endurance exercise result in **hypoxia-mediated small intestinal injury**, negative whole-body protein balance may be common in endurance athletes

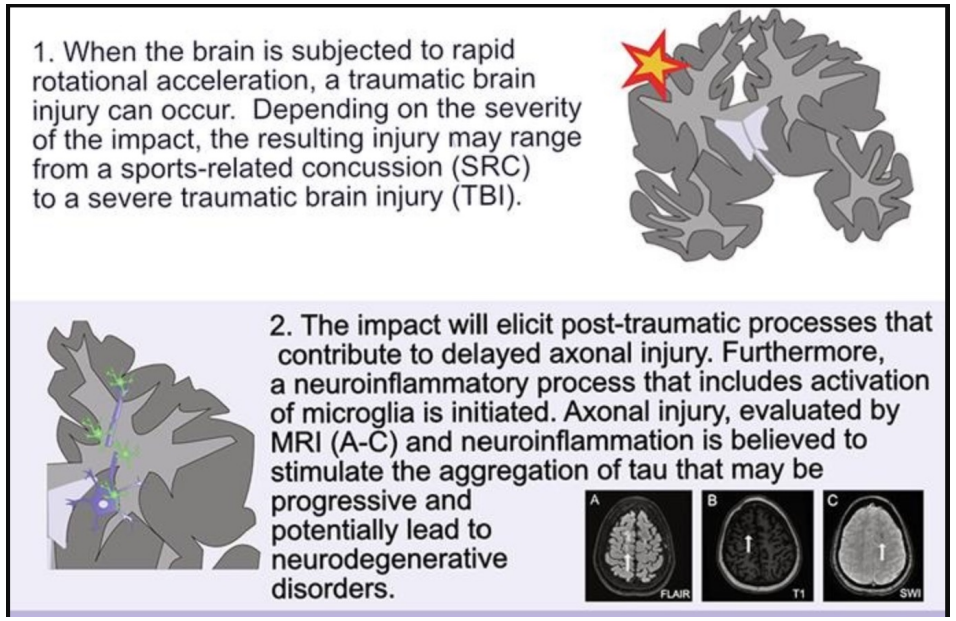
Iron deficiency in female>male; female requirement may be >70% RDA

REFERENCES

Ristolainen, L. “Training-Related Risk Factors in the Etiology of Overuse Injuries in Endurance Sports.” *The Journal of Sports Medicine and Physical Fitness* 54, no. 1 (February 1, 2014): 78–87.

Almekinders, L. “Common and Uncommon Injuries in Ultra-Endurance Sports.” *Sports Medicine and Arthroscopy Review* 27, no. 1 (March 1, 2019): 25–30.

TRAUMATIC BRAIN INJURY/SPORT-RELATED CONCUSSION IN **CONTACT SPORTS**



Boxing, rugby, American football, wrestling, basketball, soccer

Associated with tau aggregation and persistent neuroinflammation >6 months post injury via PET

Due to persistent microglial activation, mitochondrial dysfunction and oxidative stress

May progress to neurodegenerative disease

Marklund, N. “Tau Aggregation and Increased Neuroinflammation in Athletes after Sports-Related Concussions and in Traumatic Brain Injury Patients – A PET/MR Study.” *NeuroImage: Clinical* 30 (January 1, 2021): 102665.

S0 NON-APPROVED SUBSTANCES

PROHIBITED AT ALL TIMES (IN- AND OUT-OF-COMPETITION)

All prohibited substances in this class are *Specified Substances*.

Any pharmacological substance which is not addressed by any of the subsequent sections of the *List* and with no current approval by any governmental regulatory health authority for human therapeutic use (e.g. drugs under pre-clinical or clinical development or discontinued, designer drugs, substances approved only for veterinary use) is prohibited at all times.

This class covers many different substances including but not limited to BPC-157.

- Mesterolone
- Metandienone (17β-hydroxy-17α-methylandrosta-1,4-dien-3-one)
- Metenolone
- Methandriol
- Methasterone (17β-hydroxy-2α,17α-dimethyl-5α-androstan-3-one)
- Methyl-1-testosterone (17β-hydroxy-17α-methyl-5α-androst-1-en-3-one)
- Methylclostebol
- Methyldienolone (17β-hydroxy-17α-methylestra-4,9-dien-3-one)
- Methylnortestosterone (17β-hydroxy-17α-methylestr-4-en-3-one)
- Methyltestosterone
- Metribolone (methyltrienolone, 17β-hydroxy-17α-methylestra-4,9,11-trien-3-one)
- Mibolerone
- Nandrolone (19-nortestosterone)
- Norboletone
- Norclostebol (4-chloro-17β-ol-estr-4-en-3-one)
- Norethandrolone
- Oxabolone
- Oxandrolone
- Oxymesterone
- Oxymetholone
- Prasterone (dehydroepiandrosterone, DHEA, 3β-hydroxyandrost-5-en-17-one)
- Prostanozol (17β-[(tetrahydropyran-2-yl)oxy]-1'H-pyrazolo[3,4:2,3]-5α-androstane)
- Quinbolone
- Stanozolol
- Stenbolone
- Testosterone
- Tetrahydrogestrinone (17-hydroxy-18a-homo-19-nor-17α-pregna-4,9,11-trien-3-one)
- Tibolone
- Trenbolone (17β-hydroxyestr-4,9,11-trien-3-one)

and other substances with a similar chemical structure or similar biological effect(s).

2. OTHER ANABOLIC AGENTS

Including, but not limited to:

Clenbuterol, osilodrostat, selective androgen receptor modulators [SARMs, e.g. andarine, enobosarm (ostarine), LGD-4033 (ligandrol) and RAD140], zeranol and zilpaterol.

2. PEPTIDE HORMONES AND THEIR RELEASING FACTORS

2.1 Chorionic gonadotrophin (CG) and luteinizing hormone (LH) and their releasing factors in males, e.g. buserelin, deslorelin, gonadorelin, goserelin, leuprorelin, nafarelin and triptorelin

2.2 Corticotrophins and their releasing factors, e.g. corticorelin

2.3 Growth hormone (GH), its analogues and fragments including, but not limited to:

- growth hormone analogues, e.g. lonapegsomatropin, somapacitan and somatrogon
- growth hormone fragments, e.g. AOD-9604 and hGH 176-191

2.4 Growth hormone releasing factors, including, but not limited to:

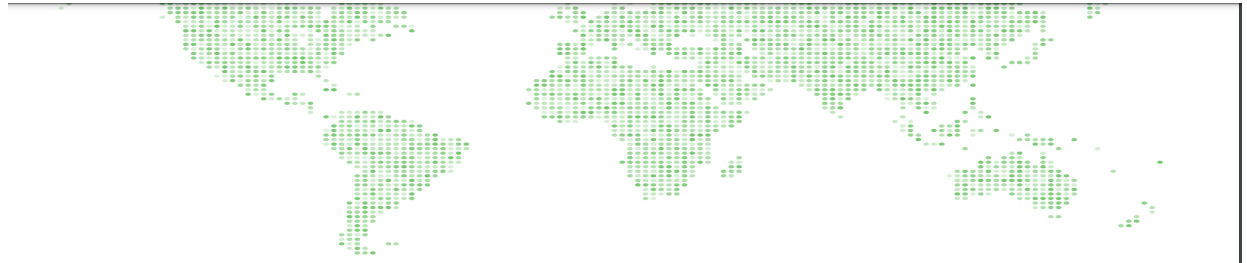
- growth hormone-releasing hormone (GHRH) and its analogues (e.g. CJC-1293, CJC-1295, sermorelin and tesamorelin)
- growth hormone secretagogues (GHS) and its mimetics [e.g. lenomorelin (ghrelin), anamorelin, ipamorelin, macimorelin and tabimorelin]
- GH-releasing peptides (GHRPs) [e.g. alexamorelin, GHRP-1, GHRP-2 (pralmorelin), GHRP-3, GHRP-4, GHRP-5, GHRP-6, and examorelin (hexarelin)]

3. GROWTH FACTORS AND GROWTH FACTOR MODULATORS

Including, but not limited to:

- Fibroblast growth factors (FGFs)
- Hepatocyte growth factor (HGF)
- Insulin-like growth factor 1 (IGF-1) and its analogues
- Mechano growth factors (MGFs)
- Platelet-derived growth factor (PDGF)
- Thymosin-β4 and its derivatives e.g. TB-500
- Vascular endothelial growth factor (VEGF)

and other growth factors or growth factor modulators affecting muscle, tendon or ligament protein synthesis/degradation, vascularisation, energy utilization, regenerative capacity or fibre type switching.

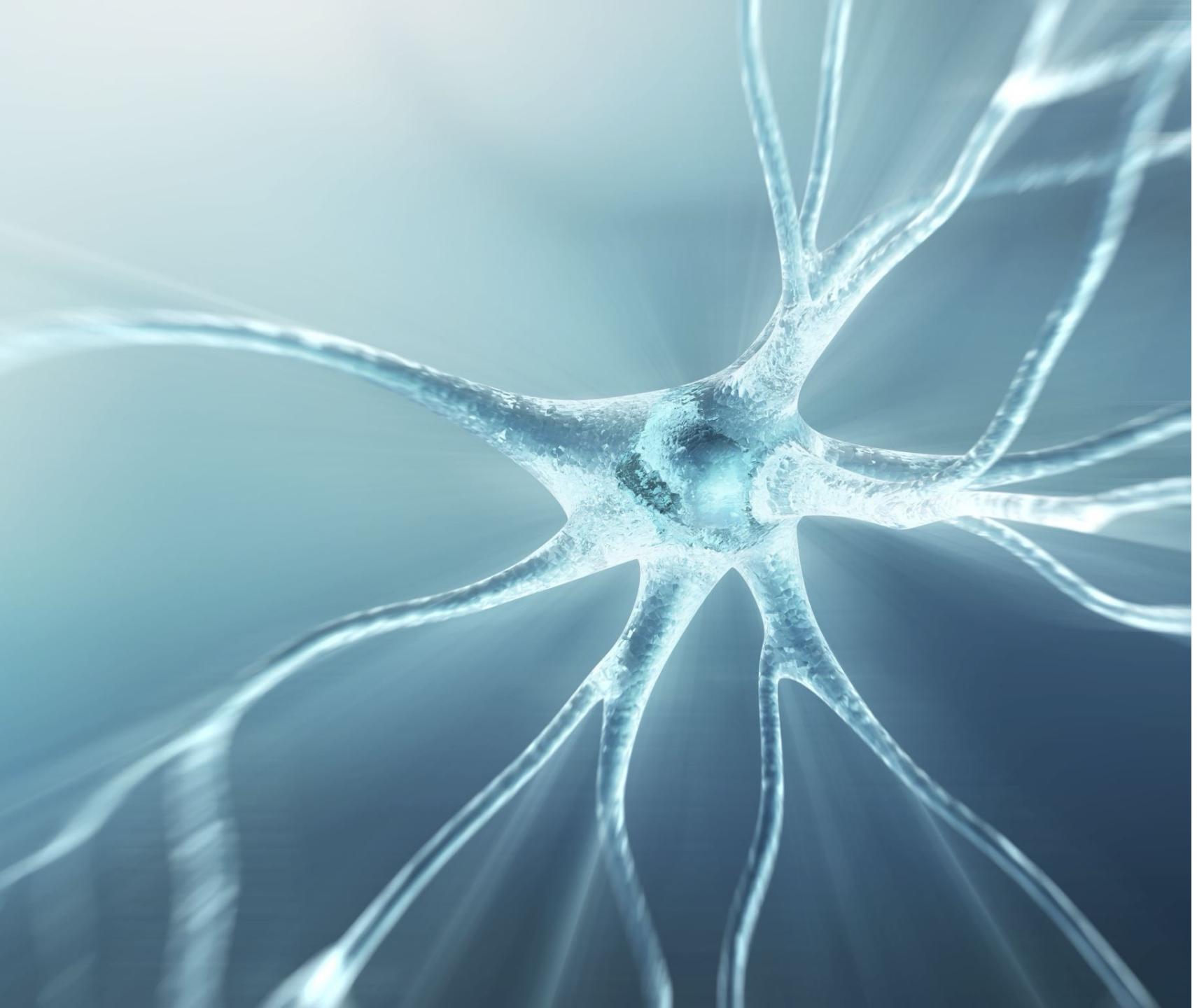


WORLD ANTI-DOPING CODE

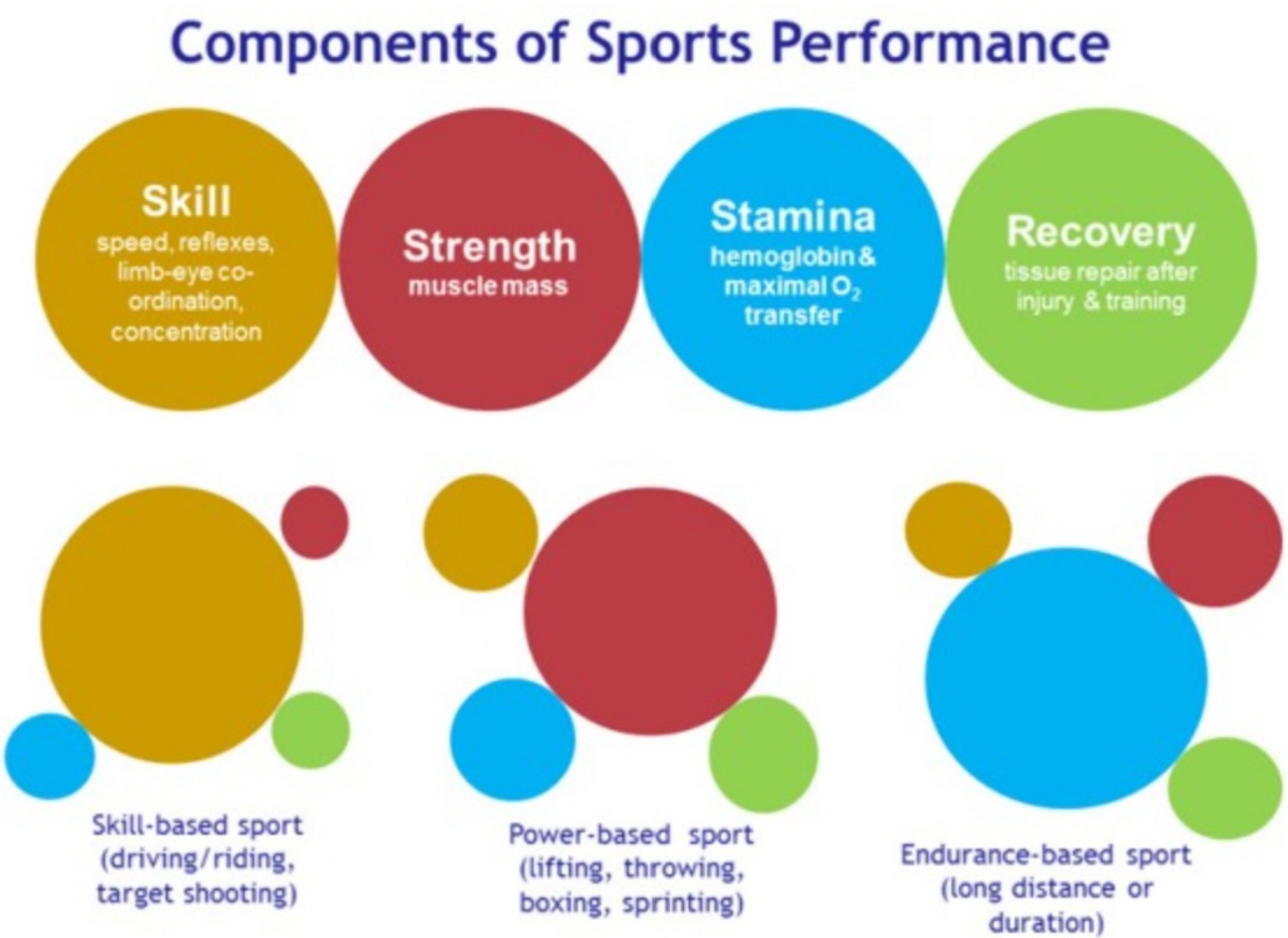
INTERNATIONAL STANDARD

PROHIBITED LIST

2022



SPORTS PERFORMANCE



HANDELSMAN, DAVID J. "FIGURE 1. [COMPONENTS OF SPORTS PERFORMANCE]." TEXT. MDTEXT.COM, INC., FEBRUARY 29, 2020. HTTPS://WWW.NCBI.NLM.NIH.GOV/BOOKS/NBK305894/FIGURE/PERFORM-ENHANC-SPORT.F1/.

TESTING

- CBC, CMP, Mg, Phos
- Myoglobin, CK, LDH
- Cystatin C
- Urinalysis
- BIA/DEXA, HRV
- Iron/ferritin
- Thyroid panel
- Vitamin D
- Lipid panel
- Testosterone, FSH, LH
- IGF-1, IGF-BP3

MACROS

Total daily calorie and protein intake (1.6-3.3g/kg) over the long term are the most crucial dietary role in facilitating adaptations to exercise

- Energy balance=energy intake (EI) = total energy expenditure (TEE). The TEE is a summation of basal metabolic rate (BMR) + thermic effect of food (TEF) + thermic effect of activity (TEA). There are many factors that go into an athlete's TEE, and it may vary depending on his or her energy needs for that day.
- Factors that may increase demand include training, environmental exposure (heat, cold, or altitude), fat-free mass (FFM), stress, illness, age and some medications. (Bytomski 2017)

Peri-training<post training **Whey Protein** induces a significant rise in muscle protein synthesis and recovery for both resistance and endurance

- 3g/kg casein/whey protein or 12g/d BCAAs sufficient to return immune, metabolic and muscular **recovery** in endurance
- 64g protein over 3h post endurance improved mitochondrial oxidation (Cintineo 2018)

Creatine monohydrate consumption amplifies the cell's ability to resynthesize ATP. enhanced force output, augmented power output, increased strength, increased anaerobic threshold, increased work capacity, enhanced recovery, and enhanced training adaptations in men and women in a variety of sports.

- 0.3g/kg/day loading, 0.03g/kg/day maintenance (Wax 2021)

SUPPLEMENTS

Creatine monohydrate supplementation increases maximal strength, maximal work output, maximal power production, sprint performance and fat free mass, speeds recovery time. Recycles ATP. 1-5g/day, cycle every 8 weeks off 4 weeks (Wax 2021)

-(-)Epicatechin/Urolithin A in maintenance of aging muscle and bone (Seo 2021, Liu 2022, Singh 2022, Gutierrez-Salmean 2014)

L-theanine in endurance athletes to maintain immune function (Juszkiewicz 2019)

Alpha GPC 600mg per day for 6 days significantly increased isometric midthigh pull peak force (Bellar 2015)

Exogenous ketones increases metabolic flexibility during exercise, reducing glycolysis and increasing muscle fat oxidation (Cox 2016). They also increase post exercise EPO, ANP (Evans 2023, Robberechts 2022)

REFERENCES FOR SUPPLEMENTS

Bellar, D. “The Effect of 6 Days of Alpha Glycerylphosphorylcholine on Isometric Strength.” *Journal of the International Society of Sports Nutrition* 12 (November 17, 2015): 42.

Cox, P. “Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes.” *Cell Metabolism* 24, no. 2 (August 9, 2016): 256–68.

Evans, E. “Ketone Monoester Ingestion Increases Postexercise Serum Erythropoietin Concentrations in Healthy Men.” *American Journal of Physiology. Endocrinology and Metabolism* 324, no. 1 (January 1, 2023): E56–61.

Gutiérrez-Salmeán, G. “Acute Effects of an Oral Supplement of (-)-Epicatechin on Postprandial Fat and Carbohydrate Metabolism in Normal and Overweight Subjects.” *Food & Function* 5, no. 3 (March 2014): 521–27.

Juszkiewicz, A. “The Effect of L-Theanine Supplementation on the Immune System of Athletes Exposed to Strenuous Physical Exercise.” *Journal of the International Society of Sports Nutrition* 16, no. 1 (January 15, 2019): 7.

Liu,S. “Effect of Urolithin A Supplementation on Muscle Endurance and Mitochondrial Health in Older Adults: A Randomized Clinical Trial.” *JAMA Network Open* 5, no. 1 (January 20, 2022): e2144279.

Robberechts, R. “Exogenous Ketosis Suppresses Diuresis and Atrial Natriuretic Peptide during Exercise.” *Journal of Applied Physiology* 133, no. 2 (August 2022): 449–60.

Seo, H. “(-)-Epicatechin-Enriched Extract from Camellia Sinensis Improves Regulation of Muscle Mass and Function: Results from a Randomized Controlled Trial.” *Antioxidants (Basel, Switzerland)* 10, no. 7 (June 25, 2021): 1026.

Singh, A. “Urolithin A Improves Muscle Strength, Exercise Performance, and Biomarkers of Mitochondrial Health in a Randomized Trial in Middle-Aged Adults.” *Cell Reports Medicine* 3, no. 5 (May 17, 2022): 100633.

“Urolithin A Improves Mitochondrial Health, Reduces Cartilage Degeneration, and Alleviates Pain in Osteoarthritis - D’Amico - Aging Cell - Wiley Online Library.” Accessed July 28, 2022.

Wax, B. “Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations.” *Nutrients* 13, no. 6 (June 2, 2021): 1915.

SARMS

- Ligandrol/LGD4033 nonsteroidal oral SARM. Increased lean body mass in 5 weeks, improved cholesterol panel.
  - Significant total testosterone and SHBG suppression at 1mg per day only
  - Hormone and cholesterol returned to normal after treatment discontinuation
  - No change in PSA (Basaria 2013)
  - Dosing 0.5mg oral
- Stenabol/SR9009 inhibits activation of macrophages/inflammasome (Reitz 2019), activates NRF2 and inhibits DDR and SASP (senescence) (Gao 2021), inhibits mast cell activation (Ishimaru 2019).
  - Reduction in cartilage damage in murine OA (Das 2018),
  - Increases exercise capacity by increasing mitochondrial biogenesis in skeletal muscle (Woldt 2013).
  - Dosing 10-30mg/day
- Oxandrolone an analog of 17a-methylDHT
  - 15mg/day decreased outward transport of amino acids, increased protein synthesis 44%. Greater anabolic with few androgenic effects (Sheffield-Moore 1999)
  - Use in burns (Guo 2016), COPD (Yeh 2002), Turner syndrome (Zeger 2011)

REFERENCES FOR SARMS

Basaria, S. “The Safety, Pharmacokinetics, and Effects of LGD-4033, a Novel Nonsteroidal Oral, Selective Androgen Receptor Modulator, in Healthy Young Men.” *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 68, no. 1 (January 2013): 87–95.

Li, H. “The Efficacy and Safety of Oxandrolone Treatment for Patients with Severe Burns: A Systematic Review and Meta-Analysis.” *Burns* 42, no. 4 (June 1, 2016): 717–27.

Sheffield-Moore, M. “Short-Term Oxandrolone Administration Stimulates Net Muscle Protein Synthesis in Young Men1 | The Journal of Clinical Endocrinology & Metabolism | Oxford Academic.” Accessed January 26, 2023. Yeh, Shing-shing, Bernadette DeGuzman, and Ted Kramer. “Reversal of COPD-Associated Weight Loss Using the Anabolic Agent Oxandrolone.” *Chest* 122, no. 2 (August 1, 2002): 421–28.

Zeger, M. “Prospective Study Confirms Oxandrolone-Associated Improvement in Height in Growth Hormone-Treated Adolescent Girls with Turner Syndrome.” *Hormone Research in Paediatrics* 75, no. 1 (2011): 38–46.

Das, V. “Pharmacological Targeting of the Mammalian Clock Reveals a Novel Analgesic for Osteoarthritis-Induced Pain.” *Gene* 655 (May 20, 2018): 1–12.

Gao, L. “Identification of a Small Molecule SR9009 That Activates NRF2 to Counteract Cellular Senescence.” *Aging Cell* 20, no. 10 (2021): e13483.

Hosokawa, H. “Nuclear Receptor Subfamily 1 Group D Member 1 in the Pathology of Obesity-Induced Osteoarthritis Progression.” *Journal of Orthopaedic Research* n/a, no. n/a. Accessed January 26, 2023.

Mayeuf-Louchart, A. “Rev-Erb-α Regulates Atrophy-Related Genes to Control Skeletal Muscle Mass.” *Scientific Reports* 7, no. 1 (October 30, 2017): 14383.

Sun, L. “Circadian Clock Genes REV-ERBs Inhibits Granulosa Cells Apoptosis by Regulating Mitochondrial Biogenesis and Autophagy in Polycystic Ovary Syndrome.” *Frontiers in Cell and Developmental Biology* 9 (2021).

Woldt, E. “Rev-Erb-α Modulates Skeletal Muscle Oxidative Capacity by Regulating Mitochondrial Biogenesis and Autophagy.” *Nature Medicine* 19, no. 8 (August 2013): 1039–46.

GROWTH HORMONE

Growth hormone (GH) is secreted by the anterior pituitary

a major stimulant in **somatic growth control**

a **pleiotropic hormone** that affects bone and **muscle mass, carbohydrate, fat, and protein metabolism, sexual maturation, and insulin resistance**

Involved in **immune regulation**, and the GH receptor is expressed by several leukocyte subpopulations, mediates **thymic development**, **promotes T cell engraftment** in severe combined immunodeficiency mice, **improves B cell responses and antibody production**, and **modulates NK cell and macrophage activity** as well as *in vivo* **Th1/Th2 and humoral immune responses**

Reduces Type I DM development by altering tolerization mechanisms such as the **cytokine environment**, **macrophage polarization, activation of the suppressor T cell population, and Th17 cell plasticity**

GROWTH HORMONE AND METABOLISM

Increases lipolysis by **increasing adipose tissue hormone-sensitive lipase** (HSL), primarily in the *fasted* state

Vijayakumar, A. Biological effects of growth hormone on carbohydrate and lipid metabolism. Growth Hormone and IGF Research. 2010 Feb;20(1):1-7.

Potently **stimulates lipogenic** glycerol phosphate dehydrogenase (GPD) in **differentiating *pre*adipocytes**, with negligible effect on *differentiated* adipocytes.

Dietz, J. Growth hormone alters lipolysis and hormone-sensitive lipase activity in 3T3-F442A adipocytes. Metabolism. 1991 Aug;40(8):800-6.

Activates ERK and PKC (**lipolysis**) in the fasted state

Bergan, H. Nutritional state modulates growth hormone-stimulated lipolysis. General and Comparative Endocrinology. 2015;217-8:1-9.

Enhances amino acid uptake by the gut lumen, providing energy and precursors for protein synthesis.

Inoue, Y. Growth hormone enhances amino acid uptake by the human small intestine. Ann Surg. 1994;219(6):715-22.

GH AND PERFORMANCE

- Growth hormone (GH) use in **adults with GH deficiency** results in **increased fitness and strength** mainly mediated by insulin-like growth factor (IGF)-1.
  - Woodhouse LJ,et al. The influence of growth hormone status on physical impairments, functional limitations, and health-related quality of life in adults. Endocr Rev. 2006;27(3):287–317.
- **Lean body mass increased** in growth hormone recipients compared with participants who did not receive growth hormone (increase, 2.1 kg [95% CI, 1.3 to 2.9 kg]), but **strength and exercise capacity did not seem to improve**.
  - Liu H, Bravata DM, Olkin I, Friedlander A, Liu V, Roberts B, et al. Review systematic review : the effects of growth hormone on athletic performance. Ann Intern Med. 2008;148(10):747–58.

GH AND PERFORMANCE

- Endurance performance was evaluated in two double-blind studies; **multiple dosing of GH did not have an effect on VO2max** and Pmax compared with placebo **in trained subjects**
  - Berggren A, et al. Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes. J Clin Endocrinol Metab. 2005;90(6):3268–73.

- **Increase in sprint performance** in a 30 s maximal sprint test (Wingate test) of approximately 1 kJ (or a 3.9% relative increase in the combined male and female group, and a 5.5% relative increase for the male group only)
  - Meinhardt U, et al. The effects of growth hormone on body composition and physical performance in recreational athletes. Ann Intern Med. 2010;152:568–77

The Effects of Growth Hormone on Body Composition and Physical Performance in Recreational Athletes: A Randomized Trial

Udo Meinhardt, MD; Anne E. Nelson, PhD; Jennifer L. Hansen, RN; Vita Birzniece, MD, PhD; David Clifford, PhD; Kin-Chuen Leung, PhD; Kenneth Graham, BSc; Ken K.Y. Ho, MD

Design:
Randomized, placebo-controlled, blinded study of **8 weeks** of treatment followed by a 6-week washout period. Randomization was computer-generated with concealed allocation. (Australianâ€“New Zealand Clinical Trials

Intervention:
Men were randomly assigned to receive placebo, **growth hormone (2 mg/d subcutaneously**), testosterone (250 mg/wk intramuscularly), or combined treatments. **Women** were randomly assigned to receive either placebo or **growth hormone (2 mg/d).**

Results:
Body cell mass was correlated with all measures of performance at baseline. **Growth hormone significantly reduced fat mass, increased lean body mass** through an increase in extracellular water, and increased body cell mass **in men when coadministered with testosterone**. Growth hormone significantly increased **sprint capacity**, by 0.71 kJ (95% CI, 0.1 to 1.3 kJ; relative increase, 3.9% [CI, 0.0% to 7.7%]) **in men and women** combined and by 1.7 kJ (CI, 0.5 to 3.0 kJ; relative increase, 8.3% [CI, 3.0% to 13.6%]) when coadministered with testosterone to men; other performance measures did not significantly change. The increase in sprint capacity was not maintained 6 weeks after discontinuation of the drug.

GH AND PERFORMANCE

IGF-1 is thought to possess **ergogenic** effects mainly through the anabolic pathway that is shared with GH.

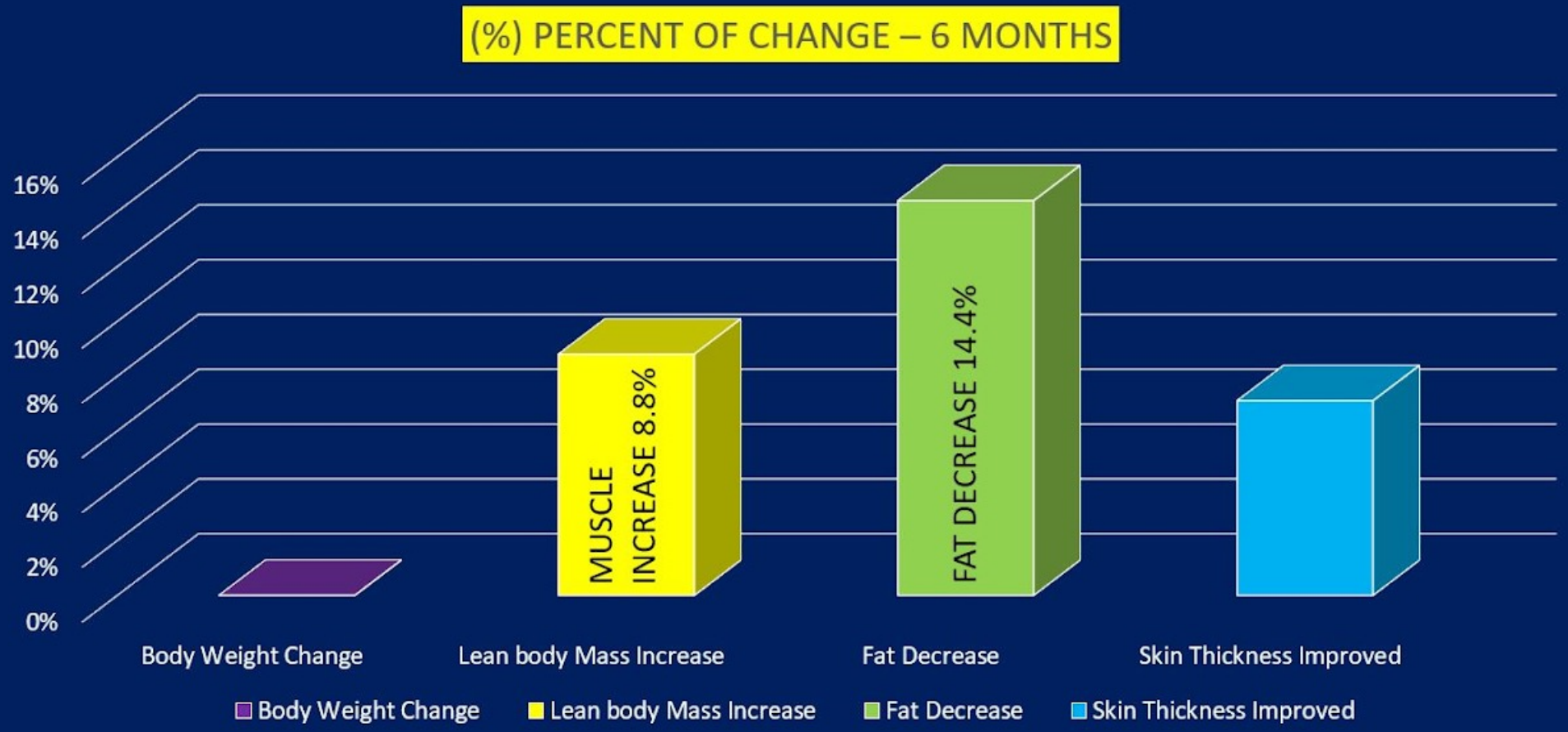
A randomized, double-blind, placebo-controlled study investigated the effects of a recombinant human IGF-1/IGF-binding protein-3 complex on body composition and aerobic performance in **untrained persons** . No effects on body composition were observed but a **slight increase in VO2max** was reported for both low (30 mg/day) and high (60 mg/day) doses.

Guha N, Nevitt SP, Francis M, Woodland JA, Böhning D, Sönksen PH, et al. The effects of recombinant human insulin-like growth factor-I/insulin-like growth factor binding protein-3 administration on body composition and physical fitness in recreational athletes. J Clin Endocrinol Metab. 2015;100(8):3126–31.

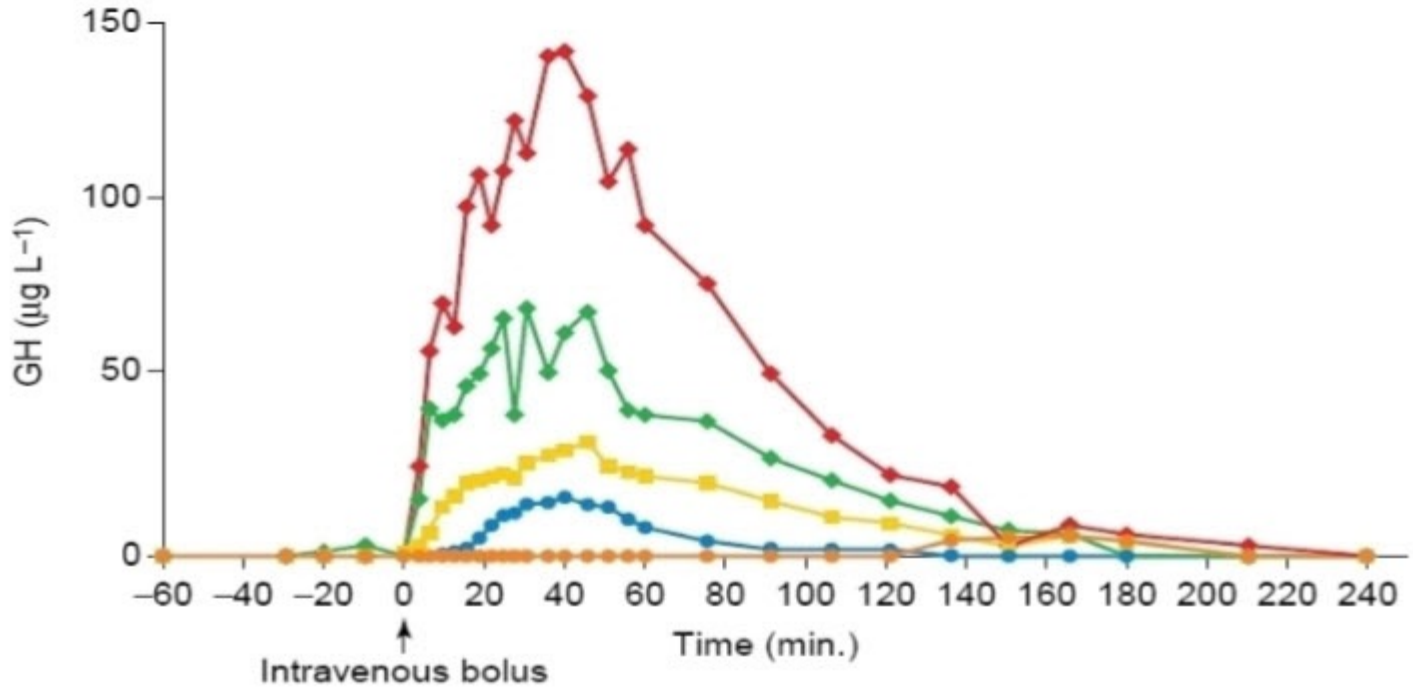
GH AND BODY BUILDING

- Growth hormone (GH) is widely used as a performance-enhancing drug. One of its best-characterized effects is **increasing levels of circulating insulin-like growth factor I** (IGF-I).
- Although benefits of GH administration have been reported for those who suffer from **GH deficiency**, there is currently very little evidence to support an anabolic role for supraphysiological levels of systemic GH or IGF-I in skeletal muscle of healthy individuals.
- The hypertrophic effects of muscle-specific IGF-I infusion are well documented in animal models and muscle cell culture systems. Studies examining the molecular responses to hypertrophic stimuli in animals and humans frequently cite upregulation of IGF-I messenger RNA or immunoreactivity. ***The circulatory/systemic (endocrine) and local (autocrine/paracrine) effects of GH and IGF-I may have distinct effects on muscle mass regulation.***

Rudman Et. Al. HGH Study



SOURCE: Info-graphic adapted from The New England Journal of Medicine, Rudman Et. Al. July 1990



Comparative growth hormone (GH) responses in individual subjects. GH responses, together with the area-under-the-curve (in μg L^{-1} after 4 h treatment) is as follows: placebo (orange, 540); 0.1 μg kg^{-1} growth hormone-releasing peptide (GHRP; blue, 916); 1 μg kg^{-1} GHRP (green, 5319); 1 μg kg^{-1} growth hormone-releasing hormone (GHRH; yellow, 2590); 0.1 μg kg^{-1} GHRP plus 1 μg kg^{-1} GHRH (red, 10,065) in two normal men J. Clin. Endocrinol. Metab. 70, 975-982

Peptide GHRPs and GHRHs

GHRP pulse HGH / GHRH release and amplify the HGH pulse

- ***CJC1295 and Ipamorelin:*** Effective and safe combo. CJC is a growth hormone releasing hormone (GHRH) analog. CJC 1295 has been shown potently to increase growth hormone and IGF-I secretion and effects with no increase in prolactin, leading to **fat loss**, and **increased protein synthesis**.

    Ipamorelin is a **selective GH-Secretagogue and ghrelin receptor agonist**. The potency of ghrelin stimulation can be compared to GHRP6 with **less appetite stimulation** properties. However, unlike other GH-Secretagogues this pentapeptide **doesn't release the same volumes of cortisol, acetylcholine, prolactin and aldosterone**. It is for this reason Ipamorelin has been considered the first selective GH Secretagogue.

- ***Tesamorelin:*** Tesamorelin is a growth hormone releasing hormone analog that has been shown to **increase IGF-1 levels in men** by an average of 181 micrograms/liter. It binds and stimulates human GHRH receptors with **similar potency as endogenous GHRH**. Stronger. Increased efficacy but expensive and higher side effect profile.

SERMORELIN

11 men aged 64 to 76 years were given 2 mg of subcutaneous sermorelin nightly for 6 weeks

Sermorelin was found to augment the duration of rhythmic GH release without pushing serum levels above physiologic norms

IGF-1 levels did not significantly increase at 2 or 6 weeks

Significant improvements in 2 of the 6 muscle strength tests and the abdominal crunch, a test of muscle endurance

No significant changes in testosterone levels were observed. Interestingly, a decrease in mean systolic blood pressure was observed

Vittone, J. “Effects of Single Nightly Injections of Growth Hormone-Releasing Hormone (GHRH 1-29) in Healthy Elderly Men.” *Metabolism: Clinical and Experimental* 46, no. 1 (January 1997): 89–96.

IGF-1

- Stimulates **muscle growth** and has been shown to benefit the heart (a muscle).
- Encourages the **absorption** of Chondroitin Sulfate and Glucosamine Sulfate (also found in Velvet Antler) that protects cartilage and joints.
- **Regenerates nerve** tissue.
- Helps **burn fat**, increases **protein transport** into cells, and reduce protein breakdown.
- Improves the production of white blood cells that **strengthens the immune** system.
- Decreases LDL **cholesterol**.

- Gatti, Rosalba, Elio Franco De Palo, Giorgia Antonelli, and Paolo Spinella. "IGF-I/IGFBP System: Metabolism Outline and Physical Exercise." *Journal of Endocrinological Investigation* 35 (June 18, 2012): 699–707.
- Gehmert, S. "Adipose Tissue-Derived Stem Cell Secreted IGF-1 Protects Myoblasts from the Negative Effect of Myostatin." *BioMed Research International* 2014 (2014): 129048.

IGF-1 LR3

"Insulin-like Growth Factor – 1 Long Arg3". An 83 aa polypeptide hormone that contains some of the same molecular structure and **anabolic effects** as insulin.

The arg3 in the name refers to **arginine in the 3rd position**,

- More potent version of IGF-1.
- Does not adhere to IGF-1 binding proteins in the bloodstream as strongly as IGF-1.
- This results in a longer half-life of 20-30 hours instead of 10-20 min.
- Doesn't promote cell hypertrophy but rather cell division and proliferation, increases total **number of muscle cells** doesn't cause them to get larger
- Binds to both the IGF-1 receptor and the Insulin receptor causing glucose uptake from the blood by muscle, nerve and liver cells. This results in a decrease in blood glucose which then triggers adipose as well as the liver to break down glycogen and triglycerides. This produces adipose catabolism.
- Highly effective in counteracting **myostatin**! (Gehmert 2014)

Side effect profile including **organomegaly**. (Gatti 2012)

IFG-1 DOSING

100mcg per day directly into muscles

LR3 gives longer t1/2: 250mcg SC 1-2 times per week, start 3-4 days after injury directly into the site of injury

SE: organomegaly, cancer?

MGF (IGF-1EC)

Splicing of the insulin-like growth factor (IGF) gene produces different forms of IGF-I in human muscle.

Goldspink G, *et al.* Gene expression in skeletal muscle in response to mechanical signs. *Am J Physiol*1992;262:R326–63

Mechano growth factor (MGF) is **produced locally in response to exercise/damage**, and it differs from the two systemic types of IGF-I.

Activates muscle stem cells and “kick starts” **tissue repair and/or hypertrophy** processes.

MGF inhibits differentiation, so levels must decrease and splicing move toward IGF-1IEb must occur for differentiation to occur.

Rw, M. “Minireview: Mechano-Growth Factor: A Putative Product of IGF-I Gene Expression Involved in Tissue Repair and Regeneration.” *Endocrinology* 151, no. 3 (March 2010).

MGF

MGF solution 0.1, 1 and 10 μg/mL was injected **into the articular cavity** once daily in the first week, once every three days in the second week, and once on the first day in the third or fourth week.

MGF remarkably **accelerated ACL regeneration** and **restored its mechanical loading capacity in rabbits** after partial ACLT for four weeks. Our findings suggest that MGF weakens the effects of pathological stress on cell mobility of ACL fibroblasts and **accelerates ACL repair**

Sha, Y. “Mechano Growth Factor Accelerates ACL Repair and Improves Cell Mobility of Mechanically Injured Human ACL Fibroblasts by Targeting Rac1-PAK1/2 and RhoA-ROCK1 Pathways.” *International Journal of Molecular Sciences* 23, no. 8 (April 14, 2022): 4331.

DOSING MGF

This protocol should closely mimic natural peaks and dips in MGF and IGF within the specific muscles being trained. While regular MGF is short lived in the body, MGF 1 hour post workout should cause an increase in cell proliferation beyond the natural system's ability and should create a larger pool of stem cells.

1hr PostWO MGF 50 - 100 mcg in muscles trained to 600mcg, max 2g/wk
24-36hrs later IGFLR3 40-80mcg every other day for 6w
Don’t take IGF postWO

PEG MGF has t1/2 3-4 days, dose 3-4 times per week 100-600mcg SC/IM, no more than 2g per week

MK677

(Ibutamoren)
This is a non-peptidic, orally active and selective agonist of the growth hormone secretagogue receptor. It mimics the action of ghrelin in the stomach, raising growth hormone and IGF-1 levels, but does not affect cortisol levels.

Human studies have shown it to increase both muscle mass and bone mineral density. Dosed at 25mg daily, Ibutamoren has been shown to increase IGF-1 levels by 60% in 6 weeks in humans. A 72% increase in IGF-1 levels was seen after 12 months.

MK 677 is non-hormonal. It is best utilized in at least a 3 month cycle with dosage increasing each month. The optimal dosing time for MK 677 is at night directly before going to bed.

Nass, R. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann Intern Me 2008 Nov 4;149(9):601-11.

AOD-9604

Synthetic analogue of the lipolytic domain of hGH, does not act by IGF-1, no negative effect on carbohydrate metabolism, no antibody production, no withdrawal or serious AE

No hyperglycemia, does not compete for the hGH receptor or induce cell proliferation (More 2014)

Activates beta 3 adrenergic receptors in skeletal muscle and fat

Chondrocyte production of collagen (Heffernan 2001)

Phase 3 trials for pain control

Osteoporosis- stimulates bone differentiation, mineralization, MSC mobilization

“Frag” is not as stable d/t no tyrosine residue for stabilization

AOD 9604

Stimulates bone mineral density in ovariectomized rats (Fawcett 2015)

Enhanced cartilage regeneration in rabbits when administered w HA (Kwon 2015)

Increased muscle capillary, glucose release to muscle from blood and changes in muscle composition to increase glucose uptake (Dehbashi 2021)

SE: mild HA, fatigue, hypoglycemia, dizziness

Dosing: 300mcg/day SC for 3 months

REFERENCES AOD 9604

Dehbashi, M. “The Effect of Eight Weeks Endurance Training, Somatropin Injection, and Its Lipolytic Fragment (AOD9604) on Cytokeratin-18 and Liver Enzymes of Mice Induced Liver Damage Due to a High-Fat Diet.” *Internal Medicine Today* 27, no. 4 (September 10, 2021): 502–17.

Fawcett, E. “The Skeletal Effects of a Growth Hormone-Derived Peptide (AOD9604) in the Aged Rat Model of Postmenopausal Osteoporosis,” 2004.

Heffernan, M. “The Effects of Human GH and Its Lipolytic Fragment (AOD9604) on Lipid Metabolism Following Chronic Treatment in Obese Mice and Beta(3)-AR Knock-out Mice.” *Endocrinology* 142, no. 12 (December 2001): 5182–89.

Kwon, D. “Effect of Intra-Articular Injection of AOD9604 with or without Hyaluronic Acid in Rabbit Osteoarthritis Model.” *Annals of Clinical & Laboratory Science* 45, no. 4 (July 1, 2015): 426–32.

Moré, M. “Safety and Metabolism of AOD9604, a Novel Nutraceutical Ingredient for Improved Metabolic Health.” *Journal of Endocrinology and Metabolism* 4, no. 3 (June 27, 2014): 64–77.