Creatine monohydrate as a supplement.

Do we know what we are doing?

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What is a supplement?

- To fill up or supply by additions; to add something to; to fill the deficiencies of.
- These substances can be legal or illegal.
- It is important to note that none of the legal supplements are subjected to quality control, nor do they have to provide proof of their claims.
Where do we get supplements?

➢ There are about 170 companies in South Africa supplying various supplements to the market, as varied as colostrum and queen jelly to prohormones and creatine monohydrate.

➢ One example is USN, they alone supply 231 different supplements.
Why use a supplement?

- To increase the ergogenic effect of exercise, to run faster, jump higher, or throw further than the competition.
- To increase the androgenic effect of resistance training.
- The supplement in this case is creatine monohydrate.
What is an ergogenic aid?

- It’s defined as any means of enhancing energy utilization, including energy production, control, and efficiency.
- Athletes frequently use ergogenic aids to improve their performance and increase their chances of winning in competition.
Ergogenic effect.

- Short term benefit only.
- Increased phospho-creatine at site of need.
- Possible faster recovery after exercise.
- Acts as a pH buffer, therefore prevents lactic acid buildup, delaying fatigue.
Androgenic aid

- Defined as a supplement to increase the muscle building effect of resistance training by any means, because some people actually want to look like...
This
What are the factors we need to look at?

- Creatine monohydrate.
- Pluripotent stem cells.
- Satellite cells.
- Androgen receptors.
- Testosterone.
- Dihydrotestosterone.
- Resistance training.
- Is there interaction between the above?
Creatine monohydrate.

- Chemically: methyl guanidine-acetic acid.

- Creatine from dietary sources provide approximately 1-2 g of creatine per day.

- 1-2 g per day is synthesized from amino acids, arginine, glycine, and methionine in the human liver, kidney, and pancreas.
History.

- Discovered 1832. First organized use 1992 by the British Olympic team.
- Marketed as an ergogenic and androgenic aid.
- Supplementation of creatine, was a $200 million a year industry in the USA in 1998.
Muscle creatine content.

- Intramuscular levels of creatine 110-160 mmol kg\(^{-1}\) dry muscle with ~60% of total creatine in the form of phospho creatine.
- Little creatine is found at the site of use, and therefore creatine must be transported from areas of synthesis to areas of storage and utilization.
Creatine and muscle.

- Uptake is muscle fiber-type dependent.
- Type 2 fibers have higher levels of creatine and phosphocreatine.
- Exercise can stimulate the muscle uptake and content of creatine.
- Exercise increases the translocation of the creatine transporter to the muscle membrane.
Creatine uptake.

- Uptake into muscles occurs via a sodium / chloride dependent transporter, (CreaT) against a concentration gradient, regulated by the intracellular concentration of creatine.

- Potential down-regulation of these systems with chronic exposure to creatine?

- Potential up regulation of transporter system?
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Pluripotent stem cells.

- They are mesenchymal cells, embryonic stem cells (ESC), or somatic stem cells (SSC) that can be stimulated to develop into any tissue under the correct stimuli.
- It is widely distributed in the human body.
- Hormonal stimulation occurs via the androgen/estrogen receptor.
- Pluripotent stem cell stimulation in one direction inhibits the proliferation in the other line.
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Satellite cells.

- “Specialized” pluripotent stem cells.
- These are cells or clusters of cells outside the basil lamina that ensheathes each muscle fiber.
- They have the potential to form new muscle under the correct stimuli.
- Various factors can produce this stimulus.
Factors stimulating satellite cells.

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Androgen receptors.

- The receptors by which the androgen hormones exert their effect.
- Where are they located and how do we know that they are responsible for the androgenic effect?
- Can their density be influenced?
Molecular mechanism of action of Testosterone and DHT.
How do we know that they are responsible for the androgenic effect?

- In pluripotent stem cell cultures, androgen receptor mRNA and protein levels were low at baseline but increased after testosterone or DHT treatment.
- The effects were blocked by bicalutamide.
Can the density of AR’s be influenced?

- Down regulation due to immobility.
- Up regulation by:
  - Exercise.
  - Supra physiological doses of testosterone/DHT.
  - Additive effect of increased androgens and exercise.
AR induction by androgens.
How does Testosterone/DHT exert their androgenic effect?

- Testosterone and DHT regulate lineage determination in mesenchymal pluripotent cells/satellite cells by promoting their commitment to the myogenic lineage and inhibiting their differentiation into the adipogenic lineage.
The effect of supra physiological doses of androgens and AR induction.
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Testosterone.

- The male androgen responsible for secondary male characteristics acting via the androgen receptor.
- Strength training combined with supra physiological doses of testosterone enhances muscle hypertrophy.
- % of the secreted testosterone is converted to dihydrotestosterone by the enzyme 5 alpha reductase.
Conversion of Testosterone to Dihydrotestosterone

5 alpha reductase

Testosterone → Dihydrotestosterone

NADPH + H+ → NADP
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Dihydrotestosterone.

- This is the most potent androgen in males and females.
- DHT’s affinity for the androgen receptor is 2-5 times that of testosterone, and has a 3-10 fold greater molar potency as a transactivator of the receptor.
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If you want to look like this, you have to do resistance training.
What happens during resistance training?

- Micro muscle damage.
- Increased Testosterone/Dihydrotestosterone.
- Resistance training increases satellite cell numbers and activity.
- Increases AR receptors.
- Muscle hypertrophy/hyperplasia.
Satellite cell response to Myotrauma.

Additive effect of androgens and resistance training.

**Journal of Endocrinology (2001) 170, 27–38**
Resistance training increases the density of AR’s.

Where do supplements, especially creatine fit into this?

- Creatine has a remarkable androgenic effect in 33% of users, a small effect in 33% of users and no effect in 33%.
- The mechanism of the androgenic effects and the reason for this variable response is unknown, or is it?
- Various theories have been put forward to explain the androgenic mechanism of creatine supplementation.
Theories.

- From the literature, the increase in muscle mass may result from:
  
  - Increased protein synthesis.
  
  - Hyper hydration / Creatine, an end product of contraction stimulates protein synthesis.
  
  - Reduced protein catabolism.
  
  - Creatine supplementation reduces exercise-induced muscle damage / Creatine supplementation increases ATP reserve, preventing transient ischemia, maintaining cell wall integrity.
Are these theories the answer?

➢ No they do not explain the underlying mechanism for the androgenic effect seen in susceptible individuals.

➢ By asking why, did I find the answer, or simply add more questions?
What is the answer?

- Double blind cross-over study.
- Leg one to last 3 weeks, then 6 weeks washout, followed by leg two also to last 3 weeks.
- Blood sampling and anthropometric measurements on day 0, day 7, day 21 during each leg.
Study protocol.

– Tried to mimic actual use of creatine by:
  – Not interfering with subject diets.
  – Allowing normal training programs as done at the SA Rugby Institute at the University of Stellenbosch.
  – Supplying creatine/glucose to be taken.
How is creatine used?

- Loading phase, 25gm of creatine + 25gm of glucose.
- Maintenance phase, 5gm of creatine + 25gm glucose.
- In responders better results are obtained if supplementation is combined with strength training.
What was the hypothesis to be tested?

- Creatine monohydrate as a supplement, increases the conversion rate of testosterone to dihydrotestosterone expressed as a % of the available testosterone.
Creatine supplementation.

% Conversion Testosterone to Dihydrotestosterone

\[ p < 0.0001 \]

Creatine group
Glucose group

Day 0 Day 7 Day 21

% Conversion
What have we got so far?

- Creatine monohydrate supplementation.
- Testosterone.
- Dihydrotestosterone.
- Pluripotent stem cells.
- Satellite cells.
- Androgen receptors.
- Resistance training.
What are the implications of creatine supplementation.

- Increase Testosterone conversion to DHT.
- Increased levels of the most potent endogenous androgen.
- Increased pluripotent stem cell activity.
- Increased satellite cell production.
- Increased androgen receptors.
- Increased muscle hypertrophy in susceptible individuals.
What of the ethical/legal issues?

- Is the use of a supplement that increases the endogenous production of a more efficient steroid acceptable?
- Is it acceptable to give a supplement that may cause diseases later in life?
- Could a positive steroid abuse test result follow the use of creatine monohydrate?
Summary.

- Resistance training increases Testosterone.
- Resistance training increases satellite cells.
- Resistance training increases AR’s.
- Creatine supplementation → increases Testosterone conversion to Dihydrotestosterone.
- Increased AR’s + increased affinity/molar potency of more Dihydrotestosterone = increased muscle hyperplasia/hypertrophy.
Take home message

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Creatine supplementation.

% Conversion Testosterone to Dihydrotestosterone

p < 0.0001

Creatine group
Glucose group

Day 0 Day 7 Day 21

% Conversion

TIME

Creatine group

Glucose group
Thank you for listening to me

- Feel free to contact me in this regard
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