Healing the Aging Metabolism

Carrie Louise Daenell, ND

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- Earned Doctorate in Naturopathic Medicine Bastyr University
- Founder of medical practice with revenue in top 1% nationwide
- Previous Managing Editor of *Journal of Naturopathic Medicine*
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- Past-President of Colorado Association of Naturopathic Physicians
- Co-author, *Better Breast Health for Life!*
- Regular lecturer to both professional and consumer audiences
- A frequent contributor to professional and consumer periodicals
- Lives and practices in Colorado
- Featured on PBS *Healing Quest* with Olivia Newton John
- Featured on PBS *American Health Journal – The Doctor Show*

Agenda

- The Aging Metabolism
- Metabolism Basics
- Consequences of Metabolic Breakdown
- Metabolic Repair
  - Resveratrol
  - D-Ribose
  - 7-Keto-DHEA
  - Ubiquinol
- Summary

The Aging Metabolism

- On average American women will gain **10 lbs** with every passing decade, after age menopause
- **Clinical challenge**: Diet and activity levels remain unchanged while body weight increases
- ***Why?*** Metabolic compromise occurs "naturally" with wear and tear of life

Weight gain during menopause: Is it inevitable or can it be prevented? Postgraduate Medicine on-line. Available at: http://www.postgradmed.com/issues/2000/09_00/silverman.shtml. Accessed June 9, 2008.

The Aging Metabolism

- ***The Good News…***

  Nutritional therapies can help restore healthy, youthful metabolism in 3 simple ways:

  1. Increase mitochondria
  2. Give your body the building blocks needed
  3. Enhance mitochondrial efficiency

"Building a Healthy Community"

1. Increase mitochondria
   - build more houses

   Resveratrol
2. Give your body the building blocks needed
   - get more wood, nails, etc.

   D-Ribose
3. Enhance mitochondrial efficiency
   - increase skill of builders

   7-Keto-DHEA

   Ubiquinol

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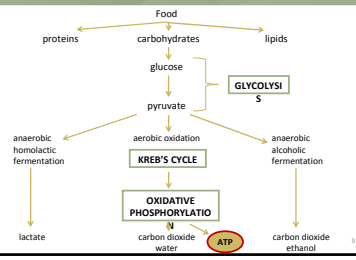
Metabolic Health Overview

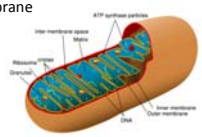
- Biochemistry of metabolism
  - Glycolysis
  - Krebs cycle
  - Oxidative phosphorylation
- Production of **A**denosine **T**ri **P**hosphate (**ATP**)

The Story of ATP



Where it Happens…

- Glycolysis – cytoplasm
- Krebs Cycle – mitochondria
- Oxydative Phosphorylation – mitochondria and inner mitochondrial membrane



The "House" of Energy Production

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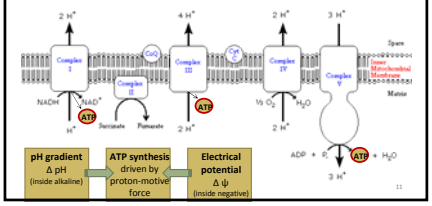
The Story of ATP Continues

Oxidative Phosphorylation: *A Closer Look*



pH gradient Δ pH (inside alkaline) ⇒ **ATP synthesis** driven by proton-motive force ⇐ **Electrical potential** Δ ψ (inside negative)

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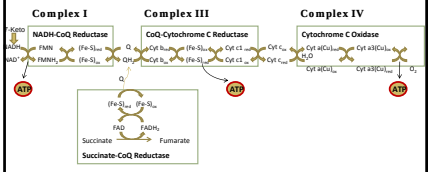
Inside the Complexes



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Metabolic Breakdown with Age

What Goes Wrong & Why?

- Decreased **number** of mitochondria
- Down-regulated biochemistry of ATP production secondary to:
  - Decreased supply of nutritional **co-factors**
  - Decreased supply of nutritional **substrates** (building blocks)
  - **Hypoxia**
- Decreased **efficiency** of mitochondria

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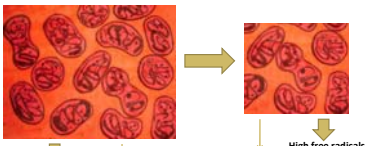
Mechanical Breakdown

Damage to Mitochondria = Diminished Supply



High ATP yield — Low free radical

High free radicals — Low ATP yield

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Metabolic Breakdown

- ATP over expenditure
  - Production of **A**denosine **D**i **P**hosphate (**ADP**)
  - Then **A**denosine **M**ono **P**hosphate (**AMP**)
  - Ultimately **adenine** (purine)
- Cellular release through membrane of AMP building blocks
  - Adenine (purine) leaks out of cell
- Permanent depletion of recycling energy pool

ATP ⟶ ADP ⟶ AMP ⟶ Adenosine ⟶ Adenine

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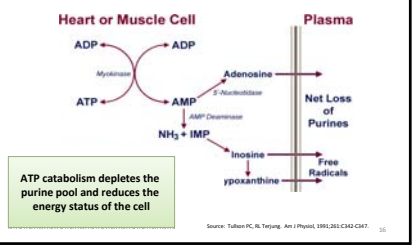
Metabolic Breakdown



ATP catabolism depletes the purine pool and reduces the energy status of the cell

Source: Tullson PC, RL Terjung. Am J Physiol, 1991;261:C342-C347.

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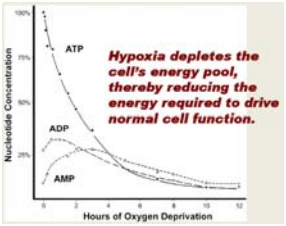
Reduced ATP in Absence of O_2



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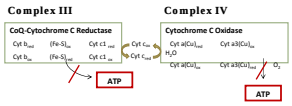
Mitochondrial Efficiency

- Mitochondrial damage increases with age
  - Higher reactive oxygen species (free radicals) yield
  - Lower ATP yield through oxidative phosphorylation
    - Complex III and IV



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The Aging Metabolism

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- Consequences of Metabolic Breakdown
- Metabolic Repair
  - Resveratrol
  - D-Ribose
  - 7-Keto DHEA
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Clinical Consequences

- Decrease in Metabolism
- Weight Gain
- Chronic Fatigue
- Fibromyalgia
- Congestive Heart Failure
- Ischemic Heart Disease
- Angina
- Arrhythmia
- Muscle Soreness (secondary to muscle exhaustion)
- Alzheimer's
- Parkinson's
- Huntington's

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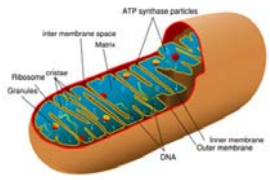
Biochemistry of Metabolic Repair

1. Create more **mitochondria**
2. Provide **building blocks** for ATP
3. Improve **efficiency** of mitochondria
   - Draw more oxygen via adequate nutritional co-factor supply
   - Substrate support

Also: Maintain adequate levels of **oxygen** (self-feeding upward or downward spiral with oxidative phosphorylation)

Mitochondria

The "House" of Energy Production



Factors of Mitochondrial Health

- **Quantities depleted by:**
  - Reactive oxygen species (free radicals)
  - Toxic exposure
  - Others
- **Quantities enhanced by:**
  - Exercise ("catch 22" – oxygen, purine depletion)
  - ALA (short half-life may compromise effect)
  - **Trans-Resveratrol**

Step 1: Mitochondria Protection

- **2-5%** oxygen in the mitochondrial membrane become reactive oxygen species (free radicals)
- Percentage may increase as wear and tear on existing mitochondria reduce its efficiency (i.e, aging)
- **Solution: Trans-Resveratrol**
  - Enhance supplies of newer more efficient mitochondria
  - Anti-oxidant support (include Japanese Sophora (rutin) & ubiquinol)

Anti-Aging Antioxidant

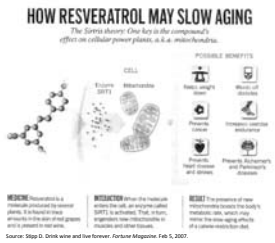
RESVERATROL

What is Resveratrol?

- Sourced from skin of French red wine grape and giant knotweed
- Standardized extract of **trans isomer**
  - Most active
  - Most researched form
- Enhances mitochondrial production
- Activates **siRT1 enzyme** (sirtuin class enzyme)
  - Associated with physical ability to survive adversity
  - Associated with increased longevity

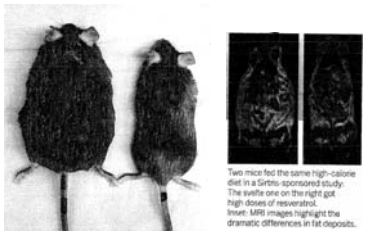
Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov.* 2006;5:493-506.
Providencia R. Scientific basis of the French Paradox. *Rev Port Cardiol.* 2006;25:1043-58.

Anti-Aging Effects



Source: Stipp D. Drink wine and live forever. *Fortune Magazine*. Feb 5, 2007.

Resveratrol & Weight Control



Source: Stipp D. Drink wine and live forever. *Fortune Magazine*. Feb 5, 2007.

Headline News

Red Wine's Resveratrol May Help Battle Obesity

Resveratrol, a compound present in grapes and red wine, reduces the number of fat cells and may one day be used to treat or prevent obesity, according to a new study. The results will be presented at The Endocrine Society's 90th Annual Meeting in San Francisco. Past research found that resveratrol protected laboratory mice that were fed a high-calorie diet from the health problems of obesity, by mimicking the effects of calorie restriction. In new research, scientists found that in a cell-based study, resveratrol inhibited pre-fat cells from increasing and prevented them from converting into mature fat cells. Also, resveratrol hindered fat storage. Most interesting was that resveratrol reduced production of certain cytokines (interleukins 6 and 8), substances that may be linked to the development of obesity-related disorders, such as diabetes and clogged coronary arteries. Also, resveratrol stimulated formation of a protein known to decrease the risk of heart attack. Obesity decreases this substance, called adiponectin.

Natural News web site. Available at http://www.naturalnews.com/021777.html. Accessed August 12, 2008.

Resveratrol Safety

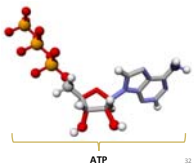
- Very well tolerated – in clinical trial doses up to 5 grams per day resulted in no serious adverse effects
- Side effects noted in practice – mitigated by gradual dosing and dose division
  - Loose stools, nausea, stimulation (men), and malaise (men)

Boocock DJ, Faust GE, Patel KR, et al. Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiol Biomarkers Prev*. 2007;16(6):1246-1252.

Step 2: Nutritional Components

The "Building Blocks" Necessary for Energy Production

- Components of ATP
  - **D-Ribose**
  - Phosphate Groups
  - Adenine (purine)

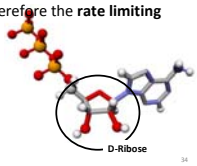


The Rate-Limiting Sugar of Life

D-RIBOSE

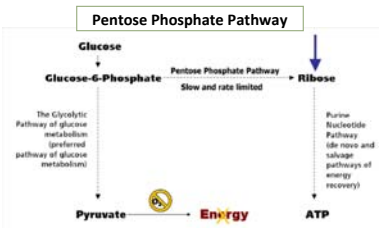
What is D-Ribose?

- 5-carbon sugar
- Structural backbone of **ATP**; also prevents purine loss
- D-Ribose availability is therefore the **rate limiting** aspect of ATP production



Fleming T, ed. D-Ribose. In: PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Company, Inc.; 2001: 139-41.

D-Ribose



D-Ribose Demands

- Not necessary as supplement under normal circumstances
- Abnormal circumstances lead to need for supplementation
  - **Low oxygen** leads to burning ADP for energy
  - **Increased energy demands** leads to burning ADP for energy

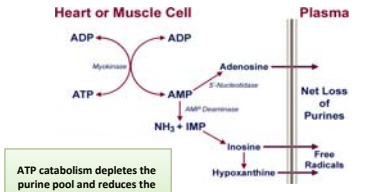
Fleming T, ed. D-Ribose. In: PDR for Nutritional Supplements. Montvale, NJ: Medical Economics Company, Inc.; 2001: 139-41.

D-Ribose Demands

- Burning ADP Yields AMP
- AMP readily metabolizes to adenosine then to adenine
- Adenine (purine) leaks out of cell
- Adenine very slow to rebuild
- ADP (immediate precursor to ATP production) supply permanently compromised

ATP ⟶ ADP ⟶ AMP ⟶ Adenosine ⟶ Adenine

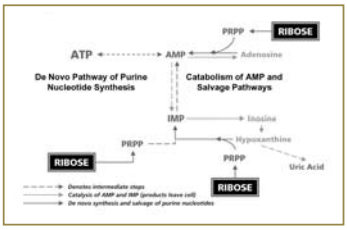
Purine Loss



ATP catabolism depletes the purine pool and reduces the energy status of the cell

Source: Tullson PC, RL Terjung. Am J Physiol, 1991;261:C342-C347.

Ribose Re-Builds Adenine Pool



D-Ribose Cardiovascular Effects

Study Design/Findings	Dosage	Citation
Prospective, randomized, double blind, placebo controlled, crossover design study with 15 patients with coronary artery disease and congestive heart failure. Supplementation: •Improved left ventricular function •**12% increase in quality of life**	Ribose or placebo 3 weeks / washout / crossover	Omran H, et al. D-ribose improves diastolic function and quality of life in congestive heart failure patients: A prospective feasibility study. *Eur J Heart Failure.* 2003;5:615-619.

D-Ribose Cardiovascular Effects

Study Design/Findings	Dosage	Citation
Randomized, double blind, placebo controlled trial of 20 patients with coronary artery disease and stable angina. Supplementation: •Increased treadmill walking time; **nearly 20%** greater improvement versus placebo •After 3 days, also improved the heart's tolerance to ischemia (oxygen deprivation)	15-g ribose 4 times daily or placebo (glucose)	Pliml W, et al. Effects of ribose on exercise-induced ischaemia in stable coronary artery disease. *Lancet.* 1992;340(8818):507-510.

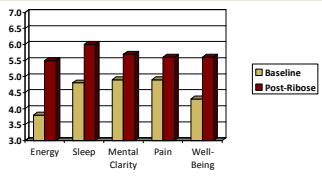
D-Ribose & Chronic Fatigue

- 3-week open label clinical study
- 41 patients previously diagnosed with **FMS** and/or **chronic fatigue**
- Quality of Life (QOL) questionnaire (visual analog scale: 1-10)
- 5 g ribose 3 times daily

Patient Profile:
- Sex: 78% female (28)
- Average: 48 years (21 – 62)
- FMS: 75%
- CFS: 58%
- Average duration of therapy:
  - 28 days (17-35)
- 5 disqualified for non-compliance
  - < 50% consumed

D-Ribose & Chronic Fatigue

- Approximately **66%** of patients experienced significant improvement
- Average increase in energy on the VAS of **45%**
- Average improvement in overall well-being of **30%**



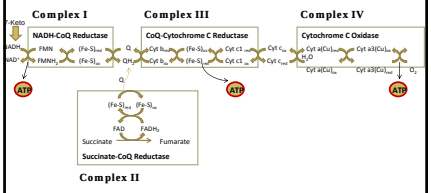
Teitelbaum JE, Johnson C, St Cyr J. The use of D-ribose in chronic fatigue syndrome and fibromyalgia: a pilot study. *J Altern Complement Med.* 2006 Nov;12(9):857-62.

D-Ribose Safety

- Clinical notes
  - Well tolerated
  - Will not raise blood sugar in type II (non-insulin dependent) Diabetes and likely therapeutic
  - Not recommended for type I (insulin dependent) diabetes
- Side effects noted in practice
  - Mild, transient hypoglycemia when taken on an empty stomach
  - Sleep disturbance when taken late in day
- Mitigation of side effects with lower dose or food
- Phosphorylated upon absorption preventing Glycation or Maillard Reaction or Enzymatic Browning

Step 3: ATP Production Efficiency

The "Construction" of Cellular Energy



Nutritional Co-Factors

The "Tools" Necessary for Energy Production

- **CoQ10** is a critical rate-limiting nutritional co-factor
  - For complete metabolic processing of oxidative phosphorylation and production of ATP
  - Must be in reduced (QH) state to support Complex III and IV as pathway moves forward
- **Niacin (B3)** used to form nicotinamide or niacinamide adenide dinucleotide (NAD)
  - NAD is required for oxidative phosphorylation
- **Riboflavin (B2)** use to form flavin adenide dinucleotide (FAD)
  - FAD is required for oxidative phosphorylation

Marriage BJ, Clandinin MT, Macdonald IM, Glerum DM. Cofactor treatment improves ATP synthetic capacity in patients with oxidative phosphorylation disorders. Molecular Genetics and Metabolism. 2004 Apr;81(4):263-72.
Marriage B, Clandinin MT, Glerum DM. Nutritional cofactor treatment in mitochondrial disorders. *J Am Diet Assoc.* 2003 Aug;103(8):1029-38.

Substrate provision, muscle defense and fat burning direction

7-KETO-DHEA

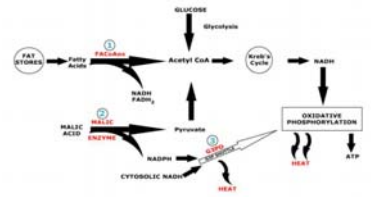
What is 7-Keto-DHEA

7-oxy-dehydroepiandrosterone (7-keto-DHEA)

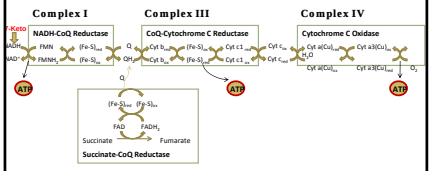
- Unlike DHEA, 7-keto DHEA does not convert to sex hormones and does not have known adverse effects
- Actions:
  - Stimulates immune system
  - Anti-catabolic (prevents muscle loss)
  - Reduces stress
  - Increases thermogenesis by activating enzymes
    - Glycerol-3-phosphate dehydrogenase (GPDH), malic enzyme, fatty acyl CoA oxidase
  - Helps normalize thyroid function
  - Improves memory

Weeks C, Lardy H, Henwood S. *FASEB J.* 1998; 12:A764.
Lardy H, Partridge B, Kneer N et al. *Proc NatlAcadSci USA.* 1995; 92:6617-6619..
Davison MH, Weeks C, Lardy H et al. *FASEB J.* 1998; 12:A764.
So CY, Lardy H. *J Biochem.* 1990; 110:207-213.
Botyleva V, Belke M, Kneer N et al. *Arch BiochemBiophys.* 1997; 341:122-128.

7-Keto-DHEA Mechanism of Action



7-Keto-DHEA provides NADH for Oxidative Phosphorylation



7-Keto-DHEA Clinical Research

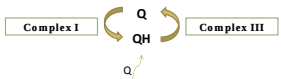
- Supplementation with **7-keto DHEA** (200 mg/day), in conjunction with exercise, reduced body weight and fat
  - Also elevated triiodothyronine (T3) level, which may affect basal metabolic rate
- In combination with additional supportive nutrients, 7-keto DHEA had more pronounced impact on weight loss in an 8-week trial:
  - 7-keto group lost 1.43 kg (or 3.15 lb) more than placebo
  - On average, treatment group lost total of 2.15 kg (or 4.74 lb), whereas placebo lost only 0.72 kg (1.59 lb)
  - Body mass index (BMI) was also decreased, confirming weight loss was due to loss of body fat vs. muscle tissue

CohenCM, Torina GC. Swain MA, et al. Double-blind study evaluating the effects of exercise plus 3-acetyl-7-oxo-dehydroepiandrosterone on body composition and the endocrine system in overweight adults. Journal of Exercise Physiology (online). 1999; 2:1-2. Available at: http\\:www.css.edu\users\tboone2\aaep\abstract\ROB.html
Zenk JL, Helmer TR, Kassen LJ, Kuskowski MA. *CurrTher Res.* 2002 Apr;63(4):263-72.

When CoQ10 is Not Enough…

UBIQUINOL

The Role of Coenzyme Q



~To Survive or Thrive

What is Ubiquinol?

- Ubiquinol is the reduced form
  - Historically unstable in this form[1,2]
  - Genetic inability to convert ubiquinone to ubiquinol seen in **30-50%** population[3]
  - Ability to convert declines with age
- Ubiquinol is shown to enhance plasma levels of total coq10 up to **162%** higher than ubiquinone[4]

1. Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. *Mol Biotechnol.* 2007;37:31-7.
2. Ueda T, Ono T, Moro M, Kitamura S, Ueda Y. Method of stabilizing reduced coenzyme Q10. Patent application number US 2005/0008630 A1. January 13, 2005.
3. Miles MV, et al. LPL and NQO1 genotypes are associated with decreased Coenzyme Q10 redox ratio. *International Congress of Clinical Chemistry and American Association for Clinical Chemistry Annual Meeting.* July, 2005.
4. Unpublished data. Kaneka Corporation. January 19, 2006.

When CoQ10 is Not Enough…

Genetics

- NQO1 SNP impacts ability to convert CoQ10 to its active form – ubiquinol (QH)
- Affects 40-50% of the population

Chronic Disease

- Many diseases associated with suboptimal CoQ10 redox ratios

	QH	CoQ10
Healthy:	97%	3%
Hepatitis:	90.5	9.5%
Diabetes:	41%	59%

Aging

- Increasing age associated with impaired ability to convert CoQ10 to QH
- QH enhances energy and stamina 5 fold over baseline in an animal model of aging
- Forestalls age-related physical decline in age-accelerated animals

Miles MV, et al. LPL and NQO1 genotypes are associated with decreased Coenzyme Q10 redox ratio. *International Congress of Clinical Chemistry and American Association for Clinical Chemistry Annual Meeting*, July, 2005.

The Role of Ubiquinol

- Ubiquinone (CoQ10) *must be* converted (reduced) to Ubiquinol (QH):
  - For maximum health benefits
  - To support completion of oxidative phosphorylation through all complexes for optimal ATP production
  - For the final metabolite (H_2), which draws O_2 into tissue from blood stream via diffusion to create H_2O
    - Maximizes ATP production
    - Resolves local hypoxic issues

1. Littarru GP, Tiano L. Bioenergetic and antioxidant properties of coenzyme Q10: recent developments. *Mol Biotechnol.* 2007;37:31-7.
2. Ueda T, Ono T, Moro M, Kitamura S, Ueda Y. Method of stabilizing reduced coenzyme Q10. Patent application number US 2005/0208630 A1. January 13, 2005.
3. Miles MV, et al. LPL and NQO1 genotypes are associated with decreased Coenzyme Q10 redox ratio. *International Congress of Clinical Chemistry and American Association for Clinical Chemistry Annual Meeting*, July, 2005.
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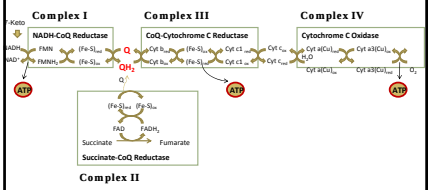
Nutritional Cofactor Ubiquinol

The "Construction" of Cellular Energy



Ubiquinol Benefits

- Enhances energy and stamina **5-fold** over baseline in an animal model of aging[1]
- Forestalls age-related physical decline in age-accelerated animals
- 3-month **clinical study**[2]
  - **3-fold** increase in ubiquinol levels
  - **24-50%** increase in ejection fraction percentages

1. Yan J, Fujii K, Yao J, et al. Reduced coenzyme Q10 supplementation decelerates senescence in SAMP1 mice. *Exp Gerontol.* 2006 Feb;41(2):130-40.
2. Langsjoen PH. Supplemental ubiquinol in patients with advanced congestive heart failure. Presented at the 5th International CoQ10Conference. November11, 2007, Kobe Gakuin University at Port Island, Kobe, Japan.

Ubiquinol Safety

- Placebo-controlled safety trial
  - No safety concerns noted
  - No changes in standard laboratory tests
  - No adverse events reported (300 mg) for up to two weeks after study completion

Hosoe K, Kitano M, Kishida H, Kubo H, Fujii K, Kitahara M. Study on safety and bioavailability of ubiquinol (Kaneka QH) after single and 4-week multiple oral administration to healthy volunteers. *Regul Toxicol Pharmacol.* 2007;47:19-28.

Case Studies – Original HAM Protocol (Sans 7-Keto-DHEA)

- 65 Yr old Female, **17 lbs 9 mo** (no diet/exercise changes)
  - Wt change 180 to 163
- 42 Yr old Female, **18 lbs 9 mo** (no diet/exercise changes)
  - Wt change 156 to 138
- 60 Yr old Female, **9 lbs 6 mo** (slight increase in exercise)
  - Wt change 145 to 134
- 46 Yr old Female, **18 lbs 9 mo** (no diet/exercise changes)
  - Wt change 191 to 173
- 30 Yr old Male MERRF, **35 lbs 9 mo** (no diet/exercise changes)
  - 1-2 1-hour naps/week down from daily 1-2 hour naps
  - T chol, Trigly, LDL decreased

Case Studies – 7-Keto-DHEA
Added to Ongoing Weight Loss Program

DATES		10/18/10	11/1/10	11/18/10	12/16/10	1/13/11	2/17/11	3/17/11	4/27/11		
AGE	63										
GENDER	Female										
FAT WEIGHT		73.7	75.4	74.6	70.6	64.8	65.8	64.3	66.8		
LEAN DRY MASS		25.4	24.4	24.2	24.0	23.8	23.9	23.8	23.9		
7-KETO INTRODUCED				✓							
7-KETO DBL DOSE											
DATES		7/29/10	8/31/10	10/5/10	11/3/10	12/2/10	2/3/11				
AGE	66										
GENDER	Male										
FAT WEIGHT		60.0	47.7	42.3	48.6	39.7	30.3				
LEAN DRY MASS		44.4	43.8	42.0	41.1	42.0	42.9				
7-KETO INTRODUCED					✓						
7-KETO DBL DOSE											
DATES		10/21/10	11/9/10	11/30/10	12/21/10	1/11/11	2/10/11	3/8/11	4/5/11	5/3/11	6/14/11
AGE	57										
GENDER	Female										
FAT WEIGHT		69.1	67.8	63.1	60.5	61.8	54.7	53.5	46.2	40.8	39.3
LEAN DRY MASS		25.8	25.4	25.6	25.3	25.2	25.0	24.7	24.6	24.2	24.7
7-KETO INTRO -1/2 DOSE		✓									
7-KETO FULL DOSE			✓								
7-KETO DBL DOSE								✓	✓		

Agenda

- The Aging Metabolism
- Metabolism Basics
- Consequences of Metabolic Breakdown
- Metabolic Repair
  - Resveratrol
  - D-Ribose
  - 7-Keto-DHEA
  - Ubiquinol
- Summary

Protocol

1. **Resveratrol** (100% trans isomer, standardized extract)
   - 125 mg per day with food
   - Divide dose to mitigate any nausea or diarrhea
2. **D-Ribose**
   - 5 g AM, noon with food (10 g per day total)
3. **Ubiquinol**
   - 50 mg AM, noon with food (100 mg per day total)
4. **7-Keto-DHEA** 100-200 mg twice per day with food
5. **Multi-Vitamin**/Mineral with Krebs Cycle Chelates
   - Containing niacin and riboflavin

Conclusion

- Healing the underlying pathophysiology associated with the aging metabolism is critical to healthy weight control and chronic disease management.
- Nutritional support is a key to enhancing cellular energy potential and achieving true healing.