Dept of
BIOCHEMISTRY

Coenzyme Q 10

By Assist. Prof. Hazim Allawi

History

- 1957 - Coenzyme Q10 was first isolated from beef heart mitochondria by Dr. Frederick Crane

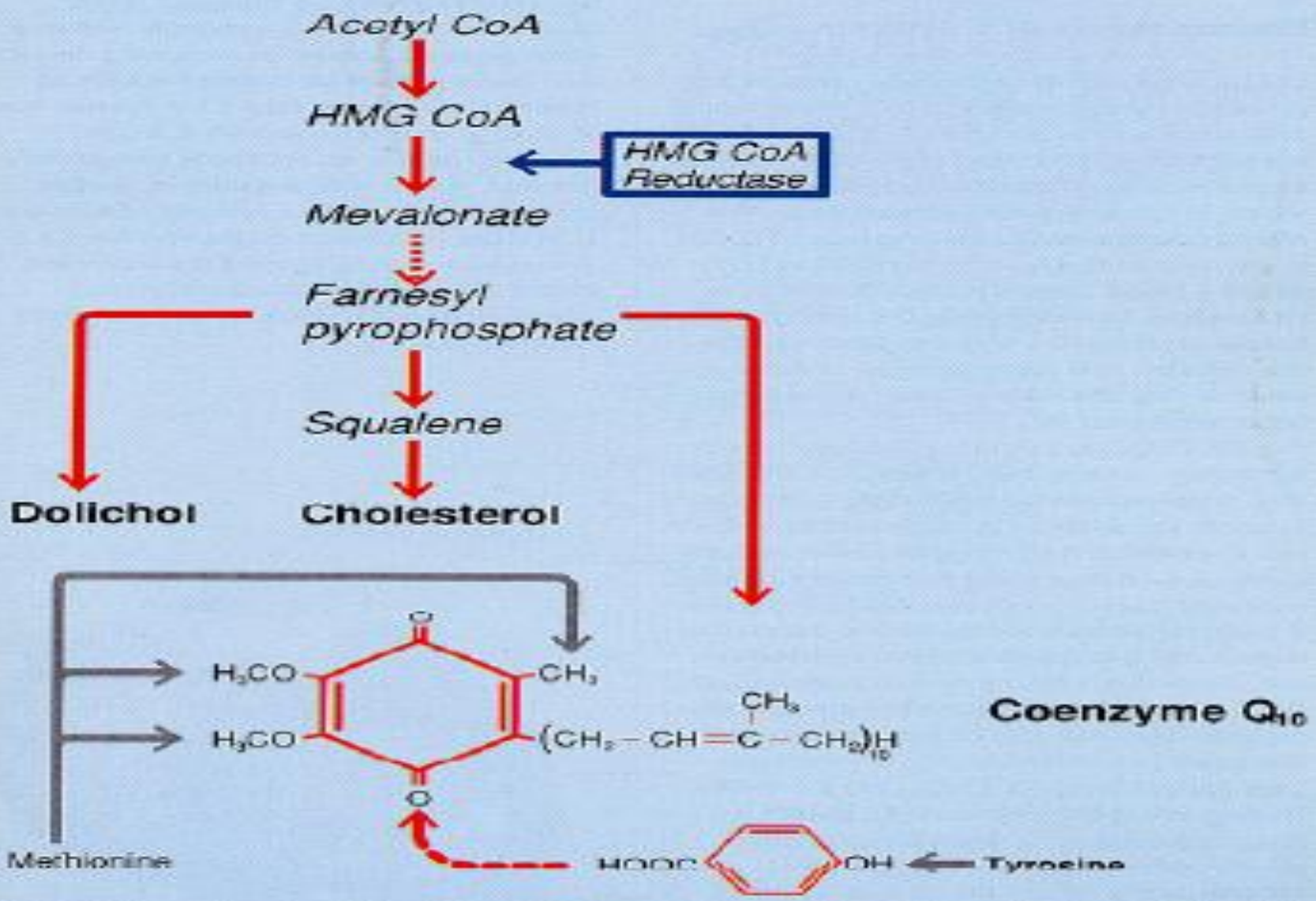
- 1958 - The precise chemical structure of Coenzyme Q10 was determined by professor Karl Folkers and collaborators at Merck, Inc.

- 1961 - Coenzyme Q10 was considered as a potential treatment for cancer.

- 1964 – Coenzyme Q10 demonstrated its usefulness for the treatment of CHF

- 1970 – Coenzyme Q10 demonstrated its effectiveness as an anti-oxidant.

Schematic representation of the biosynthetic pathway leading to Cholesterol, Dolichol and Coenzyme Q



CoQ10

is a ubiquitous quinone that is synthesized within human cells

the Q refers to the benzoquinone “head

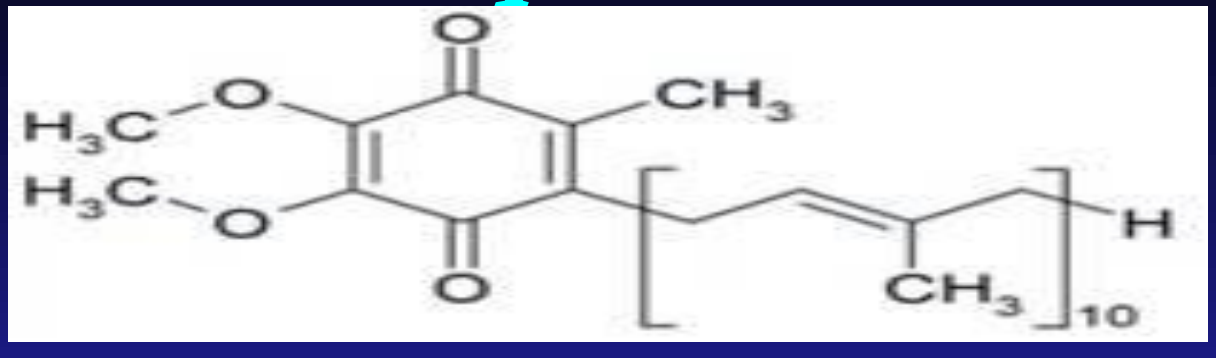
the 10 refers to the “tail” which consists of 10 isoprenyl subunits.

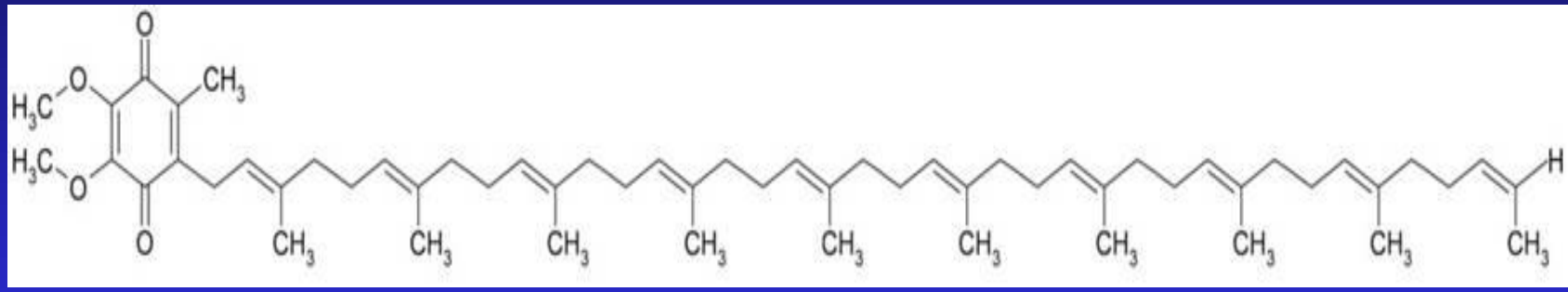
The quinone portion of CoQ10 is synthesized from tyrosine and indispensably requires vitamins B2, B3, B5, B6, B12, folic acid, tetrahydrobiopterin and vitamin C.

The isoprenyl side chain is synthesized from acetyl-CoA through the mevalonate pathway, which also requires zinc.

- The mevalonate pathway may be inhibited by as much as 40% by statins (HMG-CoA reductase inhibitors)
- Statins block production of farnesyl pyrophosphate
- Giving CoQ10 supplementation with statins has been proposed

Ubiquinone:





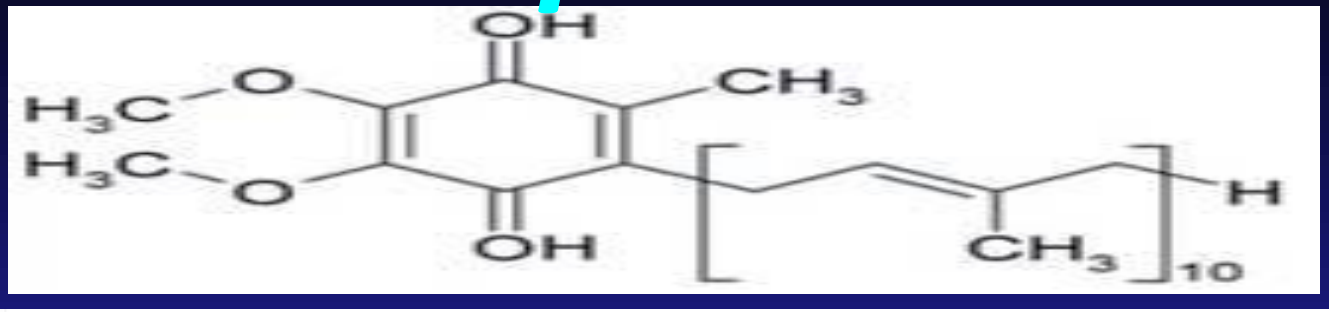
The fully oxidized form of CoQ10 is ubiquinone-10, or simply ubiquinone

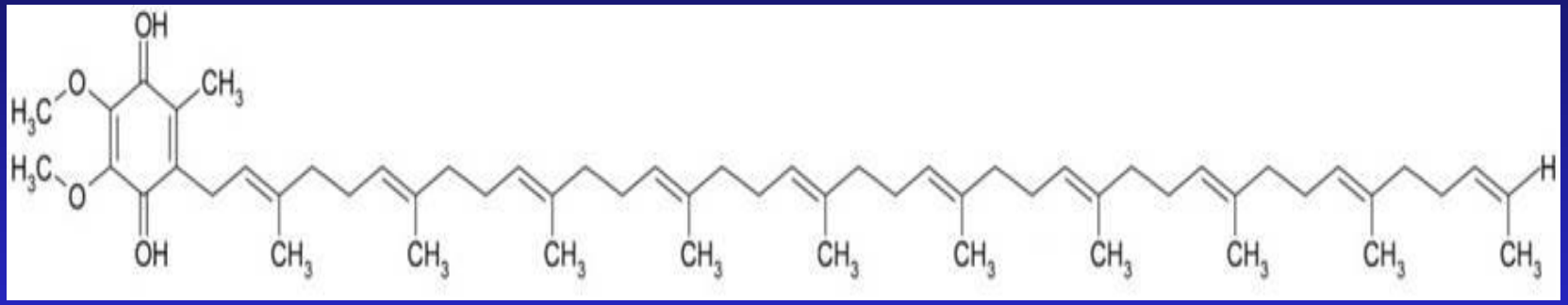
often represented as **"Q"**. Ubiquinone

is a required coenzyme of the Q cycle

involved in glycolysis and lipolysis.

Ubiquinol:





The fully reduced form of CoQ10 is ubiquinol-10, or simply ubiquinol

Ubiquinol is an effective antioxidant that protects vitamin E,

is required for function of Complex III within the electron transport chain.

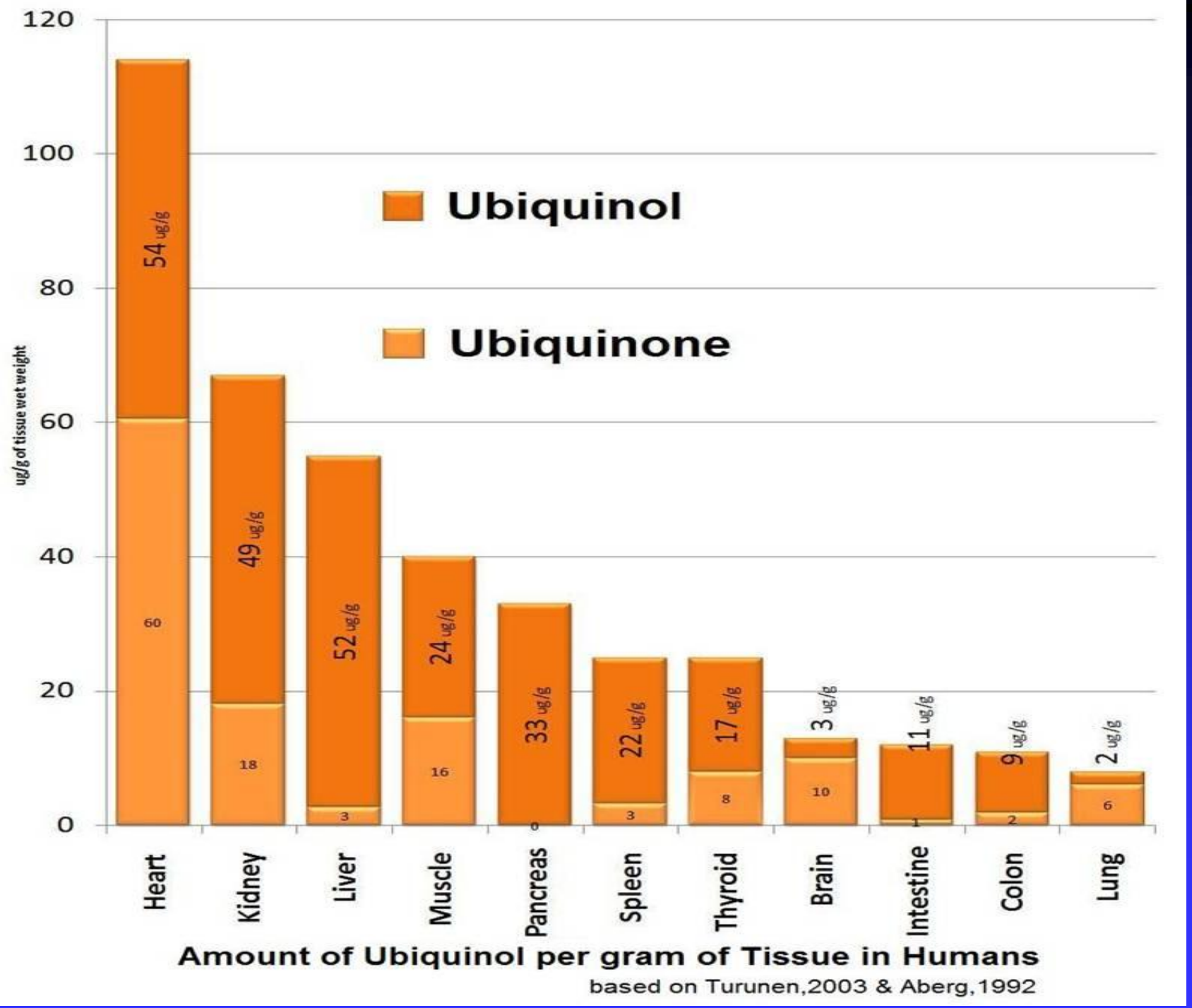
Ubiquinol levels are higher than ubiquinone levels in humans..

A little less than 50% of heart CoQ10 is ubiquinol

slightly less than 25% of brain and lung CoQ10 is ubiquinol.

It should be noted that even though the percentage of ubiquinol to ubiquinone in the heart is less than 50%

the amount of ubiquinol per gram of heart tissue is actually higher in the heart than the amount found in other tissues.

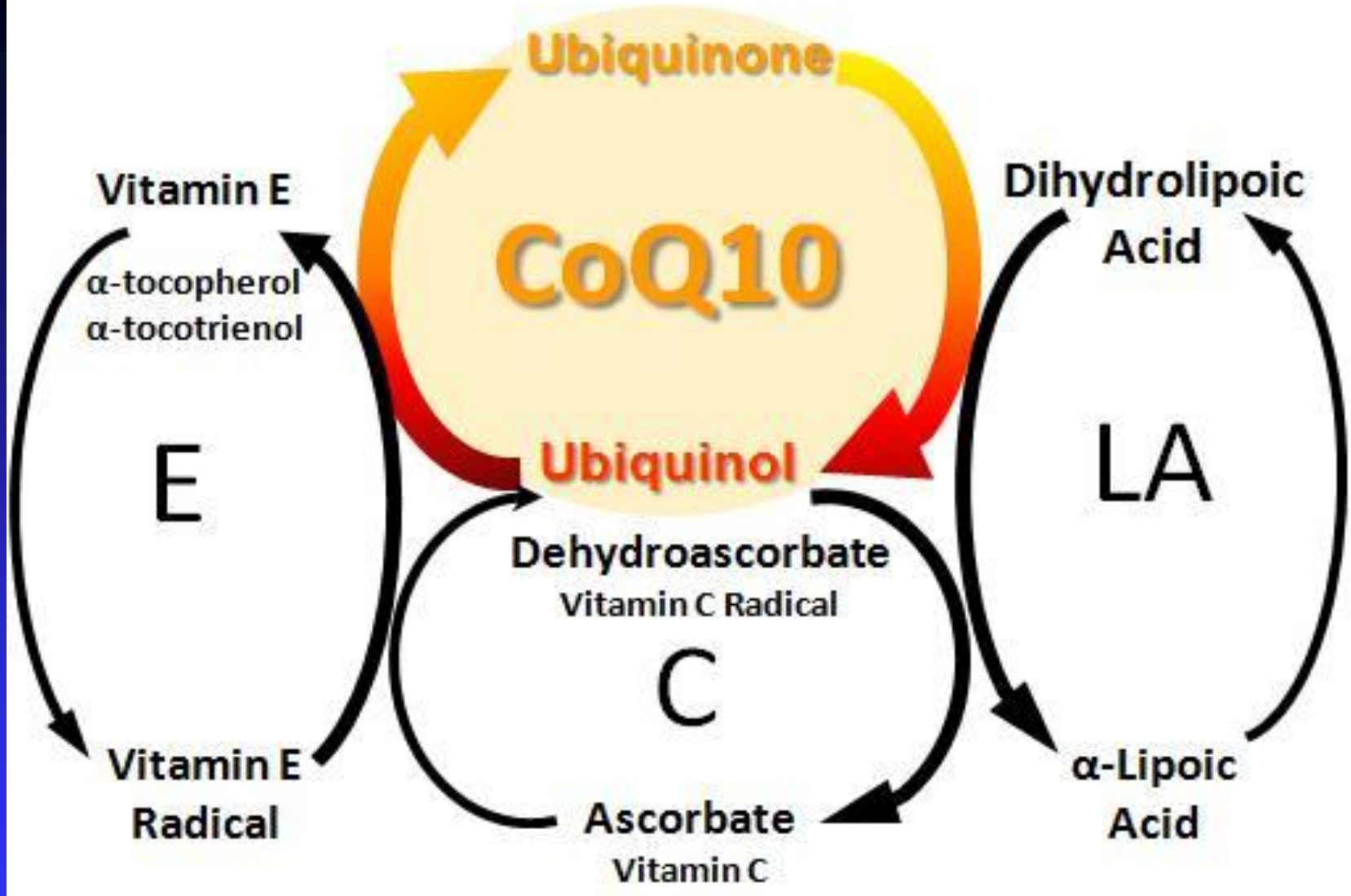

120
100
80
60
40
20
0
ug/g of tissue wet weight
Ubiquinol
Ubiquinone
54 ug/g
60
49 ug/g
18
52 ug/g
3
24 ug/g
16
33 ug/g
0
22 ug/g
3
17 ug/g
8
3 ug/g
10
11 ug/g
1
9 ug/g
2
2 ug/g
6
Heart
Kidney
Liver
Muscle
Pancreas
Spleen
Thyroid
Brain
Intestine
Colon
Lung
Amount of Ubiquinol per gram of Tissue in Humans
based on Turunen,2003 & Aberg,1992

The regeneration of ubiquinol from the oxidized form ubiquinone is essential to the maintenance of its antioxidant function.

Enzymes involved in this regenerative process include:

* lipoamide dehydrogenase.
* glutathione reductase.
* thioredoxin reductase

All three enzymes can also reduce lipoic acid to its antioxidant form dihydrolipoic acid, which can reduce ubiquinone to ubiquinol.



Antioxidant Regeneration by CoQ10

Compiled from Packer-1997, Hyun-2006 & Turunen-2004

Functions of Coenzyme Q10:

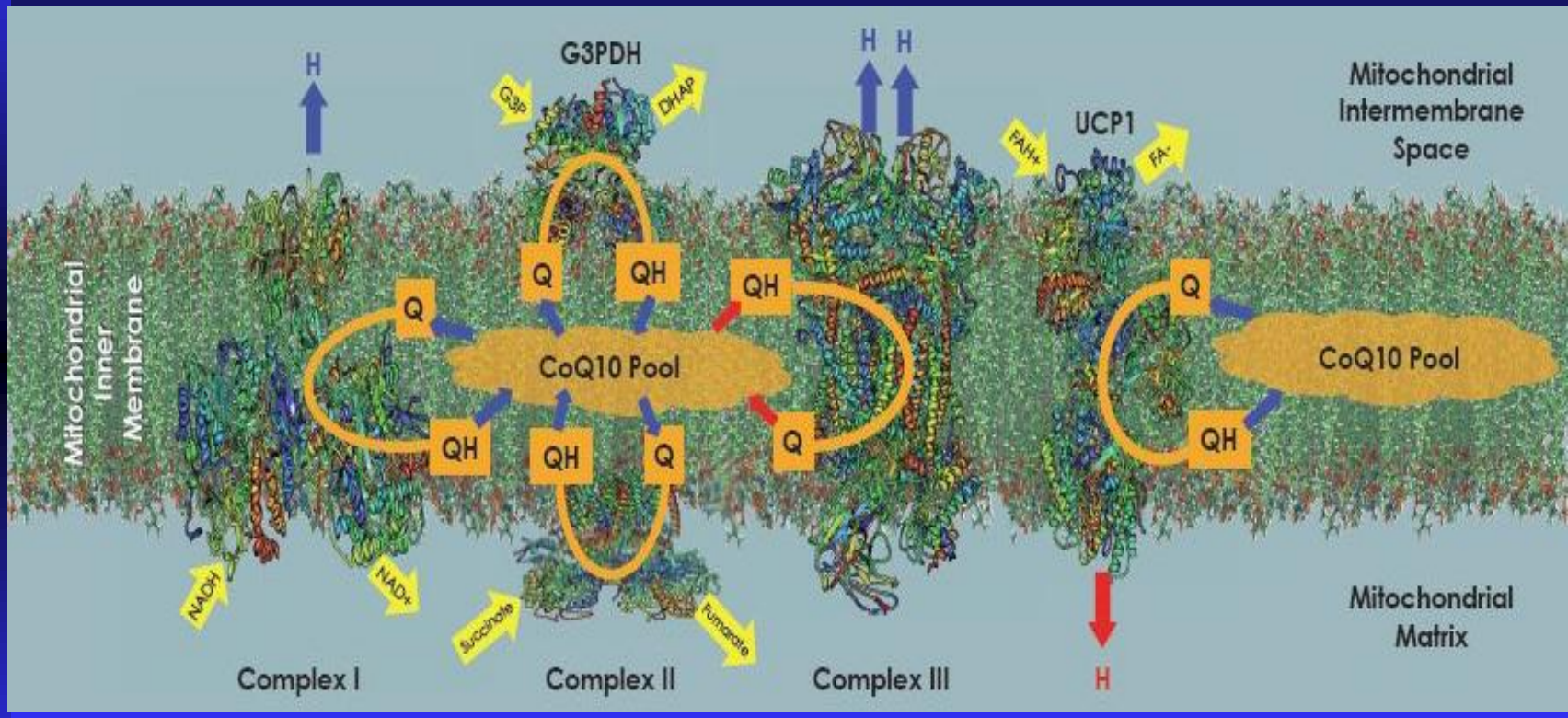
- Mitochondrial ATP Synthesis transfer electrons from complex I or complex II complex III.

- Initially is reduced to the semi-ubiquinone radical and then ubiquinone by transfering electrons one at a time to complex III

- At the same time, transfers the protons outside the inner mitochondrial membrane, generates a proton gradient across the membrane.

- The energy released when the protons flow back into the mitochondrial interior is used to form ATP.
Plays an integral role in supplying energy to chemical reactions in the body

The Q Cycle & Thermogenin



Functions of CoQ10

1.Energy Production: CoQ10 is required to convert energy from food into ATP.

2. Antioxidant Protection: prevents the generation of free radicals

3. Antioxidant Regeneration: Vitamin E, vitamin C and lipoic acid are all dependent on CoQ10 to be regenerated after they protect the body from oxidative damage.

4. Heart Protection: Often described as “cardioprotective”, CoQ10 protects both the blood vessels that feed the heart, and the heart muscle itself, from damage.

5. Nerve Protection: CoQ10 is required to protect the brain and other nerve tissues from free radical damage. This “neuroprotective” ability is in large part due to its antioxidant properties.

6. Anti-inflammatory: by decreasing the secretion of pro-inflammatory cytokines, chemical messengers that affect immune system function.

7. Promotes Thermogenesis: By supporting the function of thermogenin, a protein that derives energy from fatty acids,, and helps maintain ideal body weight.

8. Cellular Communication & Gene Expression: CoQ10 improves the ability of cells to receive messages and influences how some genes respond to those messages.

9. Supports Organ Metabolism: higher amounts of CoQ10 found in the heart, kidney and liver tissue, and lower amounts found in lung tissue.

10. Healthy Cell Growth: CoQ10 promotes cell growth and inhibits cell death in healthy tissues

Coenzyme Q10: Ubiquinone

*Produced endogenously in all tissues (~0.5g/day regenerated, with a body pool of ~2g)

* Naturally present in small amounts in a wide varied of foods

*Rich sources can be found in organ meats such as heart, liver and kidney, as well as beef, soy oil, sardines, mackerel and peanuts

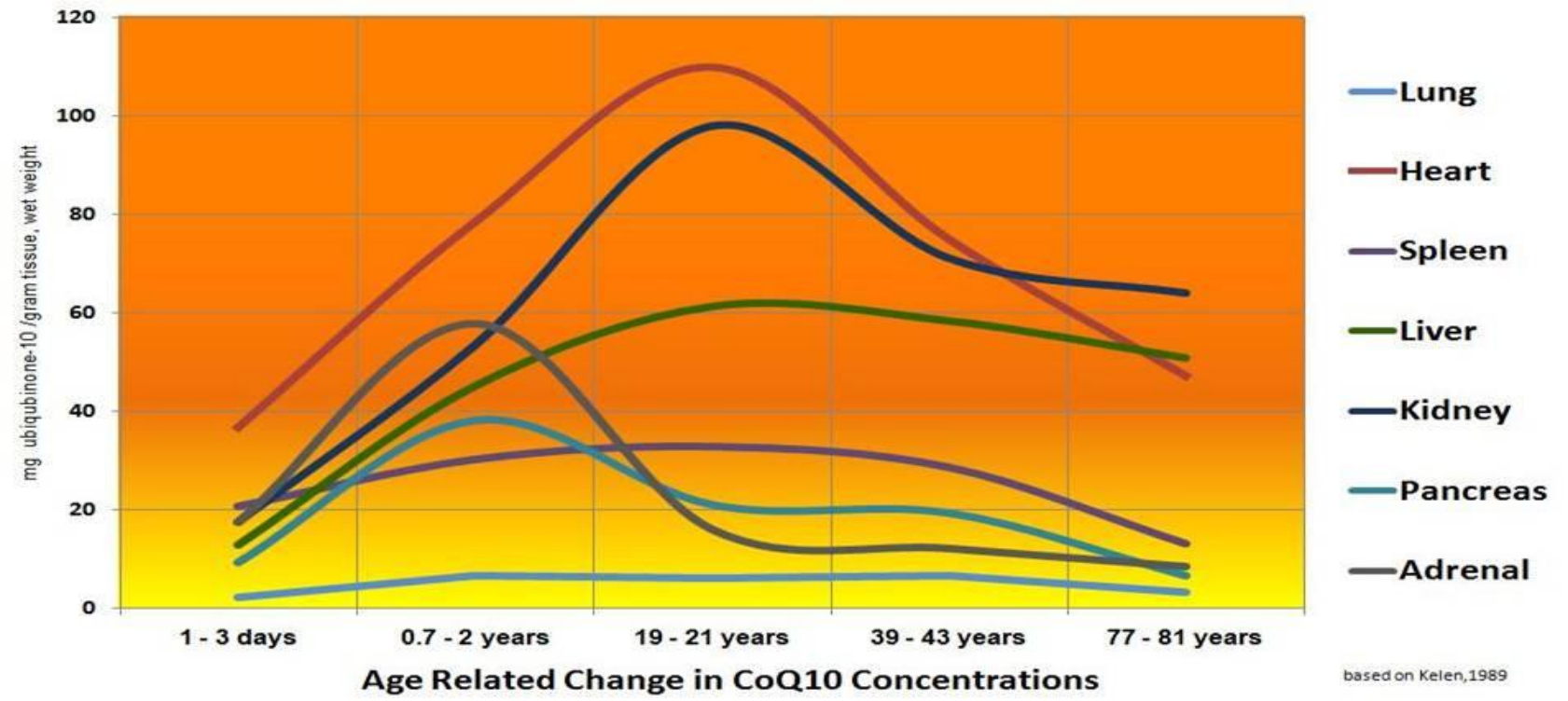
1 pound of sardines = 30 mg
2 pounds of beef = 30 mg
2.5 pounds of peanuts = 30 mg
50 times more antioxidant power than Vitamin E
Found to sustain vitamin E's antioxidant effects

Coenzyme Q10: Ubiquinone

- Exercise increases catabolism of and need for CoQ10

- Disease or other stress impairs intake and absorption of the substrate

Age Specific Changes in Tissue Levels



- The highest tissue concentrations of CoQ10 are reached at about 20 years of age in the heart, kidneys and liver,

- While CoQ10 levels peak in adrenal and pancreatic tissue at approximately one year of age.

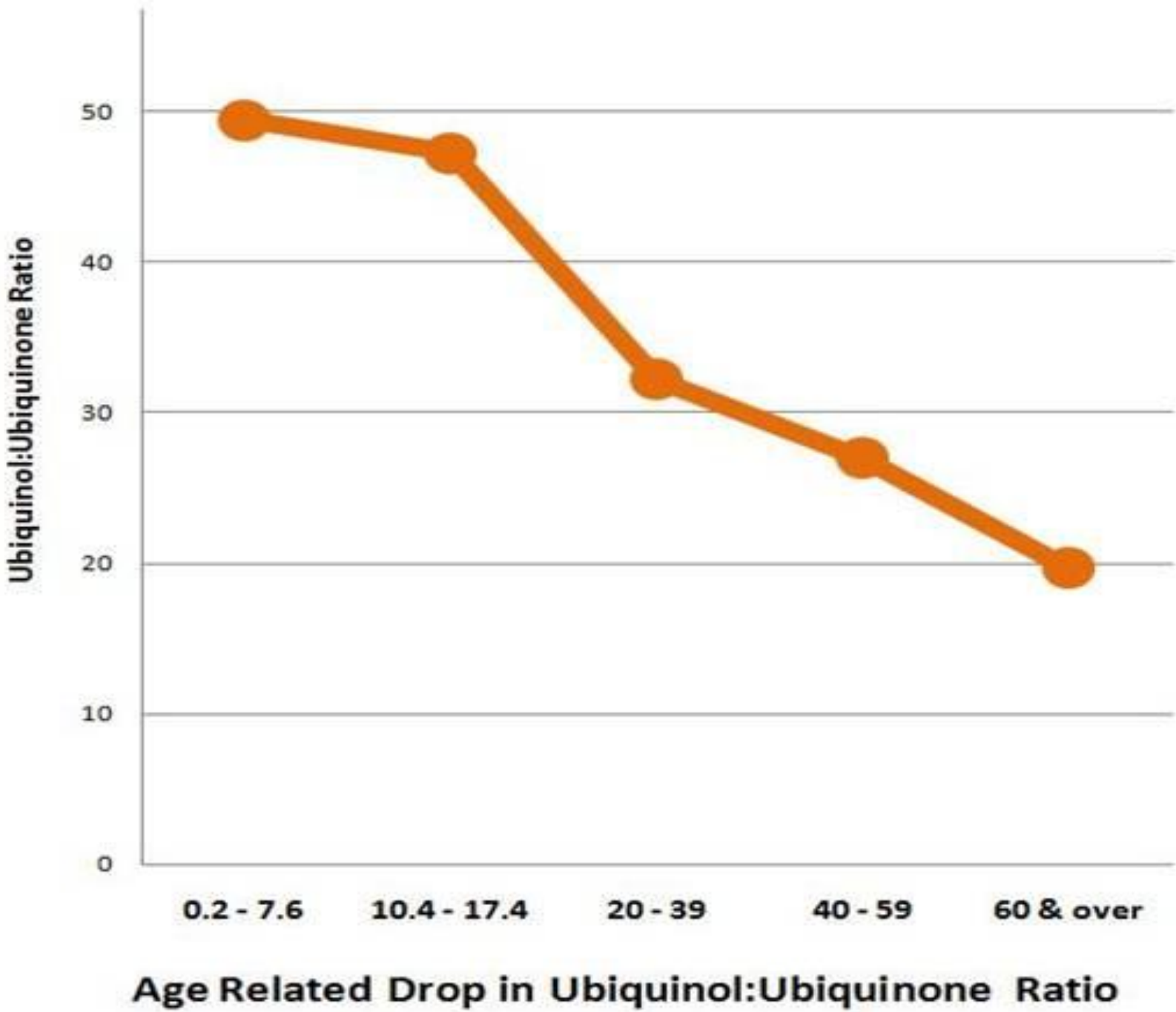
- After tissues achieve their respective peak concentrations, their levels progressively decrease with aging.

- Such that the ratio of ubiquinol to ubiquinone can be as high as 50 to 1.

- However, the ratio of reduced CoQ10 (ubiquinol) to oxidized CoQ10 (ubiquinone) can adversely change with age

- While the ubiquinol to ubiquinone ratio only drops slightly between younger children and older children.

- The average drop increases in adulthood and continues with age.



Age Related Drop in Ubiquinol:Ubiquinone Ratio

compiled from Miles, 2004 & Wada, 2007

Drug Action of Coenzyme Q10: Ubiquinone

Absorption

- Absorbed in the small intestines directly into the lymphatic system, followed by absorption into the blood stream
- Absorption tends to be poor (lipophilicity)

- ~60% or more of oral dosage forms are excreted in the feces

- Can be highly variable, depending upon dosage form and on food intake at time of CoQ ingestion

- Absorption is lower if taken on an empty stomach and higher if taken with foods, especially those with a high lipid content

Drug Action of Coenzyme Q10: Ubiquinone

- Distribution/Metabolism

*In the blood, CoQ10 is partitioned into various lipoproteins: VLDL, LDL and HDL, with peak blood levels occurring in 5 to 10 hours

* It is found in all cells of the body and is distributed to the various tissues of the body (important to know that is able to enter the brain)

* Takes roughly 3 weeks of daily dosing to reach the maximum serum concentrations

- Excretion

* Of what is absorbed elimination occurs through the bodies bile

* Low plasma clearance

* Elimination half-life of 34 hours

Cholesterol Lowering Drugs

- HMG-CoA Reductase Inhibitors "statins": deplete Coenzyme Q10

- Gemfibrozil: depletes CoQ10, E

HMG-CoA RI Lower CoQ10

- DB PC trial: 2 groups of 5 healthy subjects and 30 hypercholesterolemic patients
- Pravastatin or simvastatin 20mg/day x 1 mo.
- Results: in both healthy and hypercholesterolemic patients there was a 40% reduction in total cholesterol and a corresponding 40% reduction in CoQ10
- “A decrease of CoQ10 availability may be the cause of membrane alteration with consequent cellular damage.”

Dose-related CoQ10 Decline

- endogenous antioxidant packaged into LDL and VLDL fractions of cholesterol
- Significant dose-related decline in serum CoQ10
- Pravastatin:1.27 to 1.02 mmol/l = - 19.7%
- Lovastatin: 1.18 to 0.84 mmol/l = - 28.8%

- Will physicians subconsciously push patients who are suffering from myalgia or other side effects to stay on statins?

- Future studies should include strategies aimed at improving tolerability

  Simultaneous Coenzyme-Q10 use

  High-dose pulse therapy

Inhibition of Co Q10 by Anti-hypertensive Drugs

- Propranolol: ↓ CoQ10-succinoxidase and CoQ10-NADH-oxidase
- Metoprolol,, hydralazine and clonidine inhibit CoQ10-NADH-oxidase

Anti-diabetic Drugs

- Sulfonylureas: deplete CoQ10
- Biguanides: deplete CoQ10, B12, FA

OCs and Depletion of CoQ10 & Vitamin E

- OC use significantly decreased Coenzyme Q10 & alpha-tocopherol ($P<0.001$)

Efficacy Data

A lot of studies in the literature (70+)

- Laboratory/Animal/Preclinical studies
  - Laboratory – Coenzyme' structures and function in cell respiration
  - Animal – pretreatment
- Human/Clinical studies
  - Disease treatment

For Heart disease:

- Some large trials (up to 360 patients)
- Some long term (up to 30 months)
- Double-blind placebo-controlled trial, or meta-analysis

Others:

- Small trials (usually less than 100 people)
- Short term (up to 12 week)
- Most are double-blind randomized placebo-controlled trial
- Few are non-double blind, or non-randomized

- Since its discovery in 1957, (CoQ10) has been the subject of about 9,000 published studies

- With over 2,500 of those studies focused on the direct affect that ubiquinone and/or ubiquinol have on human health and disease.

- Almost 200 papers focus on the role that ubiquinone/ubiquinol has on congestive heart failure.

Usefulness of CoQ10 in Clinical Cardiology: A Long-Term Study

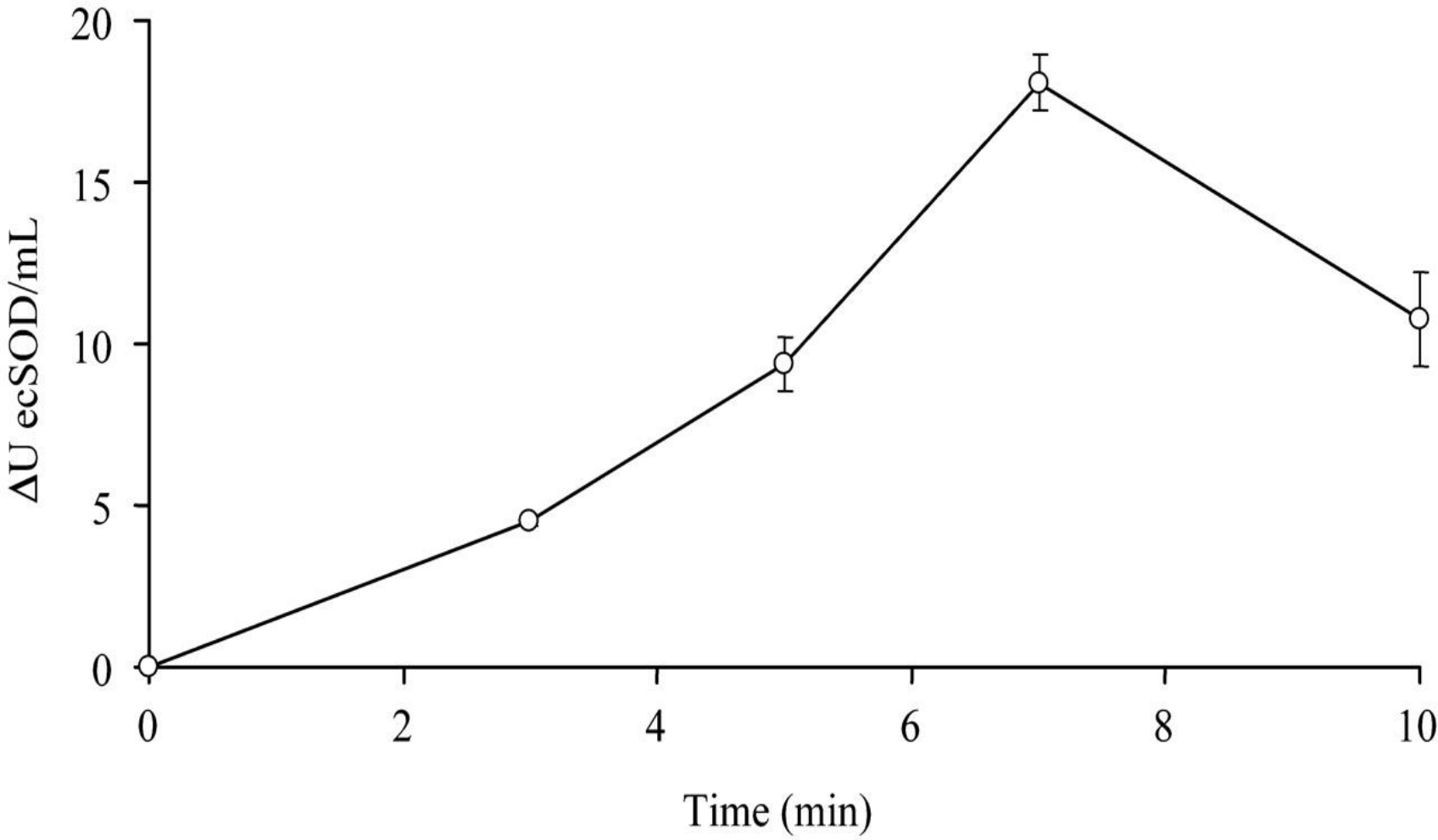
- 424 patients: primary diastolic dysfunction, ischemic & dilated cardiomyopathy, mitral valve prolapse, hypertension, valvular heart disease.
- T=17.8 mo ave; D = 75-600 mg/d (ave. 242 mg)
- 43% completely discontinued from 1 to 3 meds
- "CoQ10 safe/effective treatment for broad range of CV diseases; gratifying clinical response; eases the medical/financial burden of multi-drug therapy."

Langsjoen H, et al. Molecular Aspects of Medicine. 1994; 15 Supp: S165-75.

- Landmesser *et al.* showed that vascular ecSOD activity is substantially reduced in patients with (CAD).

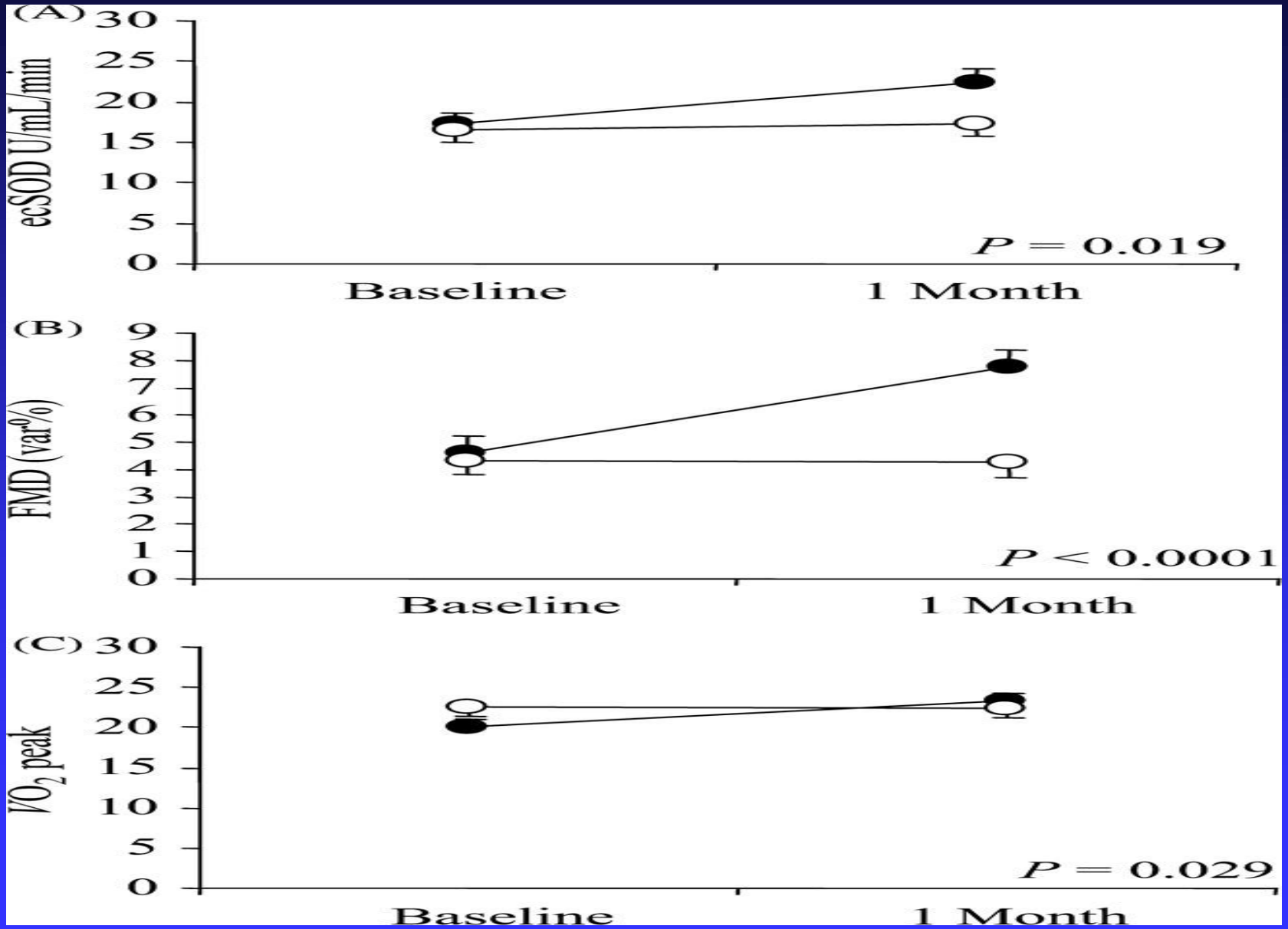
- The Flow-Dependent Endothelial-mediated dilation (FMD), a functional parameter commonly used as a biomarker of vascular function.

- A strong correlation was found between the endothelium-bound ecSOD and FMD

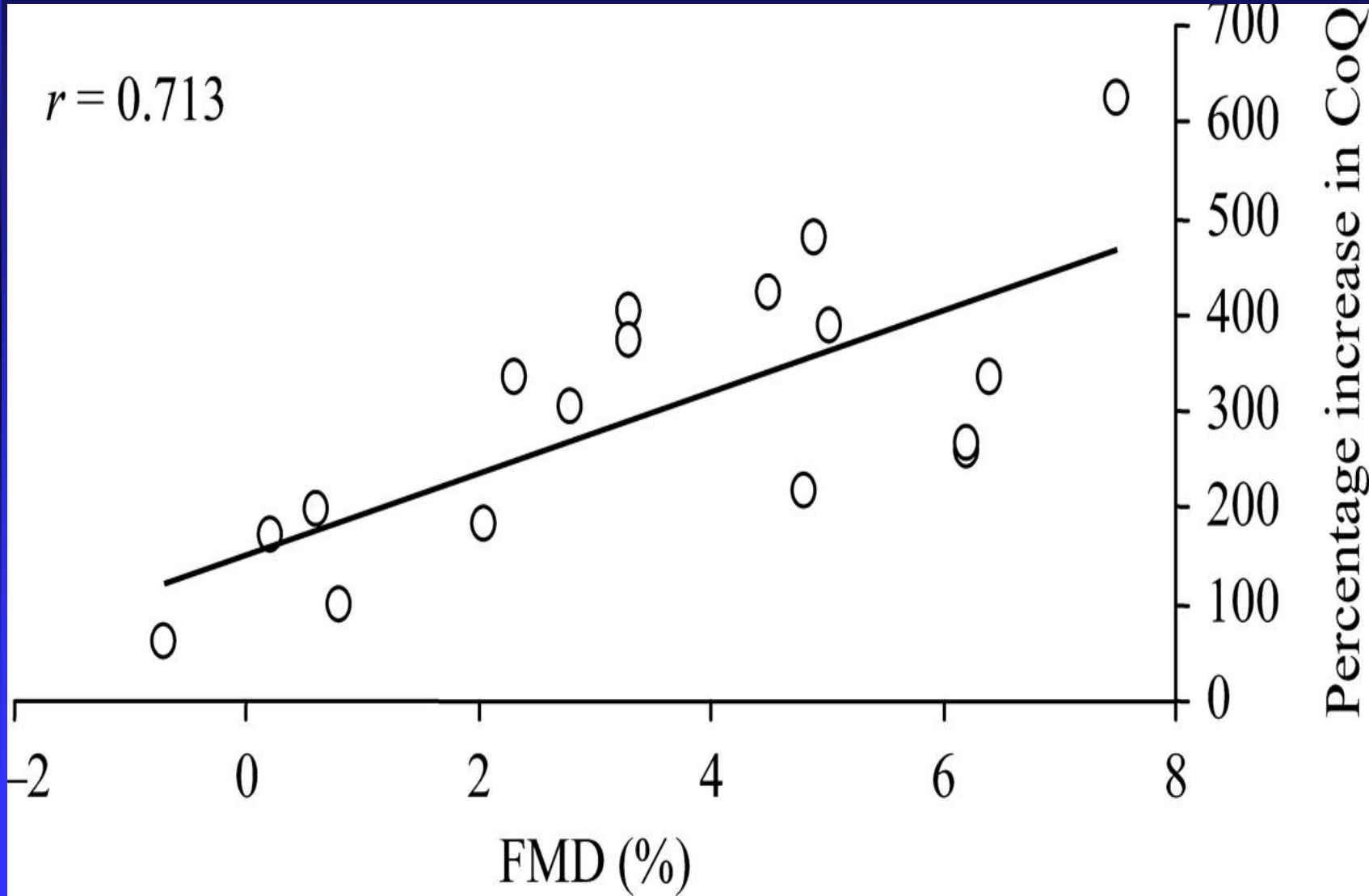


Pattern of the plasmatic extracellular superoxide dismutase activity in a single patient, following heparin bolus injection of 5000 U. Data are means ± SD of three replicate measurements for each time point withdrawal.

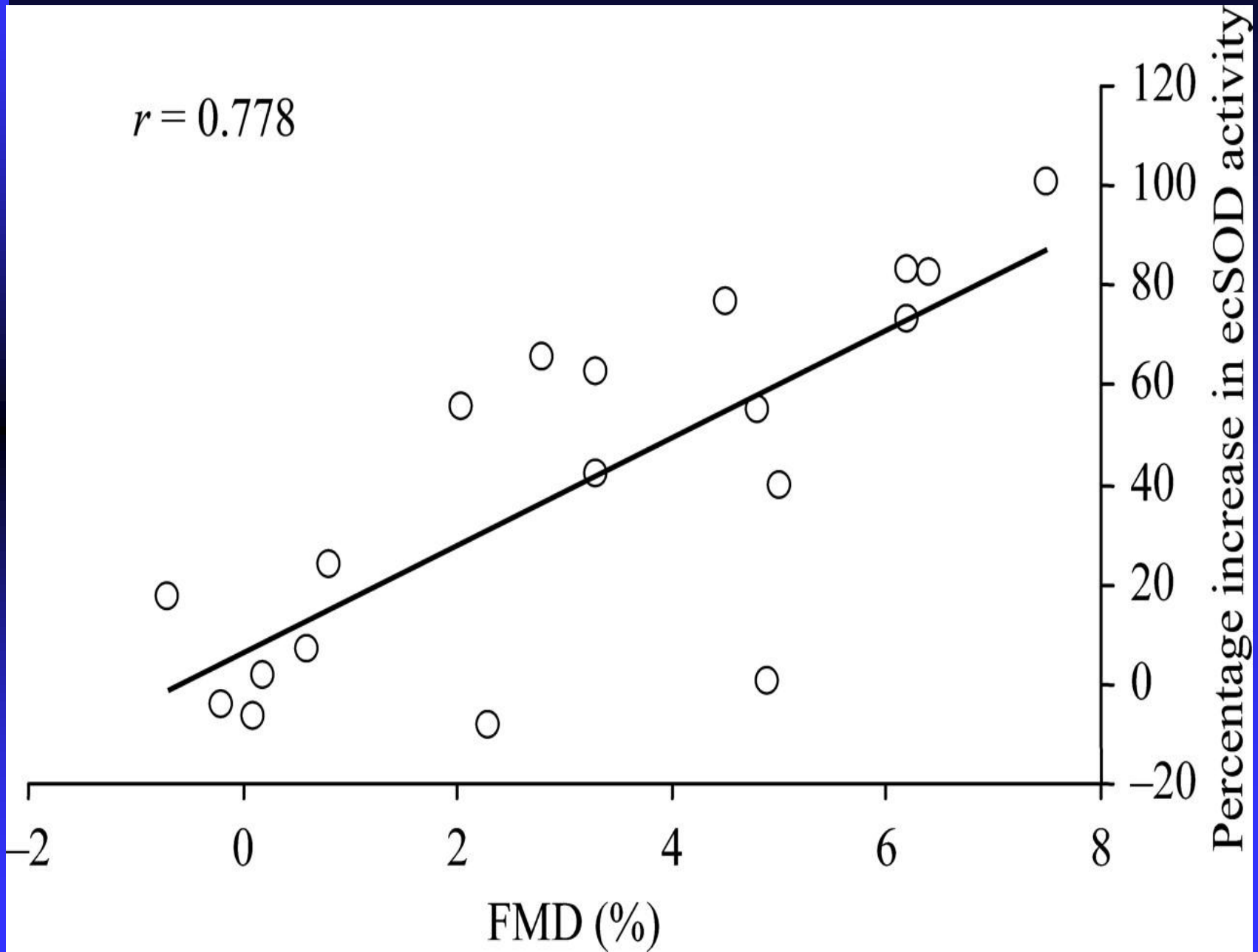
Variations in the endothelium-bound extracellular superoxide dismutase (A), flow-mediated dilation (B), and VO2 peak (C) in CoQ10-treated patients (black) and placebo (white).

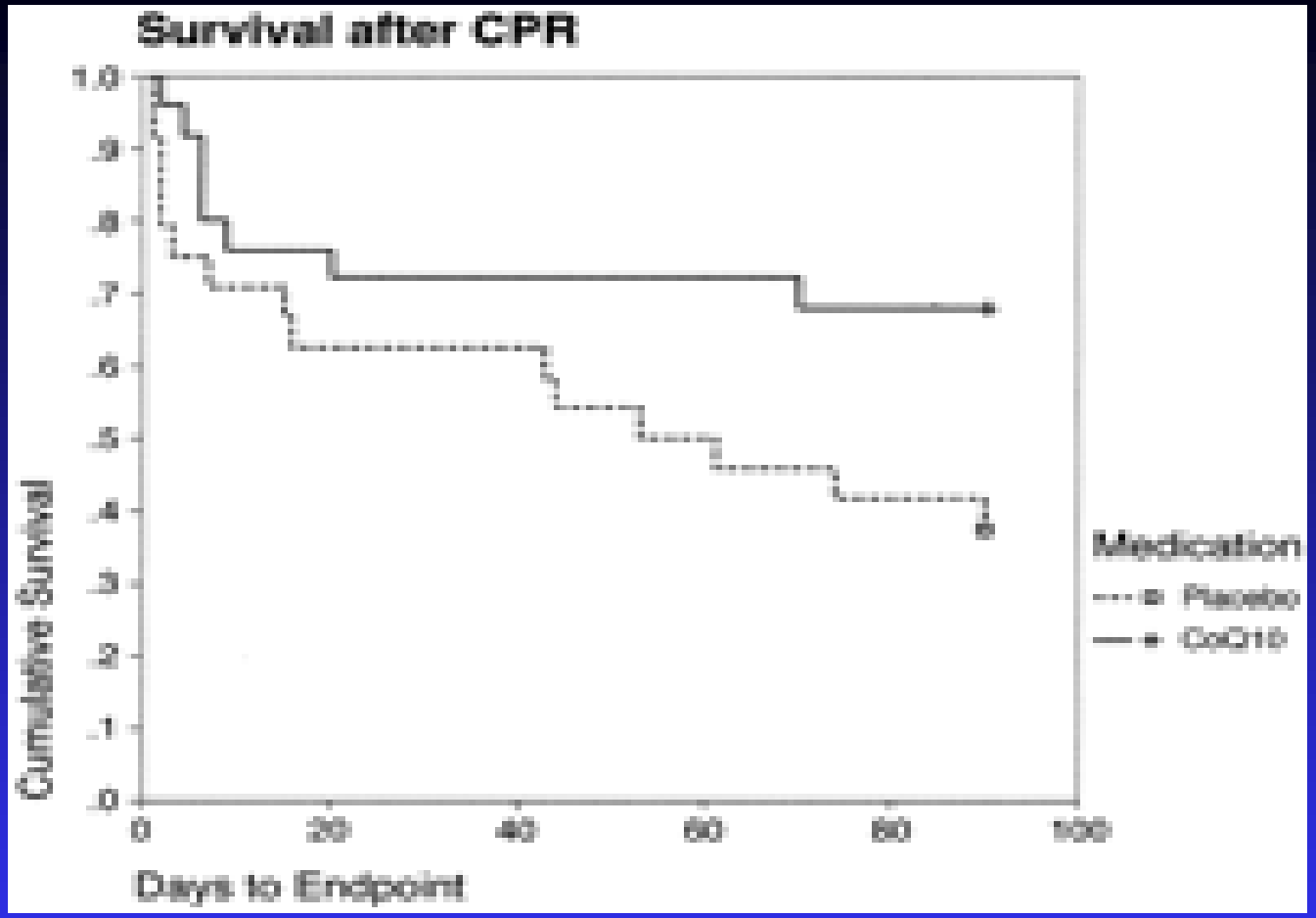


Correlation between percentage increase in plasmatic concentration of CoQ10 and flow-mediated dilation.



Correlation between percentage increase in the ecSOD activity and the flow-mediated dilation in CoQ10-treated patients.





The 3-month survival rate was significantly higher in the CoQ10 group: 17 of 25 (68%) in the CoQ10 group survived, but only 7 of 24 (29.2%) in the placebo group survived (*P*=0.0413; log rank test)

Disease Treatment of Coenzyme Q10: Ubiquinone

Reliable and relatively consistent scientific data showing a substantial health benefit for Angina and Hypertension

* Singh *et. al.* – double-blind, placebo-controlled study
  59 men already on hypertension medications had 120mg Coenzyme Q10 daily for 8 week
  Blood pressure reduced by about 9% as compared to placebo

* Burke *et. al* – double-blind, placebo-controlled study
  83 people with isolated systolic hypertension had 60mg Coenzyme Q10 daily for 12 week
  Blood pressure reduced

- Ubiquinol percentage is lower in hyperlipidemic patients that have high blood pressure compared to subjects without high blood pressure.

- CoQ10 supplementation supports the body's natural blood pressure regulatory mechanisms with a normalizing affect on both systolic and diastolic values.

- CoQ10 may also normalize the elevated blood pressure associated with metabolic syndrome by attenuating the increase of oxidative stress and nitrative stress markers and inflammatory markers typically seen in that syndrome.

Treatment of Essential Hypertension with Coenzyme Q10

- 109 patients: in 80 % of patients, average time of diagnosis = 9.2 yr.
- Average dose = 225 mg/day added to their existing antihypertensive medications
- 51% of patients were able to completely discontinue from 1 to 3 medications within the first 6 months (average time 4.4 months)
- Only 3% required addition of 1 more drug

Langsjoen P, et al. Molecular Aspects of Medicine. 1994; 15 Suppl: S265-72.

- CoQ10 levels are lower in both the serum and the heart tissue of patients with heart muscle disorders with decreased heart function.

- Ubiquinol was able to dramatically increase plasma CoQ10 levels in patients with decreased heart function, even after supplementation with ubiquinone failed to reach therapeutic goals.

- The ubiquinol intake was associated with improvement in ejection fraction.

- Ubiquinol showed superiority over ubiquinone for improvement of biomarkers of cardiac function in a group of patients with heart muscle disorders.

- When patients were switched from average daily dosage of 450 mg of ubiquinone to 580 mg of ubiquinol, plasma levels of CoQ10 increased from an average of 1.6 ug/ml to 6.5 ug/ml, revealing a four-fold increase in levels with only a 28% increase in dosage.

- Their average ejection fraction improved from an average of 22% to 39%.

- Supplementation with CoQ_{10} resulted in a pooled mean net change of 3.67% (95% CI: 1.60%, 5.74%) in the EF

- Subgroup analyses showed significant improvement in EF for crossover trials, trials with treatment duration ≤12 wk in length, studies published before 1994, and studies with a dose ≤100 mg CoQ_{10}/d

- 2013 American Society for Nutrition

Effect of CoQ10 Therapy in Patients with Congestive Heart Failure: A Long-term Multicenter Randomized Study

CHF = frequent hospitalization/life-threatening arrhythmias, pulmonary edema, cardiac asthma.

- 1 year DB trial Q=319 (2mg/kg/d), P=322
- Hosp: Q=73 (22.9%) P=118 (36.6%) = ↓ 37.4%
- PulEdema: Q=20 (6.3%) P=51 (15.8%) = ↓ 60%
- C-Asth: Q=97 (30.4%) P=198 (61.5%) =↓50.6%

Addition of CoQ10 to conventional therapy significantly reduces hospitalization for worsening of heart failure.

Morisco C, et al. Clinical Invest. 1993; 71(8 Suppl): S134-36.

Clinical outcomes are dependent on increased bioavailability

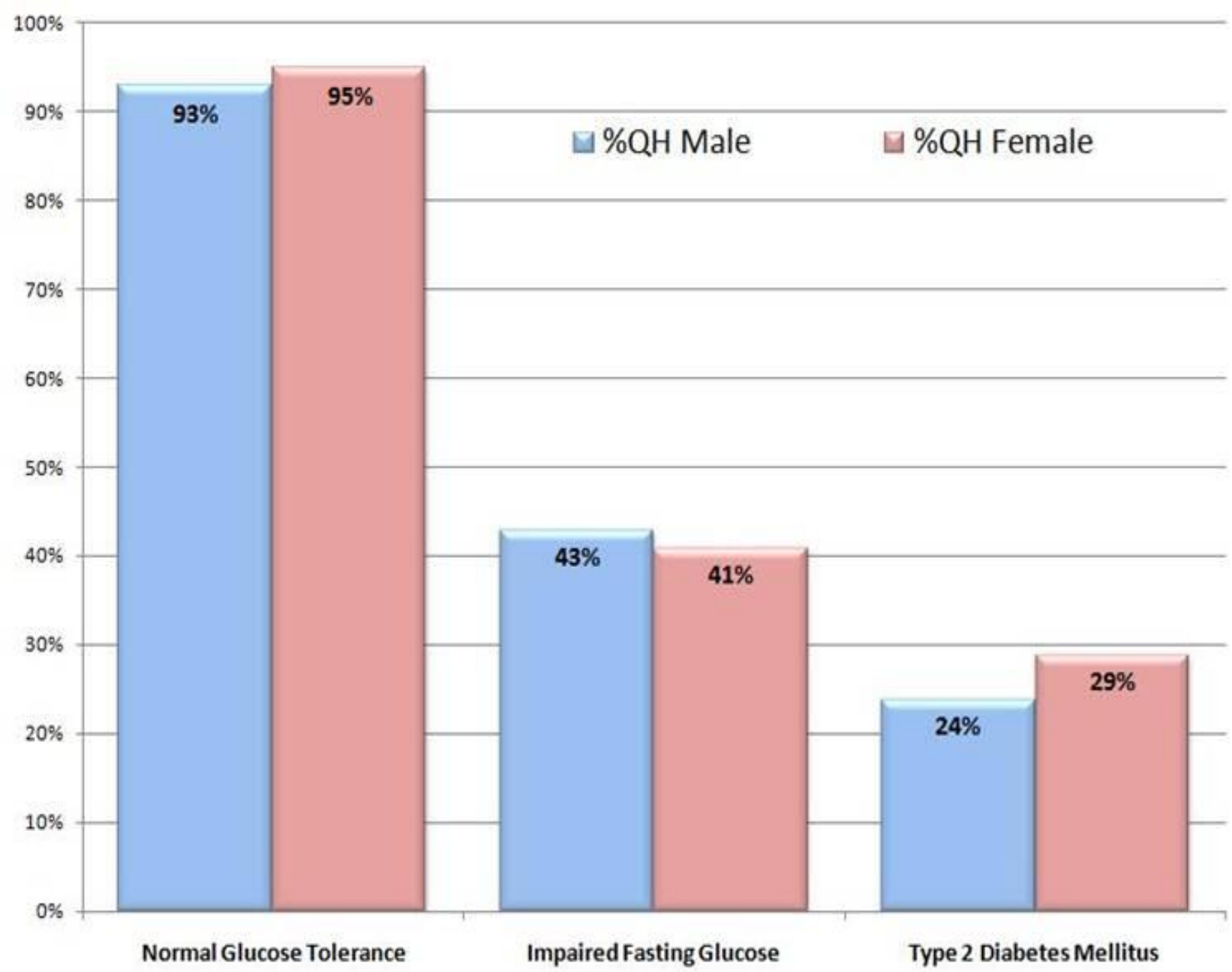
- Increased clinical improvement in (CHF) patients is only seen with plasma CoQ10 levels of at least 2.5 ug/ml.

- Therapeutic plasma levels in CHF are now considered to be greater than 3.5 ug/ml.

- Ubiquinol percentage of total CoQ10 is significantly lower in the presence of metabolic conditions accompanied by high and very high blood sugar levels.

- Patients with very high blood sugar levels may have ubiquinol percentages as low as 24% in males and 29% in females.

- The change in ubiquinol %, reveals increased oxidative stress which may contribute to increased risk of cardiovascular disorders.



Decreased % of Ubiquinol in Dysglycemias

based on Lim,2006

- The lower ubiquinol % levels are recognized as a sign of increased oxidative stress, which may be responsible for the increased observance of vascular and micro-vascular co-morbidity seen in Type 2 diabetes.

- It is the low percentage of ubiquinol levels, not the total CoQ10 levels, that are recognized as clinically relevant in a number of conditions that have increased oxidative stress as a component of their pathology, including :

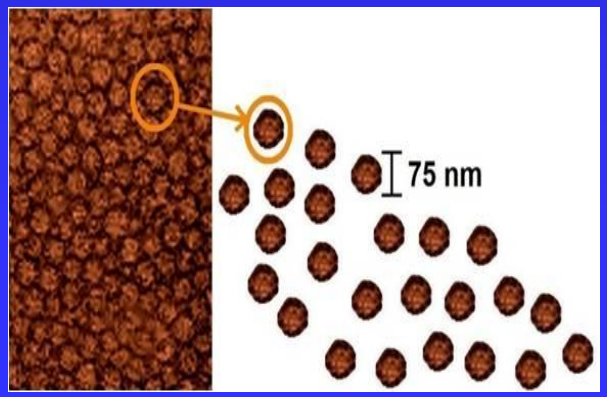
*Various neurological
* Cardiovascular
* Pulmonary
* Genetic mitochondrial
* Hepatic disorders
* **Dysglycemic** disorders.

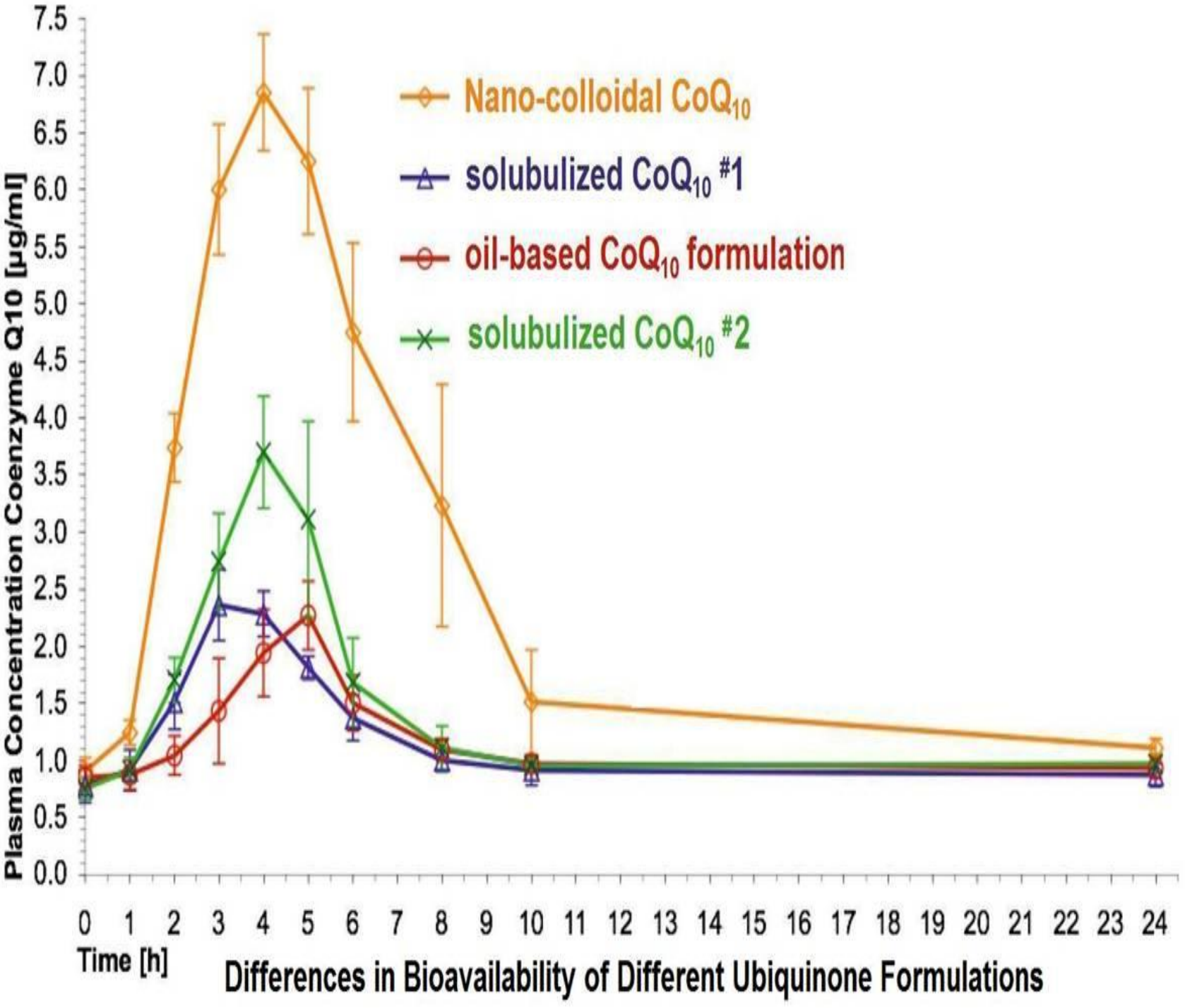
Bioavailability of CoQ10

- Suspension, solubilizates, oil based formulations and even micro-emulsions are not able to achieve and maintain therapeutic levels of CoQ10 that are readily achieved by nano-colloidal delivery systems

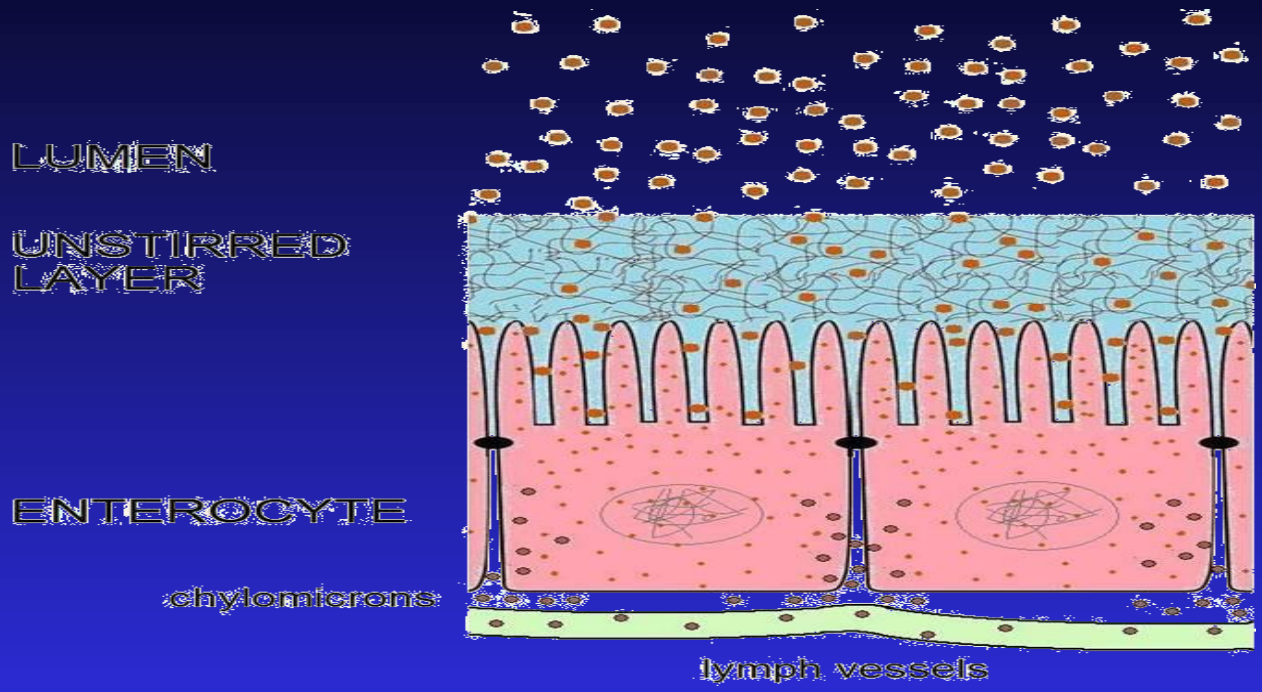
- This nano-colloidal CoQ10 delivery system releases nano droplets with a well defined average diameter of 70 to 75 nm

- As observed in the cryo-electron micrograph of the nano-colloidal formulation used in the graph.

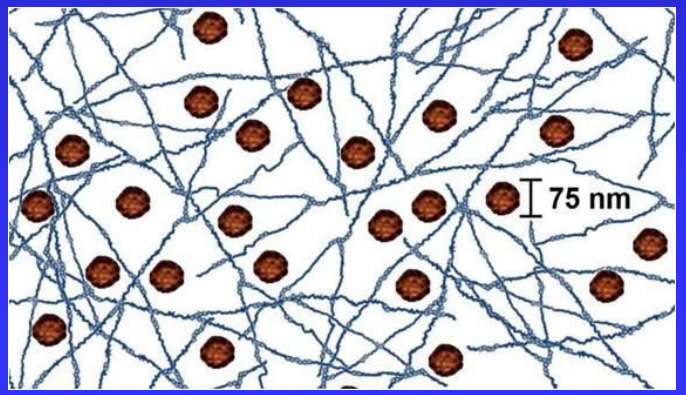


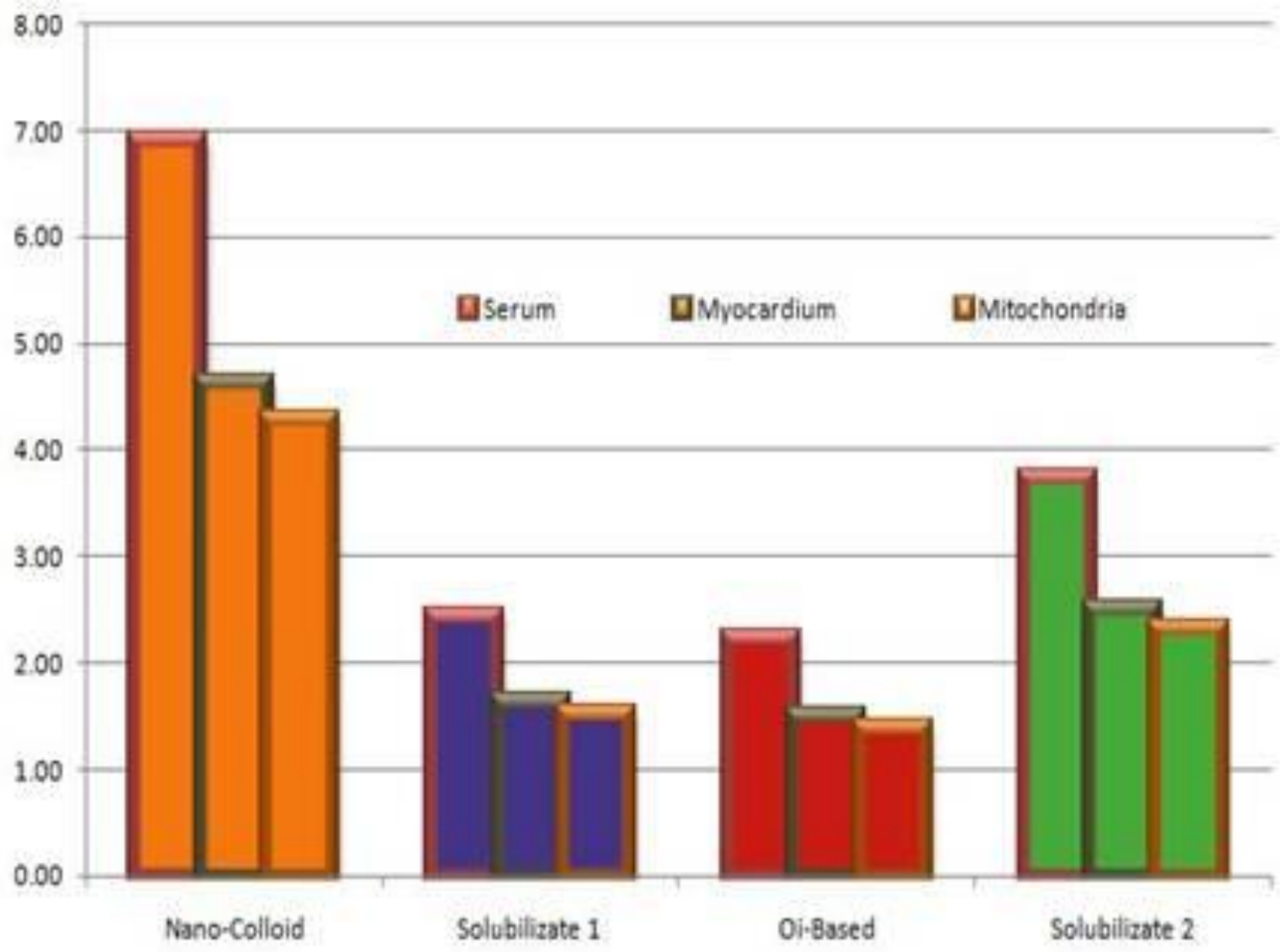

Plasma Concentration Coenzyme Q10 [µg/ml]
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Nano-colloidal CoQ10
solubulized CoQ10 #1
oil-based CoQ10 formulation
solubulized CoQ10 #2
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Time [h]
Differences in Bioavailability of Different Ubiquinone Formulations

Nano-Colloid Delivery of CoQ10



The nano-colloidal CoQ10 delivery system is able to effectively increase bioavailability of CoQ10 by penetrating the mucus mesh and easily diffusing across the unstirred water layer.





Relative Concentrations in Serum, Myocardium & Mitochondria

based on Liu, 2009 & Rosenfeldt, 2005

Dosage Forms of Coenzyme Q10: Ubiquinone

*Capsules (10 mg, 30 mg, 75 mg, 100 mg, 150 mg)

* Chewable Tablets (100 mg, 200 mg)

* Liquid softgel (30 mg/5 ml)

* Tablets (25 mg, 50 mg, 60 mg, 200 mg)

* Wafers (60 mg, 200 mg)

* Vcaps (bio-grown CoQ10; 22mg)

* Can also be found in a number of skin products on the market

Monthly cost of Coenzyme Q: Ubiquinone vs. Vitamin E and Altace

*Medical conditions, 150 mg a day: $36.00, 30 day supply

* Medical conditions, 400mg to 600 mg of vit E a day: $3.60, 30 day supply

* Ramipril: 5mg for the maintenance dose (180 capsules): $43.20, 30 day supply