Mevalonate Ageing

There are 3 main driving factors of ageing:

1. direct cell death by radiation (UV, radioactivity, heat) and ROS (prolonged cell stress)
2. cell senescence and death by shortened telomeres (programmed cell death)
3. reduced function of cell pathways like the glucose or mevalonate pathways

Point one is best counteracted with antioxidants, which reduce ROS and the damage by them. And of course by avoiding the negative influences like UV, smoke, inflammation in the first place.

Point two is determined by genes in all humans equally and limits the count of cell divisions over the lifetime. Best way to deal with this is not wasting cell generations by point one influences (particularly in younger years, when it's still not visible).

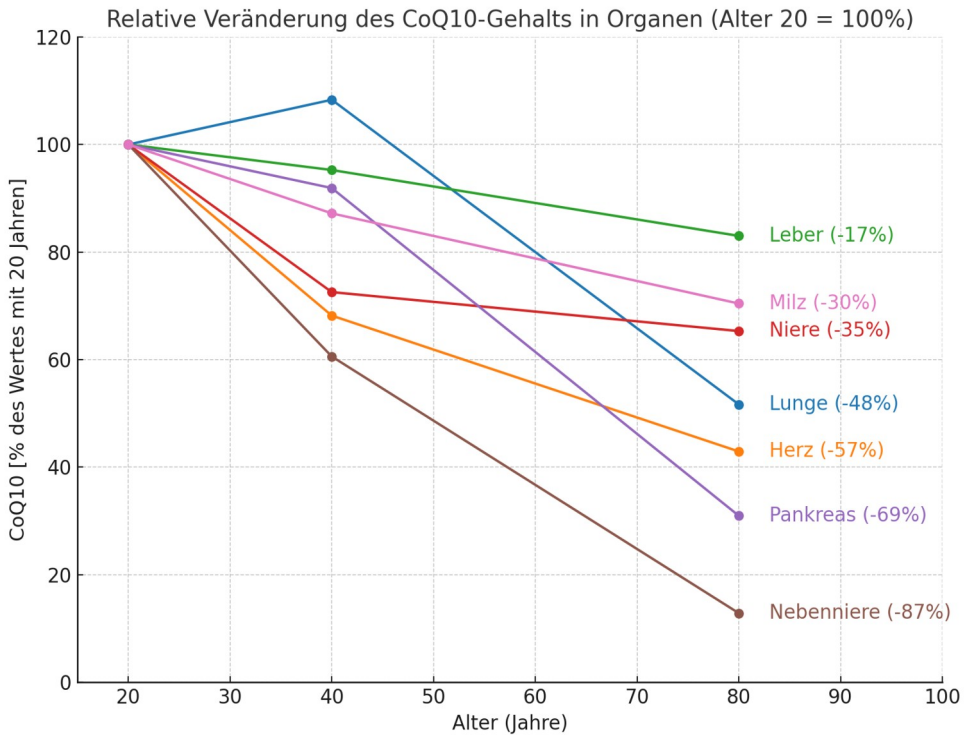
Point three is when the complex net of signals within the body is gets out of balance. One example is the glucose pathway in insulin resistance, leading to glycation of proteins and more.
And the Mevalonate pathway, which governs many life functions like energy production, repair and growth.

The Mevalonate-Pathway

...is the pathway which begins by making mevalonate from food. And from this many of the essential life molecules in humans, animals and plants. These include coenzyme Q10, cholesterol, all carotenes, some vitamins, immunoglobulins, hormones, muscles and much more.

The mevalonate pathway appears to decline with increasing age and is directly linked to many signs of ageing. For example, with coenzyme Q10, muscle mass and sex hormones.

A good example is **Coenzyme Q10** (also known as ubiquinol or CoQ10 for short). There are studies that investigated the reduction of CoQ10 with age [1]. Here's the data:



As we can see, CoQ10 in the heart decreases by 30% at the age of 40 and by 57% at the age of 80. This explains the decline in performance over the years, as CoQ10 is necessary for the production of ATP energy in the mitochondria.

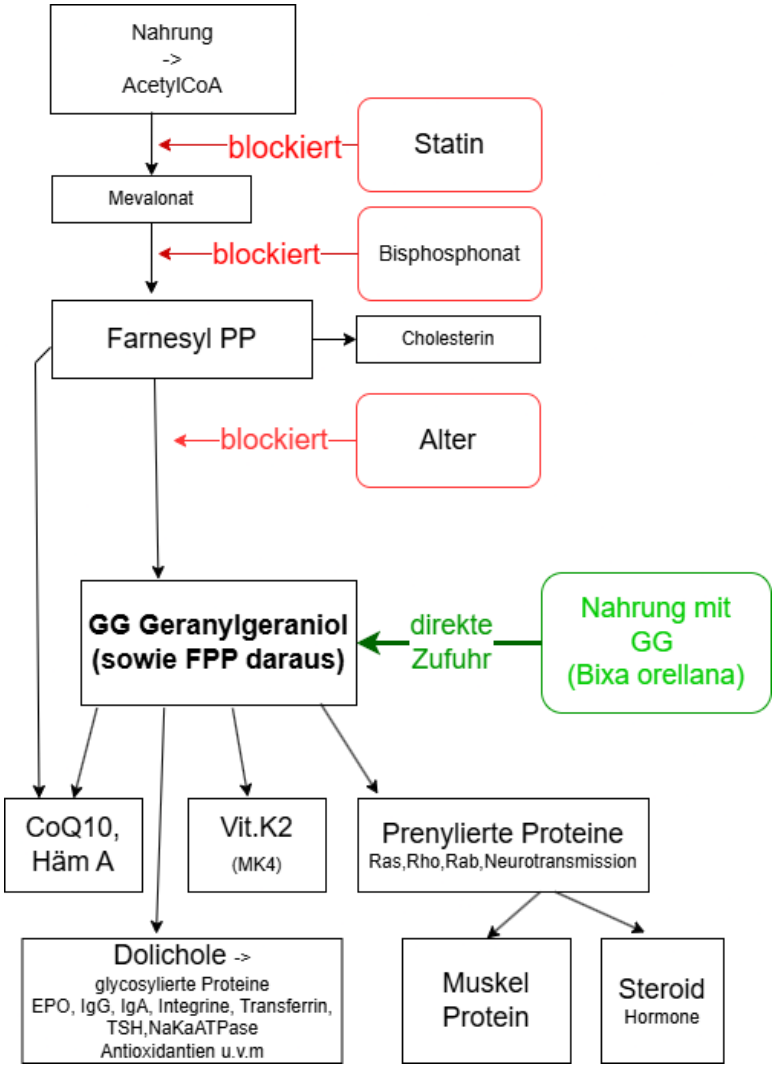
There are similar graphs for declining muscle mass and sex hormones with age. These are all end products of the mevalonate pathway.

Is there nothing we can do, are we doomed to these phenomena?

The mevalonate pathway appears to play an important role in ageing. But you can support it by directly supplying yourself with an intermediate product, namely geranylgeraniol (GG for short). This molecule is formed from mevalonate and is precisely the building block that is needed so often.

GG is found in food. After all, it is needed in every multicellular organism. Olive oil (extra virgin), for example, contains up to 4 mg per 100g or spinach up to 1 mg. However, these are only small amounts compared to the estimated 150 mg required per day.

A researcher from the USA, Dr Barrie Tan, has now found a plant that contains as much as 490 to 2600 mg: Namely Bixa orellana (also known as annatto, achiote, roucou). This is a plant from the Amazon jungle that has been used by the indigenous people there for many centuries. Thanks to his initiative, GG is now extracted from the plant.



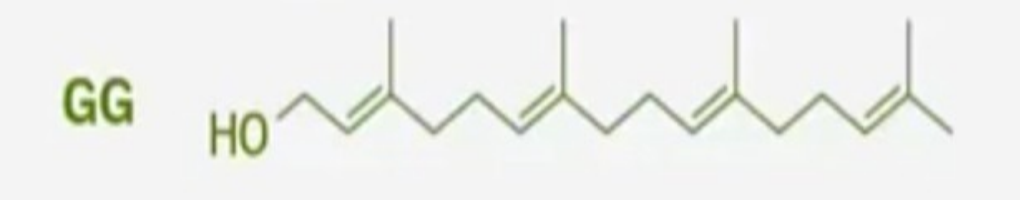
Let's take a look at how this works: This is the Mevalonate pathway.

In the upper part we see the steps up to the side path to cholesterol. Most publications only look at this part.

But the pathway goes on with GG (geranylgeraniol) and its many follow up products. This is also the stage where dietary GG enters the picture.

Our body makes geranylgeraniol from mevalonate. As you can see, this process is slowed down by ageing and some medications. However, it can also be obtained directly from food.

GG is a simple chain (C20) with four double bonds. It's the basic substance for many end products. It is easily absorbed in the intestine and blood and has its own transporters through the cell membranes.



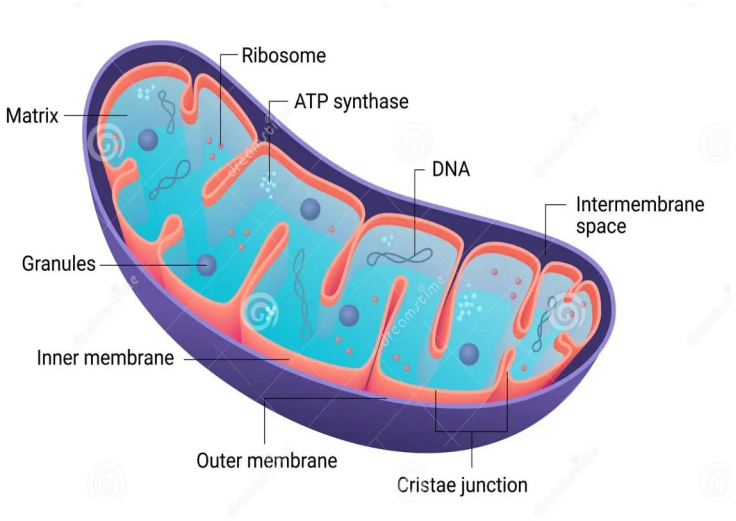
Some products of the Mevalonat Pathway

Let's take a look at some of the end products in the pathway, with consequences of low supply:

QoQ10	Reduced performance in all organs (Muscle, Brain, Liver, Kidney)
Heme A	Acts like CoQ10 in the respiratory chain, same effect
Vitamin K2	Calcium metabolism, bones, arteries
Steroid-Hormone	Declining libido, bone density and muscle mass
All prenylated proteins	
- Rheb, Rab, Rho, Rap	Growth factors for many tissues, e.g. muscles
- G-Protein-γ	Signal forwarding
All glycosylated Proteins	
- immunglobulins (IgA,IgG)	Immune defence and digestion
- EPO	Red blood cells
-Transferrin	Transport of iron in the blood
- Receptors	For example insulin
- secretory enzymes	Digestion

These products are inhibited by age and by the drugs mentioned. Let's take a look at the most important ones in detail:

Coenzyme Q10 (Ubichinon, Ubichinol)



100% of all energy in the body is produced in the mitochondria. This takes place at the inner membrane, where the oxidation of food and ATP production occurs.

This process requires B vitamins, iron, copper, magnesium, heme A.

And coenzyme Q10. The mitochondria make their own coenzyme Q10 inside.

But by the age of 40 CoQ10 has already fallen by 30%. Why? Probably because too little of the building block GG (geranylgeraniol) is available. It can be shown that the intake of GG increases coenzyme Q10 again.

GG reduces our mevalonate age by decades.

CoenzymeQ10 can also be taken directly. It is the most widely taken dietary supplement in the world. You may already know and take it.
But there's a catch - it doesn't reach the inner membrane where ATP energy is produced.

CoQ10 is a huge molecule, C59 with 10 double bonds. It is therefore poorly absorbed in the intestine (1-7%), even if it is pre-treated (solubilised or ubiquinol instead of ubiquinone). It then has to be transported to the cell via the lymph, liver and bloodstream, through the cell membrane. Then through the outer mitochondrial membrane and the inner mitochondrial membrane. There is no transporter for the inner membrane. It may not even get in at all, at least according to the four studies [2] to [5]. Even the positive studies [6] to [7] document CoQ10 only **at** the mitochondrion and not inside. Presumably it only acts as an antioxidant (which is good), but does not help the respiratory chain at all.

The solution is: GG - geranylgeraniol, which is small enough to get into the mitochondrion and there is a transporter for it.

It goes even further: in addition to CoQ10, the mitochondrion also needs *heme A* to produce energy. H*eme A* acts at complex IV (*cytochrome c oxidase*) and its also produced within the mitochondrion, with the help of GG. Double effect of GG for mitochondrial energy.

Statins

Statins are cholesterol-lowering drugs that are prescribed very frequently worldwide (top-selling drug worldwide). There are mass studies that document a significantly lower risk of cardiovascular disease through cholesterol reduction (at least in the first 10 years). Cardiologists are obliged to recommend them.

Statins block the mevalonate pathway right at the beginning and thus simultaneously inhibit all other GG-dependent pathways. Also CoQ10 and muscle synthesis. And this quite strongly. They are supposed to lower cholesterol significantly.

This explains the frequent and serious side effects of statins. Myopathies (SAMS, muscular problems) in particular are quite common. Approximately 25% are affected by muscular problems caused by statins.

Statins increase our mevalonate age by decades.

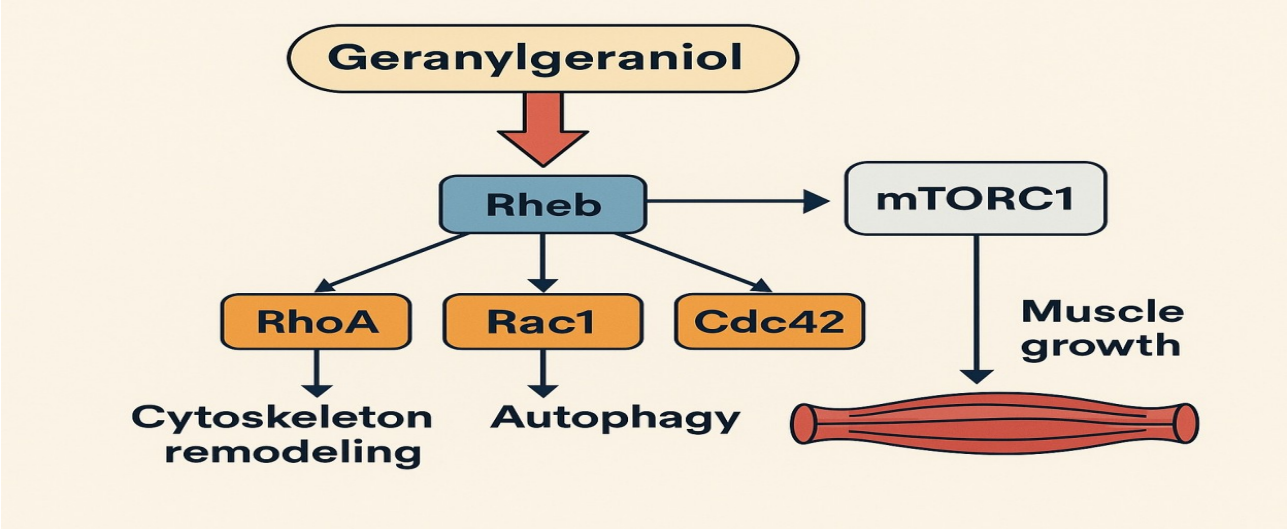
Attempts are being made to alleviate the side effects of statins by administering CoQ10 at the same time. The studies have produced mixed results. Muscle pain and cramps are reduced, but this can be explained by CoQ10 being an excellent antioxidant. There is no evidence of improved mitochondrial activity through CoQ10 with statins.

So far, there is no means of counteracting the side effects of statins. This could change within this year (2025). A high-quality human study is currently underway (in Texas), investigating GG (geranylgeraniol) in patients with myopathies caused by statins. The preliminary studies with cells and animals have already produced very good results. Apparently, GG can alleviate the side effects of statins without affecting cholesterol reduction.

Muscle build up and sarcopenia

Sarcopenia is the loss of muscle mass with age. Muscle loss starts as early as the age of 30, becomes significant from the age of 40 (3% per year) and from 50 or 60 onwards is so pronounced that older people can be unable to cope with even the simplest tasks such as climbing stairs. This is definitely an important problem in our ageing society.

In fact, the mevalonate product GG (geranylgeraniol) is essential for muscle build up.



The connection is that the (prenylated) protein Rheb controls the messenger substance mTORC1.

This mTORC1 in turn is the messenger substance that triggers muscle growth (in addition to other factors such as training, protein and sex hormones).

This in turn explains how age causes muscles to shrink (sarcopenia), as well as the muscular problems caused by statins.

In this case, it even goes beyond signs of ageing. Younger people would also like to increase their muscle mass. GG could help with this. Individual case reports already confirm this.

There are already quite successful animal studies on the development and strength of muscles through GG. Experimental animals were given significantly stronger muscles and more muscle power through GG.

As a remedy for sarcopenia, GG would be important for our ageing population.

Sex hormones (testosterone, also oestrogens)

Sex hormones such as testosterone belong to the prenylated proteins and therefore depend on GG. Of course, it is also known that the level of sex hormones drops significantly with age.

As a result, one might expect GG to naturally increase testosterone levels. This has now been confirmed by a high-quality (human, dose-escalation, randomised, placebo-controlled) study [9]. The men in the study had an average increase in their testosterone levels of around 15%. But only when testosterone was already somewhat low (< 700 ng/dL).

This confirms an assumption derived from the theory of the Mevalonat pathay.

Vitamin K2

Vitamin K2 has many positive effects that go beyond the usual classification (bone growth). It is

- Vasodilatory (vasodilator, lowers blood pressure, improves blood circulation)
- it improves the hormone status
- it is effective against arteriosclerosis and heart attacks
- It has functions in the immune system
- it acts in the calcium metabolism (per bone)

Vitamin K2 is vitamin K1, which has its saturated tail replaced with GG. In this respect, GG is even important for the production of a vitamin. The result is MK4 (menaquinone-4).

Vitamin K2 exists in several versions of different lengths, from MK3 to MK13. All these versions of vitamin K2 are converted into MK4. The tails (length 4-13) are already separated in the intestine. This produces vitamin K3 (menadione), which is then converted into MK4 in the organs.[10] MK4 (not MK7) is therefore the actual active form of vitamin K2.

If the mevalonate pathway is inadequate (age, statins), less of this conversion can take place. In addition to the oestrogen level in women, this explains the decline in bone density in old age.

Bisphosphonates are prescribed to combat decreasing bone density. They reliably prevent bone loss. However, bisphosphonates also inhibit the mevalonate pathway (similar to statins, but not as strongly). However, this restricts bone formation, due to less vitamin K2. Bisphosphonates work against themselves by this way. To remedy this, vitamin K2 (preferably MK4) and/or GG geranylgeraniol could be given.

Dentists are aware of a clinical picture called BRONJ (Bisphosphonare Related Osteo Necrosos of the Jaw). There are studies documenting BRONJ improvement with GG or vitamin K2.

Further downstream products in the mevalonate pathway - downstream of geranylgeraniol

The table above lists a number of other downstream products in the mevalonate pathway. Particularly all prenylated and glycosylated proteins such as Ras, Rho, Rab, dolichols, EPO, IgG, IgA, TSH, integrins, transferrin, sodium-potassium ATPase, antioxidants, neurotransmitters.

The dependence on the mevalonate pathway and geranylgeraniol is already known, but there are no human studies that document, for example, symptom relief through the intake of GG or the exacerbation of symptoms by statins, for example.

I think we can assume that many other signs of ageing and also side effects of statins and bisphosphonates stem from these molecules being disrupted. Such symptoms could be alleviated by dietary geranylgeraniol.

Conclusion

I have tried to depict the mevalonate pathway not only as the beginning of cholesterol production, but also to describe the many other molecules that depend on it.

This point of view has only become apparent now that geranylgeraniol is available as an inexpensive extraction.

The result is a plea in favour of geranylgeraniol. Firstly against various signs of ageing. Then for muscle building and maintaining performance in athletes.

Due to its connection to the side effects of cholesterol-lowering drugs, it can be expected that GG - GeranylGeraniol could become very well known in the years to come.

References

[1]: Kalén, A., Appelkvist, E.-L., & Dallner, G. (1989). Age-related changes in the lipid compositions of rat and human tissues. Lipids, 24(7), 579–584.

doi:10.1007/BF02535072

[2] bis [5] Table of studies showing that Q10 does not enter the mitochondria

Autor (Jahr) – Modell	Design & Dosis	Methode & Ergebnis	Titel & PubMed-Link
Zierz et al. (1990) – Patienten mit mitochondrialer Myopathie	Orales Ubidecarenon (Dosis nicht exakt angegeben)	Muscle biopsies before/after; no increase in muscle CoQ_{10}	Exogenous coenzyme Q (CoQ) fails to increase CoQ in skeletal muscle of two patients with mitochondrial myopathies
Bresolin et al. (1990) – Patienten mit mitochondrialer Myopathie	CoQ_{10} vs. Placebo (Doppelblind), Dosis ~2 mg/kg/d, 6 Monate	Muscle biopsies: no significant increase in CoQ_{10} in the muscle	Ubidecarenone in the treatment of mitochondrial myopathies: a multi-center double-blind trial
Morén et al. (1996) – Patienten mit mitochondrialer Myopathie	1200 mg/Tag oral über 6 Monate	Muscle biopsies; no increase in CoQ_{10}, possibly slight decrease in subsarcolemmal mitochondria	Clinical and biochemical correlations in mitochondrial myopathies treated with CoQ_{10}
Chan et al. (1992) – Patienten mit mitochondrialer Enzephalomyopathie	150 mg/Tag oral über ca. 10 Monate	Muscle biopsy + ^{31}P-NMR: no clear increase in CoQ_{10}, but slightly improved mitochondrial function	31P NMR spectroscopy and ergometer exercise test as evidence for muscle oxidative performance improvement with coenzyme Q

[6],[7] Some studies that have also demonstrated CoQ10 at mitochondria

Autor (Jahr) – Modell	Design & Dosis	Ergebnis in Mitochondrien	Titel & Link
Scialò et al. (1998) – Ratte	Single oral administration of CoQ10	Significant increase in CoQ10 on brain mitochondria	Coenzyme Q10 administration increases brain mitochondrial concentrations
Cooke et al. (2019) –	Long-term oral administration of CoQ10-	Increases CoQ10 content in muscle mitochondria	Prolonged oral CoQ10–β-cyclodextrin

Autor (Jahr) – Modell	Design & Dosis	Ergebnis in Mitochondrien	Titel & Link
Review (Mensch & Tier)	β-cyclodextrin (water-soluble modified CoQ10)	(horse animal study)	supplementation increases plasma and skeletal muscle CoQ10 concentrations

[9] The Effects of Geranylgeraniol on Blood Safety and Sex Hormone Profiles in Healthy Adults: A Dose-Escalation, Randomized, Placebo-Controlled Trial *Nutraceuticals* 2023, *3*(4), 605-618; https://doi.org/10.3390/nutraceuticals3040043

[10] Ellis JL, Fu X, Karl JP, et al.: *Multiple Dietary Vitamin K Forms Are Converted to Tissue Menaquinone-4 in Mice.* Journal of Nutrition. 2022;152(4):981-993. doi:10.1093/jn/nxab332