You are what you eat!

Nowadays almost everyone is aware of the link between high blood cholesterol levels and cardiovascular disease. There are effective treatments that target blood cholesterol. his overview highlights some well known and some new mediators implicated in cardiovascular disease with the common theme that all of them can be influenced by the diet.

On the influence of diets, nutrition supplements, and new metabolites

Endothelial cells are situated at the interface between the blood and the blood vessel wall and control vascular tone and homeostasis. Nitric oxide (NO) derived from the endothelial NO synthase (eNOS) plays a crucial role in these processes and in the modulation of endothelial cell activation and vascular inflammation. The continued generation of NO by eNOS has long been associated with a healthy vasculature while decreased NO bioavailability, as a consequence of reduced eNOS activity or the reaction of NO with superoxide anions, has been

In blood and tissues, there are various enzymatic and non-enzymatic systems that can further metabolize nitrite to NO and other bioactive nitrogen oxides. Just how important this mechanism can be has been demonstrated by studies using antibacterial mouthwash, which have resulted in hypertension in particularly susceptible healthy individuals. Similarly, a bonus of dietary nitrate (often in the form of beetroot juice) has been shown to decrease blood pressure in a number of different patient populations.

How garlic protects blood vessels

NO is not the only gaseous molecule that plays an important role in the regulation of cardiovascular

The decrease in CSE activity could be linked to increased vascular inflammation which induced the phosphorylation and inactivation of the enzyme. , as Sofia-Iris Bibli from our research team recently discovered (Bibli et al., 2019). Shortly thereafter plasma cystathionine was reported to be associated with both cardiovascular and noncardiovascular mortality among patients with suspected or established coronary heart disease.

Is there a way to increase H_2S production? There are of course H_2S donors in development, but there are also alternative potential dietary sources of H_2S – including garlic, which may be part of the explanation as to why people

linked with cardiovascular disease. Certainly, in humans a genetic predisposition towards enhanced NO signaling is clearly linked with a reduced risk of developing coronary artery disease, peripheral artery disease and stroke in humans.

Nitrogen oxide, saliva, and mouthwash

What does this have to do with diet? Well, NO can also be generated from dietary nitrate (NO_3^-) and nitrite (NO_2^-) by nitrate reductase expressing bacteria in the mouth. Circulating nitrate (mainly derived from green leafy vegetables), is excreted by the kidneys, but up to 25% is actively taken up by the salivary glands, concentrated, and secreted in saliva. In the mouth, much of the nitrate is reduced to nitrite, resulting in salivary levels of nitrate and nitrite that exceed plasma levels by orders of magnitude, which is subsequently swallowed, and absorbed to enter the circulation.

regulation of cardiovascular homeostasis. A second, somewhat underappreciated, member of this group of compounds is hydrogen sulfide (H_2S- best known from the smell of rotting eggs). The biosynthesis of H_2S is controlled by a number of enzymes, with cystathionine g lyase (CSE), being the principal one in the cardiovascular system.

To exert its effects, H_2S transfers sulfur to cysteine residues in a process referred to as persulfidation or sulfhydration, which alters the function of its target proteins. Recently it became clear that circulating concentrations of the CSE substrate, i.e. the amino acid L–cystathionine, were elevated in patients with endothelial dysfunction, a phenomenon that correlated with reduced H_2S generation. This implicated that CSE activity is decreased in subjects with endothelial dysfunction making it a potential useful biomarker of cardiovascular disease.

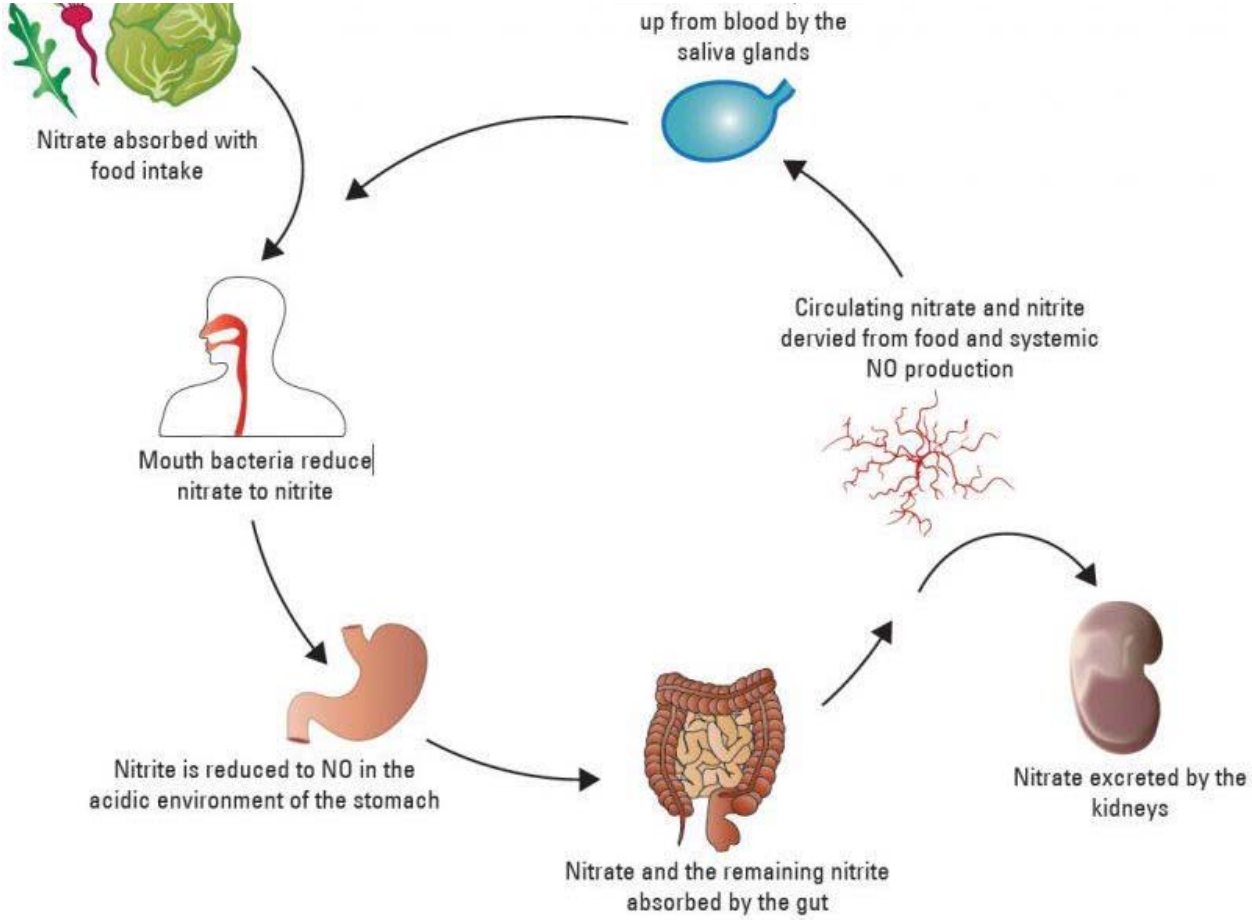
who eat a Mediterranean diet have good cardiovascular health.

Omega-3 fatty acids instead of margine

About 90% of dietary fat comes in the form of triglycerides, which are composed of fatty acids and glycerol. Fatty acids are “monounsaturated” if there is one double bond, and “polyunsaturated” if there are two or more double bonds. Depending on whether the first double bond in on the 3rd or the 6th carbon atom from the methyl end of polyunsaturated fatty acids (PUFAs), they are referred to as omega-3 or omega-6 PUFAs. Both of these groups are important components of cell membranes and are precursors to many other substances in the body such as those involved in regulating blood pressure and inflammatory responses.

Transformation of nitrate, nitrite and NO in the body

The author



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Exactly 150 years ago, margarine was

In addition, dietary supplements may

Red meat and the gut

Exactly 150 years ago, margarine was introduced – a plant-based fat with a high amount of omega-6 fatty acids. Its widespread distribution increased the percentage of omega-6 fatty acids in Western diets. However, it is meanwhile known that the health benefits from using margarine – despite early claims – is doubtful.An increase in the dietary intake of saturated fatty acids and omega-6 PUFAs; such as arachidonic acid and linoleic acid, has been associated with increased obesity, excessive visceral fat deposition, hypertension, endothelial damage, cardiovascular hypertrophy, inflammation, atherosclerosis, ventricular contractile dysfunction, fibrosis and fatty liver disease.

Diets enriched in omega-3 PUFAs (fish oils), on the other hand, are generally thought to protect against the development of both diabetes and heart disease. Early findings associating a diet rich in fish oils (eicosapentaenoic acid or EPA and docosahexaenoic acid or DHA) with protection against cardiovascular disease boosted the research field but more recent clinical trials failed to demonstrate any significant benefit of

In addition, dietary supplements may contain a mixture of EPA and DHA. However, protective effects have only been established for EPA, as shown in a Japanese study in which EPA was used in combination with statin therapy. The most recent EPA intervention studies (REDUC-IT) also show that icosapent ethyl, a highly purified EPA ethyl ester, induced a significant reduction in cardiovascular events. In this trial, a dose of 4 grams per day of highly purified EPA ethyl ester lowered triglyceride values and reduced the risk for ischaemic events such as heart attack and stroke (Bhatt et al., 2017, Bhatt et al., 2018). Studies show that derivatives of DHA, on the other hand, contribute to the development of vascular instability and diabetic retinopathy (Hu et al., 2017).

How could fish oils exert an anti-inflammatory effect? This is difficult to answer as much less is known about the mechanism of action of the omega-3 PUFAs at the molecular level than the omega-6 PUFAs. However, omega-3 PUFAs can modify tissue and blood lipid metabolism, blood lipid concentrations, blood coagulation, immune function,

Red meat and the gut microbiome

A interesting recent development is the realization that bacterial flora in the gut can produce bioactive metabolites that can impact on host physiology and pathophysiology and thus influence the development of cardiovascular and metabolic diseases. One example of such an interaction is the pro-atherosclerotic metabolite trimethylamine oxide (TMAO), which is generated by the oxidation of trimethylamine in the liver (Wang et al. 2011; Jie et al. 2017). The latter compound is produced by gut microbiota from choline, phosphatidylcholine, and L-carnitine – which is abundant in red meat.

Consistent with this, there are clear dietary influences in the generation of trimethylamine and TMAO as vegetarians and vegans have minimal capacity to form TMA from carnitine. Inhibition of gut microbiota-dependent.The association of TMAO levels and adverse clinical consequences has been shown in numerous independent cohorts and

fish oil supplements.

Why did omega-3 PUFA supplementation failed to obtain significant effects? Firstly, the different studies performed failed to determine the optimal concentration of each omega-3 PUFA, or the ratios of omega-3/omega-6 PUFAs required to elicit protection. Second, there is a large variability of quality of the over the counter supplements on the market. The analysis of the most sold fish oil dietary supplement in the US, for example, revealed a high percentage of fatty acids in these supplements.

inflammation and the function of vascular endothelial cells. EPA and DHA are readily incorporated into cells and tissues to modify membrane properties, signal transduction processes and gene expression.
EPA also serves as a substrate for the formation of the specialized proresolving mediator resolvin E1. The latter is an anti-inflammatory metabolite that has been shown to promote the resolution of inflammation in diverse disease models. Resolvins are reported to exert their effects at very low concentrations (pico-nanogram), making them potentially more efficient than their parent PUFA, EPA, as anti-inflammatory mediators.

inhibition TMAO production has been suggested as a promising strategy for the treatment of atherosclerosis. New developments in this field are expected to result in a wave of probiotics aimed at altering the gut flora and the generation of metabolites that impacts of cardio-metabolic health.

These examples show that we are only gradually coming to understand the molecular interdependencies between nutrition, and the health of heart and blood vessels. Meanwhile, research can increasingly better explain why people who eat a predominantly Mediterranean diet are less prone to cardiovascular diseases. And one thing is also certain: it’s not enough to just take a pill that lowers cholesterol.

By Ingrid Fleming

In a Nutshell

- Nitrogen oxide protects blood vessels. The body produces it predominantly through green leafy vegetables. Saliva and mouth bacteria play an important role.
- Sulphurous amino acids, such as

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those found in garlic, guard against atherosclerosis and heart attacks.
- With regard to dietary supplements containing omega-3 fatty acids, the composition is critical. In the mixture of EPA and DHA, EPA promotes vessel health, whereas DHA can be harmful to some people.
- Bacterial flora in the gut produces metabolic products from red meat that promote atherosclerosis. This gives vegans and vegetarians a health advantage.

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This article originally appeared in German in the research magazine Forschung Frankfurt 2/2019 “von Herzen”

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