

Omega-3 fatty acids and cardiovascular diseases

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1- General info on omega-3 and cardiovascular protection

No-one seriously disputes any longer that omega-3 fatty acids have a protective effect against cardiovascular diseases. Many epidemiology publications have demonstrated the inverse relationship between eating fish, fish oils or omega-3 and the frequency or severity of these diseases. Studies analysing the protective effects of plant-based omega-3 fatty acids (alpha-linolenic acid) and precursors for very long chains present in fish oils give comparable results. Intervention trials (randomised studies) have demonstrated that by rectifying omega-3 deficits, it was possible to achieve a highly significant decrease in the frequency of heart complications in high-risk populations. The most spectacular effects were seen in the risk of death (a reduction in the risk of around 30%) and **above all the risk of "sudden cardiac death"**, generally attributed to specifically myocardial complications (malignant ventricular arrhythmias) **with nearly a 50% reduction in the risk, which no specialised "cardiology" medication is able to achieve**. You can find a good summary of this knowledge in references 1 to 3.

In terms of the physiopathology, it is important to recall that administering omega-3 intravenously seems to provide patients who have implantable cardioverter defibrillators (and at very high risk of sudden cardiac death) with an extraordinary degree of protection from malignant ventricular

arrhythmias (4), which are the triggering mechanism for sudden cardiac death.

There is little point here in describing the dietary intervention studies that have tested omega-3 under various conditions (see reference 1 to 3); but it should be noted that at present, and without considering studies with methodological problems that make them uninterpretable, particularly the recent study by M. Burr (5), just one randomised trial has used omega-3 in capsule form. This is the GISSI study (reference 6) conducted with Italian patients who had survived a recent myocardial infarction, and in which a significant reduction in mortality was observed in the 3 and a half year monitoring period, but without any apparent effect on the risk of a non-fatal infarction recurring. This difference in the morbidity and mortality results should probably be attributed (at least in part) to the fact that the patients in both groups had been advised (before the selection draw was made) to go on a traditional Mediterranean diet after their last infarction. This type of diet is very protective in its own right, despite the relatively low level of omega-3, particularly through its anti-inflammatory effects, which probably contributed to reducing the difference between the two groups in terms of heart disease progression (7,8), but on the other hand highlighted the specifically myocardial effects of very long chain omega-3 fatty acids (EPA and DHA) present in the GISSI capsule (6). These myocardial effects were observed at low doses of omega-3 (less than 900 mg), which could appear astonishing, but could again be explained by the fact that the Mediterranean diet followed by the patients is characterised by a very low consumption of omega-6 fatty acids (whose effects conflict with those of omega-3) and also of omega-3, in favour of a high consumption of olive oil which is low both in omega-3 and in omega-6; which means that patients following a classic Mediterranean diet using foods available today are relatively deficient in omega-3.

These considerations are important to take on board in understanding the spectacular effects of the dose of omega-3 tested in the GISSI study.

2- Sudden cardiac death syndrome

By definition, this is a death occurring within an hour of the first thoracic symptoms. This is both too broad a definition (encompasses certain non-cardiac deaths) and too restrictive a definition (excludes many ventricular arrhythmia deaths), but which is generally, and internationally, accepted. The underlying idea is that this death is the consequence of ventricular fibrillation (the heart stops contracting properly) without myocardial necrosis, i.e. myocardial infarction. Once all the possibilities of false diagnostics have been taken into account, it can be assumed that at least 80% of sudden cardiac deaths are actually the result of ventricular fibrillation (3).

This type of mechanism means extreme myocardial vulnerability, since the heart stops without a myocardial infarction taking place. There is no lace in this text for an in-depth discussion of the physiopathology of the syndrome, but it is clear that at present there is no available medication for its prevention, except for beta-blockers, but their effectiveness is low, and furthermore they have side effects that lead many patients to stop taking them.

As discussed in a recent article (3), apart from the implantable cardioverter defibrillator, the only really effective strategy (that is also free from any dangerous or harmful side effects) for preventing sudden cardiac death is the dietary strategy. In the first instance, omega-3 must be used, as it has no contra-indications and is remarkably effective, even at low doses.

In summary, myocardial vulnerability caused by the biological substrate of sudden cardiac death syndrome, can be explained, at least in part, by chronic omega-3 deficit, from which the majority of the population suffers, especially in France.

According to the AFSSA [French Food Safety Agency], the average intake of omega-3 among the French is just 30% of the recommended intake.

Furthermore, these recommended intake levels fall well short of the optimal intake levels for the health of the heart.

So there is a large deficit in terms of cardiac prevention. In addition, these evaluations were conducted on selected populations and are therefore a manifest over-evaluation of the actual intake of many at risk or fragile groups (the very young, particularly adolescents, children and babies, pregnant women, the elderly and very elderly, the sick, particularly those suffering from heart disease, diabetes and obesity, as well as anyone following more or less strict diets, the socio-economically disadvantaged, vegans, etc.) leading one to suspect that in these fragile groups, there are genuine deficiencies. In addition to the dietary intake deficits, there are other mechanisms aggravating the deficits, among which should be mentioned (as part of anti-cholesterol diets) the excessive consumption of poly-unsaturated omega-6 fatty acids (which disrupt the omega-3 metabolism) and the prescription of anti-cholesterol medication (which also promotes the metabolism of omega-6 to the detriment of omega-3), which is far from anecdotal in epidemiology terms, since it has been established that around 6 million French adults take this type of medication. It should be noted, and this is a very important point, that these anti-cholesterol medications do not have any effect on the risk of sudden cardiac death and that blood cholesterol is not a predictive factor for sudden cardiac death (10,11). This means that any patient receiving anti-cholesterol medication should at the same time increase their omega-3 consumption (and reduce their omega-6 consumption) to try to counterbalance the harmful effects of these medications on the metabolism of these fatty acids, and above all to provide themselves with real protection from the risk of sudden cardiac death.

In terms of epidemiology, an important question is to find out what sudden death syndrome represents in our populations in order to really gauge their consequences. An extraordinary study conducted in the USA in 1998

answers this question (12). During 1998, there were 719,456 recorded cardiac deaths in the USA among adults aged over 35. Of these 456,076 (i.e. 63%) were sudden cardiac deaths. Of the deaths among individuals aged between 35 and 54, the proportion was above 72%. In other terms, the vast majority of persons dying from a heart attack die suddenly without the time to receive any emergency treatment and in the vast majority of cases, it is the first (and also the last) manifestation of heart disease. For women in particular, the risk of sudden cardiac death rose by 21% between 1989 and 1998 among women aged between 35 and 44. Apart from dietary problems, smoking tobacco proved to be the predictive factor for the syndrome in these young women.

It is therefore fundamental to understand that the prevention of cardiovascular diseases must fight to prevent sudden cardiac death.

A crucial final question is: how do omega-3 fatty acids affect the risk of sudden cardiac death? Or in other words, why can a deficit of omega-3 cause sudden cardiac death? Some answers are given in the next section.

Finally, the effectiveness of omega-3 in cardiovascular diseases cannot be reduced to a single effect on the risk of sudden cardiac death. The local anti-inflammatory (i.e. vascular) properties of omega-3 also seems to contribute to the stability of atherosclerotic plaques (13), the rupture of which leads to the thrombotic obstruction of the artery lumen, which can lead on to myocardial ischemia. This anti-inflammatory aspect of omega-3 is discussed below regarding interaction with aspirin.

3- Argument for a predominance of DHA in an omega-3 cardiovascular supplement?

There are two main reasons:

- the biological properties of DHA as opposed to those of EPA

- the present (and growing) nature of heart diseases in France

We will discuss these two issues in the following sections.

4- The biological properties of DHA

The essential fatty acids have many biological properties (they are involved in many “biological processes”) that are now conventionally described in two categories, metabolic and structural. It is impossible to summarise the state of knowledge on these extremely complex subjects that demand multiple expertise in biochemistry, biophysics, cellular and molecular biology and physiology, but we will go through some aspects of the rationale. It was believed for a long time that EPA had primarily metabolic properties, because of its competition with arachidonic acid in the metabolic cascade leading to the synthesis of eicosanoid derivatives, and that DHA only had structural properties. In fact, though DHA is actually the longest and most desaturated of the polyunsaturated membrane fatty acids (with a crucial role in membrane structuring), it appears that its positioning in the membranes and its interaction with many receptors, ion channels and other membrane proteins give it important biological and metabolic roles. The work of Mori and Storlien, for example (references 14 to 19), clearly demonstrated that DHA (rather than EPA) could be significantly involved in complications related to metabolic syndromes (dyslipemias, diabetes, hypertension) that are major risk factors for coronary heart disease, and that are therefore very often found in cardiac patients requiring protection. In particular, it has been demonstrated on credible experimental models that **DHA (but not EPA) had an impressive rectifying effect** in experimental diabetic neuropathy (reference 20).

This “neurological” aspect of cardiac protection is certainly crucial in explaining the “anti-sudden cardiac death” effects of omega-3. These can be explained in two ways. **Firstly**, and according to the work of Alexander Leaf (a good summary of which can be found in reference 1), omega-3 interferes with membrane ion channels (especially slow sodium

and calcium) and contributes to stabilising the electrical activity of each cardiomyocyte, thereby regularising the heart's overall electrical activity (which is associated with an anti-arrhythmia effect). Although cellular experiments have not demonstrated any difference between EPA and DHA in this respect, the high predominance of DHA in the membranes suggests that it is the in vivo omega-3 protector. Furthermore, the McLennan group in Australia has demonstrated on various experimental models that DHA was the most important omega-3 fatty acid in this anti-arrhythmia activity (reference 21). **Secondly**, it has been demonstrated that the autonomic nervous system, in particular the balance between the vagal and sympathetic systems (the simplest translation of which is the heart rate variability index), was important in the risk of sudden cardiac death. The Christensen group in Denmark (and other investigators since) have demonstrated that enriching the diet (and therefore the cells) with omega-3 had a very favourable effect on heart rate variability indexes and **that this effect was essentially due to DHA** (reference 22 and 23). Furthermore, it is known that Western populations (and also the better-off classes of the emerging countries) are affected by a new epidemic of metabolic syndromes (more or less systematically combining resistance to insulin or diabetes, dyslipemias, obesity and hypertension) and that these patients, particularly diabetics, very soon develop a cardiac autonomous nervous system malfunction with altered baroreflex sensitivity and reduced heart rate variability, which are factors favouring sudden cardiac death syndrome (24-27). As could be expected, on the one hand omega-3 seems to have a beneficial effect on the heart rate variability of diabetics (28) and on the other hand, cardiac mortality for diabetics is inversely related to fish consumption (29), emphasising the importance of omega-3 in these specific pathologies, as already indicated above in experimental diabetic neuropathy (20).

Finally, the specifically myocardial protective effects of omega-3 have also been linked to the so-called "preconditioning" mechanism, which means that the myocardium is capable of generating anti-ischemia self-

defence mechanisms in the event of an ischemic heart attack, a sort of rectification of myocardial vulnerability caused by an omega-3 deficit. In fact, cell membranes with a high omega-3 content develop powerful preconditioning activities (references 30), and it has been suggested that it is the high DHA concentration (rather than EPA) in the internal mitochondrial membranes that was responsible for this effect (reference 31), which results in a reduction of nearly 50% in the infarct size (30). A protective effect of this sort is always associated with a considerable improvement in the clinical prognosis.

5- The clinical characteristics of heart diseases in France

This aspect of things is of prime importance in defining an effective cardiovascular prevention strategy using an omega-3 capsule.

Omega-3 supplements can be justified whatever the individual's state of health, whether for patients known to have cardiovascular diseases or high-risk subjects (because they have physiological or biological parameters typical of heart diseases: those with hypertension, diabetics, hyperlipidemics, smokers, those with a sedentary lifestyle; hence also those with a metabolic syndrome) or even subjects apparently in good health and who want to remain in good health, the issue is posed on just about the same terms. In fact, at one moment or another, these patients or these subjects will combine one or more of the following characteristics:

- high consumption of omega-6 fatty acids, which is typical of the French population, and which is encouraged and upheld by the medical authorities (under the pretext of combating cholesterol) and which amplifies the omega-3 deficit (reference 32).
- high probability of being prescribed an anti-cholesterol medication (which also amplifies the relative omega-3 deficit).
- high probability of being prescribed aspirin (for cardiology or vascular reasons) or anti-inflammatory medication (analgesic) that inhibit the metabolism of EPA (such as arachidonic acid), minimising the potential role of EPA as a rival for arachidonic acid and its eicosanoid

derivatives, and encouraging the anti-inflammatory effect of DHA and eicosanoid derivatives (reference 33 and other works by Serhan et al). The theory stipulating that in patients taking aspirin (the vast majority of coronary or vascular patients in France), DHA is the basis of substances (resolvines) with local anti-inflammatory properties, is of considerable importance in cardiovascular medicine. In fact, there is no point in giving patients EPA supplements if it is DHA derivatives that play the essential role in prevention. **In other words, it is wiser to take DHA supplements**, because it is the most active omega-3 on the cardiovascular system.

- probable poor synthesis of DHA from EPA, as demonstrated in several studies (reference 34) and particularly in France in the Lyon study among coronary patients (references 7 and 8), again amplifying the DHA deficit.
- high probability of metabolic syndromes in these patients (and we saw the dominant, if not exclusive role of DHA in this context above)
- marked preference by certain patients and subjects for simple solutions: taking capsules rather than making a radical modification to their dietary habits.

6- A new omega-3 capsule

A new omega-3 capsule must aim to satisfy all the issues posed above. It must therefore contain **a minimum quantity of EPA** and have about the same quantity of EPA in the capsule tested in the GISSI study in order to cover the proportion of the protection due (theoretically) to EPA. But it will have to contain **much more DHA**, on the one hand because of the aforementioned properties of DHA, and also since the target population is very different from the GISSI population in terms of omega-6 consumption, taking associated anti-cholesterol medication, aspirin and other anti-inflammatory analgesics, and in terms of various metabolic syndromes (the frequency of which is rising exponentially in France and which are

increasingly frequent in new cardiac patients diagnosed every year in France).

The daily dose of **DHA must therefore be 1000 mg minimum** (EPA/DHA ratio of 1/3).

7- **Other common ingredients in sea foods**

Though the EPA/DHA ratio is not necessarily a crucial element for the **beneficial effects of omega-3**, it is important not to be too far from it or at the very least provide in the capsule the minimum quantities of EPA and DHA tested at GISSI, since the GISSI study is the only randomised study (published to date) to have tested a capsule containing omega-3 to help cardiac patients rectify their dietary imbalances and prevent the major complication of coronary disease that is sudden cardiac death. It must however be underlined that the EPA/DHA ratio in GISSI is quite different from the EPA/DHA ratios measured in the flesh of the majority of fatty fish (more like a 1/2 to 1/3 ratio), which probably correspond to a sort of "natural" balance of these fatty acids (see reference 9).

Furthermore, and despite the controversy on this subject, **selenium** intake is low and while we cannot talk of a generalised deficit (as for omega-3), it is clear that we are a long way off the optimal intake levels for preventing chronic diseases, particularly cancers. On the other hand, while the risk of toxicity from excessive intake is not zero, in general we are a considerable distance from the safety limits, which for most experts are around 1000 micrograms per day. The recommended doses of selenium are 1 microgram per kilo bodyweight per day.

Though selenium is important as an antioxidant, immunomodulator (particularly as an antiviral), antitoxic (against heavy metals) and in certain hormonal systems (thyroid), its importance in the cardiovascular system has still not been well established, although it appears certainly to be more important in myocardial contractility (and therefore also in myocardial vulnerability as described with regard to omega-3 deficits) than in the vascular alteration processes themselves (35). It is therefore

recommended for patients with manifestations of cardiac disease to ensure that they do not have a selenium deficit, which would aggravate their symptoms. A dose of 60 micrograms per day is a minimum recommendable dose.

8- Conclusion

It is important to recall that the French population (and the European population in general) has an omega-3 deficit, more like a deficiency in certain at-risk groups. This deficit is in part responsible for many chronic pathologies, particularly cardiovascular diseases and certain psychiatric diseases.

That does not mean that rectifying this omega-3 deficit will miraculously save us from all these diseases, which are clearly multi-factoral. It does not mean either that this deficit will unavoidably cause us to develop these diseases, but in the space of an average individual's lifetime living in our climate and normal conditions, there can be no doubt that the probability of developing one or more of these diseases is considerably increased by this deficit. Whether these are clinically manifested sooner or later will largely depend on associated factors, particularly family predispositions (or non-modifiable genetic factors) and other environmental factors (that are by definition modifiable), for example smoking tobacco or a lack of exercise.

Rectifying our omega-3 deficit is therefore a simple and effective measure that should brook no delay.

This of course applies all the more to subjects with special risks of cardiovascular diseases, the prevalence of which has significantly risen in our time.

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