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Omega–6/Omega–3 Fatty Acid Ratio: The Israeli Paradox

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While the *amount* of fat is very important in terms of public health in dealing with the current epidemic of obesity, an equally significant issue is the *type* of fat consumed. As polyunsaturated fatty acids (PUFA) have long been shown to possess cholesterol-lowering effects [1], increasing their consumption has been promoted in the management of coronary artery disease (CAD) [2]. These recommendations followed both experimental and population based studies that showed decreasing rates of CAD in countries with increasing polyunsaturated/saturated fat (P/S) ratios over the past years.

The dietary habits in Israel appear to be as recommended: low in total calories, in total fat and in saturated fat, while high in hypolipidemic omega–6 fatty acids (ω6) as compared with other western countries [3, 4]. Unexpectedly, the rates of modern-world illnesses are about the same as they are in the USA and Europe [3, 5, 6]. The reason for this is not clear. Recent evidence suggests that a high intake of omega–6 fatty acids may prove harmful [2, 7–9]: these fatty acids may elevate the risk of hyperinsulinemia and its associated metabolic disorders, atherogenesis, and cancer. Another group of PUFA, the omega–3 fatty acids (ω3), have demonstrated cardioprotection in observational [10–15] and intervention studies for both secondary [16–18] and primary [18] prevention. An example for this is shown in figure 1: an Indo-Mediterranean diet, rich in the plant-derived omega–3 fatty acid alpha-linolenic acid, markedly decreased the risk for a cardiac event among both those with established coronary artery disease, or those only with risk factors [18]. A recent meta-analysis showed that both dietary and non-dietary sources are equally beneficial [19], and the health benefits of plant- derived or fish- derived omega–3 fatty acids now seem to have a sound basis [20]. As the omega–6 and omega–3 fatty acids compete for

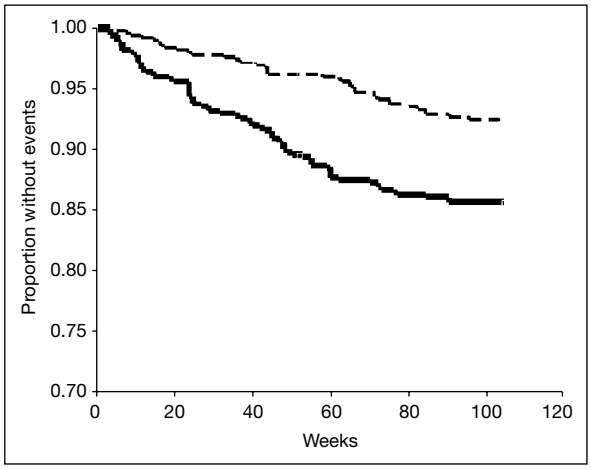

Fig. 1. Kaplan Meier cumulative survival curves of proportion of subjects without fatal MI, nonfatal MI, or sudden cardiac death among experimental (broken line) and control (continuous line) groups in the Indo-Mediterranean Diet Heart Study. The experimental group received a diet enriched with alpha-linolenic acid, a plant-derived ω–3 fatty acid. The control group was advised to consume the National Cholesterol Education Program Step I diet. The risk for cardiac events at the end of a 2-year follow-up was 50% lower in the ω–3 supplemented group. Data from Singh et al. [18].

the same enzymes in their metabolic pathways, the levels of one may influence the other. The end product of the omega–6 pathway is arachidonic acid (AA), a factor in insulin resistance and a common precursor for several pro-inflammatory and tumor- enhancing eicosanoids. The competition of omega–3 on the metabolic enzymes may therefore reduce AA levels, resulting in a lower incidence of diabetes mellitus, atherosclerosis, and cancer. This is the basis for discussion regarding the dietetic, and hence in vivo ratios between omega–6 and omega–3 fatty acids. The unexpectedly high incidence of chronic western diseases in Israel, despite a seemingly protective diet, provides evidence for the importance of the ratio or, better, the balance, between these fatty acids.

Omega–6/Omega–3 Fatty Acid Ratio

The Dangers of a High Omega–6 Intake

While considering the potential harm of omega–6 PUFA, especially the more common linoleic acid (LA, C18:2ω6), one must keep in mind that these are *essential* fatty acids, which must be consumed to ensure normal

functioning of membranes, inflammatory, immune and coagulation responses. Therefore, a range of recommended intake is usually suggested, and not only an upper limit as is given for saturated fatty acids (SFA). The recommended range of LA intake is 2–3% of total energy [21]. Though essential, there are possible dangers of high PUFA intake [2, 7–9]. Low-density lipoprotein (LDL) particles rich in omega–6 are more prone to oxidation [22]. This process may be blocked by the antioxidative properties of vitamin E, but large amounts of LA will overwhelm its protective capabilities. With the current concept that oxidized LDL is atherogenic, this process is undesirable, as it may promote atherosclerosis and CAD. Omega–6 fatty acids may also increase the secretion of insulin leading to hyperinsulinemia and insulin resistance [7]. Insulin, in turn, activates phospholipase A_2, which releases more PUFA from cell membranes. These free fatty acids act as substrates for eicosanoid formation, and some of these leukotrienes and prostaglandins are proinflammatory, thrombogenic, vasoactive, arrhythmogenic and carcinogenic. In this way, high omega–6 levels might augment the occurrence of CAD and its thrombotic events, insulin resistance and related diabetes, dyslipidemia and hypertension, and cancer. Despite these apparent detrimental effects, the original idea of the benefits of LA intake still survives: recent studies have shown that increasing LA intake was protective of CAD [23] while increased plasma levels were protective of stroke [24]. An explanation might be that the polyunsaturated fatty acids should also be considered in relation to the antioxidative (redox) status, that is in relation to vitamins E and C levels. If the latter are sufficient, then probably these beneficial effects might be dominant [25]. It should be disclosed that there are actually no convincing human studies that consumption of omega–6 fatty acids are indeed harmful.

The Omega–6/Omega–3 Ratio

It has been known for about 40 years, that alpha-linolenic acid (ALA, C18:3ω3) – the basic ω–3 fatty acid – inhibits LA metabolism into arachidonic acid (AA, C20:4ω6) [26]. Equally, LA can interfere with the metabolism of ALA, as they compete for the same enzymes. One of the first studies to discuss different ratios between these two essential fatty acids was probably that of Mohrhauer and Holman [27]. It was later determined that the omega–6/omega–3 ratio has implications in several major health conditions. Mathematically, a ratio can be enlarged either by increasing the nominator or by decreasing the denominator. Biologically, these effects are neither necessarily comparable nor equal and, because of this, some researchers do not like the term ‘ratio’. However, many studies discuss the concept and therefore, in this review, it has been retained – but one should keep in mind these caveats. Given the growing evidence that omega–3 fatty acids have many health benefits [10–20, 28], it seems that decreasing

the omega–6/omega–3 ratio without deliberately increasing omega–3 levels is unacceptable.

General recommendations from an international workshop devoted to this issue are to reduce plant oil-derived LA consumption, and to increase omega–3 consumption [21], attempting to reduce the omega–6/omega–3 ratio by changing both constituents of the 'ratio'. The desirable increase in omega–3 consumption is also reflected in the latest American Heart Association dietary recommendations, where at least 2 weekly servings of fish are advocated [29]. One major health problem in which this ratio is of consequence is coronary artery disease (CAD). In a prospective study that included data on LA, ALA and CAD, a modest reduction in fatal disease was shown when the LA:ALA ratio was lower than 10 [15]. It is noteworthy that this effect was less than that of the individual fatty acids alone. Data from the NHLBI Family Heart Study showed that increasing quintiles of ALA intake were protective of CAD only when the LA:ALA ratio was lower than 8.5 [23]. Here, increasing the intake of both fatty acids was beneficial; the protective effect of LA was seen even after adjustment for ALA intake.

An additional health benefit of a decreased omega–6/omega–3 ratio is a reduction in carcinogenesis [9]. The suggested mechanism involves the attenuation of AA production, and hence its carcinogenic metabolites. This is the case, for example, of breast cancer [30]. A study of breast adipose tissue from either breast cancer patients or those with benign disease showed a 60% lower adjusted risk of cancer in patients in the lowest vs. highest tertiles of omega–6/omega–3 ratios [31]. While tertile cutoff points were not given, the average omega–6/omega–3 ratio in cases and controls was around 15–16:1. A ratio of 1–2:1 is suggested as that which best suppresses growth and development of this tumor [32].

Another emerging health benefit of a low omega–6/omega–3 ratio lies in bone turnover: animal studies show that a low omega–6/omega–3 ratio has beneficial effects on bone mineral density [33]. Only 3 human studies conducted so far had contradictory results [34–36], so a final verdict in this matter is not yet available.

The optimal omega–6/omega–3 ratio is not known. A value of 1–2:1 has been shown by Simopoulos [37] to be the ratio in the traditional diet of Crete, which is consistent with the estimates of the Paleolithic diet by Eaton et al. [38], yet this could be an unachievable goal in modern western nutrition. National and international recommendations range from 2:1 in Japan and 2.3:1 in USA, to 5:1 in Sweden and, until recently, 5–10:1 by the WHO [39]. Current recommendations from the Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Diseases suggests consuming omega–6 PUFA at 5–8% of energy, omega–3 PUFA at 1–2% of energy – hence ratios would be

expected to range 2.5:1 to 8:1 [40]. The way of reaching these values would be a reduction in LA (only in those areas with excess intake) and increasing nut, oil, and fish intake as sources of omega–3 [21]. It is noteworthy that essentially all foods containing LA, ALA (or both), affect the dietary omega–6/omega–3 ratio, and not only from oils. Walnuts, a food component repeatedly shown to have cardioprotective properties, have an LA:ALA ratio of 4.2 [41]. This is due to the much higher content of ALA (9 g/100 g edible portion) as compared with other common types of nuts. Therefore, even a hypothetical diet of walnuts alone would not bring this ratio to its minimum. The meat of beef fed on grass had an omega–6/omega–3 ratio of 2:1, while that of grain-fed beef, as modern cattle is raised, has a ratio of 15:1 [9]. This same concept occurs in humans as 'we are what we eat'. Another interesting fact is the LA:ALA ratio in, for example, eggs: while US eggs have about 60% more LA, Greek eggs have 1.300% more ALA, resulting in a much more favorable LA:ALA ratio (2.3:1 in Greece, but 50:1 in USA supermarkets) [32]. The total omega–6/omega–3 ratio in these eggs is 1.3:1 in Greece, but 19.4:1 in the USA. In sum, altering the balance between these fatty acids in a population might require changes in many nutrient sources; it seems that the diet recommended by many organizations to be rich in fruit, vegetables, whole grains, nuts and fish is a feasible way to lower the omega–6/omega–3 ratio.

The Israeli Paradox

Based upon adipose tissue analysis, LA intake in Israel has increased in recent years and was estimated to be approximately 12% of energy intake [6]. Recent data from Jerusalem suggested that an average of 10% is about the current intake [42]. Ninety percent of subjects in this study consumed more than 6% PUFA, and a quarter consumed more than 12% PUFA, of total energy intake. The P/S ratio was 0.9 on average, with a quarter of subjects reaching a value of 1.2 and above. This proportion of PUFA intake in Israel is very high, resulting in what is possibly the highest adipose content of LA in the world, around 25% (references in [6]). The recommended LA intake by an international workshop on the subject is 3% [21], while that of a British Nutrition Foundation task force is 6%, with a 'safe range' of 3–10% [43]; a report prepared for the Food and Drug Administration recommended that LA constitute 4–7% of total energy [2]. Until recently, the World Health Organization recommended PUFA comprising between 3 and 7% of total energy intake [44]; the study group stated then that this upper limit was set as '…existing population average intakes seldom exceeded 7% of energy…'. These data position Israel as a country with one of the highest levels of LA consumption in the world,

probably due to the high LA content of the marketed oils in the country. Soy bean oil is the most common oil produced and consumed in Israel, accounting for over 85% of vegetable oils in the market [45]. Its LA content is about 50%, and its ALA content is about 7%.

With the establishment of the State of Israel and the arrival of many groups of immigrants, oil and fat intake rose from 15 kg/year/capita in 1950 to 21 kg/year/capita in 1970 [45]. In concert, fish intake dropped from 17 kg/year/capita in 1950, to 10 kg/year/capita in 1973. Current data from the Negev Nutritional Studies suggest that fish consumption in this relatively dry part of the country approximates only 3.6 kg/year/person [unpubl. obs.]. Hence, the omega–6/omega–3 ratio in Israel has been rising slowly for many years.

The dietary omega–6/omega–3 ratio in Europe has been estimated at 10–14:1 [6]. This ratio in the nutrition of British men was around 10:1 in 1980 and 8:1 in 1992, but adipose tissue analysis, which reflects long term actual consumption, suggested a practical ratio of 16:1 [46]. In Japan, this ratio approximates 4:1, due to both a low fat diet and a relatively high consumption of fish and ALA-containing vegetable oils [47]. In contrast to these regions of the world, Israelis are estimated to consume a much higher dietary omega–6/omega–3 ratio – about 22–26:1 [6]. Yet all these figures are far from a recommendation of 2:1 suggested by Okuyama et al. [9] for industrialized countries. This ratio is based on the observed increase in cancer, allergy and atherosclerotic disease in Japan, related, at least in part, to an increase in the omega–6/omega–3 ratio from 2.8:1 to 4:1 in the past 40 years.

The total amount of energy consumed in Israel during the late 1980s was lower than that of the USA and European countries except Sweden [3]. Data from the Israeli Central Bureau of Statistics showed that in 1992–1994, the average energy intake in Israel was about 3,100 kcal/day/capita, compared with about 3,300 kcal/day/capita in the Netherlands, 3,600 kcal/day/capita in the USA, and 3,700 kcal/day/capita in Belgium [4]. Similar relations were found for total fat intake, and all western countries consumed more total fat: about 120 g/day/capita in Israel, but 140 g/day/capita in UK, France and Italy, 150 g/day/capita in Canada, Spain and Greece, and 160 g/day/capita in the US [3]. Though a Mediterranean country, olive oil consumption in modern Israel is quite low, probably because of price constraints. In contrast to other western countries, animal fat intake is lower than that of vegetable oil – a supposedly positive nutritional choice. For example, butter consumption in Israel in the mid 1990s was the lowest among 20 countries worldwide [3].

Taken as a whole, the Israeli diet, low in total energy, total and animal fat, combined with high levels of cholesterol-lowering PUFA, seems a solid recipe for good health. Therefore, in Israel, a low prevalence of CAD and other dietary fat-related diseases, like diabetes and several types of cancer, may be anticipated.

Yet the prevalence of CAD, diabetes mellitus and cancer in Israel is comparable with other western countries. In Israel of 1995, the standardized mortality rate from CAD was 235 (males) and 168 (females) compared with 246 (males) and 131 (females) in the US and Europe [5]. The prevalence of diabetes mellitus in Israeli Jews in 1996 was 3.4%, compared with 5.4% of US citizens of the same year [48], yet the rate of deaths from diabetes mellitus in Israel ranked first worldwide [3]. The incidence of colorectal cancer was similar to that in the UK, Canada, Italy, and US whites [3]. Compared with the non-Jewish population of Israel, which have a more traditional diet, Jews have a much higher incidence of most types of cancer [5, 6]. Therefore, the theoretically promising nutrition profile in Israel does not translate to less morbidity. This is termed the Israeli Paradox, as it appears that high omega–6 intake, along with a high omega–6/omega–3 ratio, counteract the expected health benefits of the other components of the Israeli diet.

Lowering the Omega–6/Omega–3 Ratio Despite High LA Intake

Studies of omega–3 supplementation proved it could lower CAD and its risk factors in the general population. But can the high background LA intake be overcome with increasing omega–3 intake? Can the Israeli paradox be modified? Several studies in animals and man suggest that this may be possible in animals and man.

Adding fish oil to the diet of rats with dietary fat induced hyperinsulinemia can prevent the development of insulin resistance [49]. A cross-over study among hyperlipidemic subjects in Israel showed that ingestion of 15 g fish oil/day (=5.2 g of omega–3 PUFA) reduced triglyceride levels by 40% within 2 weeks of treatment [50]. This was accompanied by a 12% increase in HDL levels, without affecting total or LDL cholesterol levels. Serum, platelet and erythrocyte levels of omega–3 fatty acids were elevated, while the levels of LA and AA in erythrocytes were reduced. In another study, omega–3 supplementation was given to 48 hyperlipidemic, statin-treated CAD patients in Israel. This resulted in a reduction in CAD risk factors [51]. Compared with an olive-oil control group, there was a decrease in both total and LDL cholesterol, in triglyceride and in insulin levels. Here, the omega–3 fatty acids were offered in the form of a spread. In another study population – one with high LA intake (mean 7.5%) and a baseline LA:ALA ratio of about 17, increasing ALA intake and its levels in plasma cholesteryl-ester were associated with a decrease in blood pressure, but an increase in plasma triglycerides [52]. Yet in this study, even the subjects in the highest quintile of plasma ALA had

high dietary LA:ALA ratios of 12.4. This point reinforces the fact that high background LA consumption can possibly mask the health benefits associated with ALA alone.

Future Research

While the optimal omega–6/omega–3 ratio is still not known, future research is needed. Large interventional studies with varying intake ratios would definitely be helpful but probably financially impossible to perform. A recent study from Israel correlated adipose tissue fatty acids, a measure of long term fatty acid intake, with acute myocardial infarction [42]. Here, tissue LA, tissue ALA, or the ratios between omega–6/omega–3 in adipose tissue, did not differ between subjects with myocardial infarctions and controls. However, AA levels were significantly higher in the cases. Interestingly, dietary PUFA amounts correlated well with tissue LA – but not with its metabolic end-product, AA. Hence, the path of dietary fat-adipose fat-CAD should be further elucidated. While the adipose tissue analyses are believed to be a true and objective reflection of dietary fat intake [53, 54], these results suggest that methods to assess the optimal dietary omega–6/omega–3 ratio should incorporate tissue analysis as well.

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