The prevention of type 2 diabetes: should we recommend vegetable oils instead of fatty fish?\textsuperscript{1,2}

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More than 50 y ago Scott and Griffith\textsuperscript{(1)} reported on the very low prevalence of diabetes in Alaskan Eskimos in *Metabolism*; they observed only one patient with diabetes. Since that time, it has been suggested that omega-3 polyunsaturated fatty acids (FAs) could play a role in the etiology of type 2 diabetes and insulin resistance. Landmark animal studies by Storlien et al\textsuperscript{(2)} showed, for example, that replacing part of omega-6 FAs with omega-3 FAs improved insulin sensitivity in liver and muscle, supporting this hypothesis.

Thereafter, several epidemiologic cohort studies showed a lower incidence of diabetes in participants who consumed (more) fish compared with non–fish eaters. For example, we observed this finding in a small cohort of Dutch elderly men and women and in men from Finland and the Netherlands\textsuperscript{(3, 4)}. More recently an inverse association between the intake of omega-3 FAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and the incidence of diabetes was reported in the EPIC (European Prospective Investigation into Cancer and Nutrition)-Norfolk study\textsuperscript{(5)}. However, our investigation of the Rotterdam study showed no significant association, and even pointed at a weak positive association between fish consumption and diabetes risk\textsuperscript{(6)}, which was similar to the positive association between long-chain FAs and diabetes as reported for the Harvard cohorts\textsuperscript{(7)}.

This issue of the Journal includes 2 interesting articles that may shed some more light on these rather conflicting observations. The first one is a cohort study from Asia on omega-3 FAs and diabetes, which is, to my knowledge, the first such study from this region\textsuperscript{(8)}. The article shows that total omega-3 FA intake is inversely associated with diabetes incidence in the Singapore Chinese Health Study, an association which is entirely due to omega-3 FAs improved insulin sensitivity in liver and muscle, supporting this hypothesis.

Of interest, the second article in this issue includes these biomarkers. Djousse\textsuperscript{e} et al\textsuperscript{(9)} studied the association between plasma omega-3 FAs and incident diabetes in the Cardiovascular Health Study (CHS). They measured plasma phospholipids in \textasciitilde3100 elderly individuals, a cohort in which 204 incident cases occurred. Their results are interesting; they confirm recent observations that intake of fish or EPA/DHA is not associated with diabetes risk but in contrast show that plasma EPA/DHA is associated with a reduced incidence. The risk is especially reduced in the highest quartile of plasma EPA/DHA.

For ALA, the results are slightly different. The reduced risk of diabetes in the highest quartile of plasma ALA is even stronger than that for EPA/DHA. And, in contrast to the results for EPA/DHA, ALA intake is also associated with a reduced risk. The authors conclude that ALA is associated with a reduced risk, and that previous studies of fish and EPA/DHA intake may have shown a positive association with diabetes due to residual confounding or due to other ingredients in fish.

This is indeed an interesting explanation for the contradictory findings using fish consumption as the exposure variable. We previously suggested\textsuperscript{(6)} that nutrients such as selenium could be involved, because selenium was shown to increase diabetes risk in the SELECT (Selenium and Vitamin E Cancer Prevention Trial) Study. Alternatively, contaminants may also play a role. Regarding the plasma observations, we recently reviewed studies on plasma FA and glucose tolerance, including prospective studies on diabetes\textsuperscript{(10)}. The cohort studies showed no clear association of plasma EPA/DHA with diabetes, and 4 out of the 5 cohorts

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showed no association with plasma ALA. One cohort study, the Atherosclerosis Risk in Communities Study (ARIC), showed that ALA was associated with lower diabetes risk, which strengthens the observation by Djoussé et al in the CHS. Why the other cohorts did not find an association with ALA, and the CHS and ARIC study did, needs more investigation. One curious difference seems to be the plasma FA measurement: in both the CHS and the ARIC plasma phospholipids were used, whereas the other studies used choleseryl esters. It is of note that a recent article from EPIC-Potsdam reported a lack of association with any omega-3 FAs measured in erythrocytes (11).

ALA, the vegetable oil omega-3 FA, has so far been studied less frequently in relation to diabetes and glucose metabolism. The 2 studies in this issue of the Journal suggest that ALA can be protective, and this is a good hypothesis, which merits more attention. The obvious variation in intake and sources between various countries suggests that additional cohort analyses may provide some interesting evidence. But additional biomarker studies are equally welcome.

Genetic research and molecular epidemiology could perhaps help us out as well. Plasma concentrations of FAs are determined not only by intake but also by desaturase and elongase activities, which are affected by substrate, but are also partly under genetic control (10, 11). We should now accept the notion that diabetes is preceded by low $\delta^5$-desaturase activity (10, 11). It can be speculated that if plasma ALA is high, intake is high, $\delta^6$-desaturase is low, or both. Kröger et al (11) observed a strong positive association between estimated $\delta^6$-desaturase activity and diabetes risk, which therefore would not be consistent with higher “diabetes preventing” ALA concentrations. But, that there is “something going on” in this area is obvious.

Fortunately, the nice thing about diabetes is that we can perform intervention studies on glucose metabolism and insulin resistance or conduct longer-term trials, in high-risk subjects, to corroborate our observations. Regarding EPA/DHA, for example, the KANWU (Kuopio, Aarhus, Naples, Wollongong, and Uppsala) trial by Vessby et al (12) already indicated in 2001 that the results regarding diabetes may be less promising than previously thought, because the 3-mo intervention with fish-oil supplements (3.6 g omega-3 FAs/d) did not improve insulin sensitivity in healthy participants. This was, of course, a short-term experiment compared with our cohort observations, but at least it indicates that the effect on glucose metabolism may not be very large.

In summary, the 2 studies in the present issue suggest that ALA can reduce diabetes risk. To what extent enzyme activities play a role is not clear. A good trial using ALA is so far lacking but does not seem impossible. Finally, studies on dietary patterns and diabetes should also take a closer look at ALA and its main sources.

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REFERENCES