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Fish intake and prevention of selected nutrition-related diseases

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Summary

In addition to the DGE guideline "Fat intake and prevention of selected nutrition-related diseases" focussing on the nutrient fat (including long-chain n-3 fatty acids), this publication describes the data on the association between intake of fish as food and prevention of dyslipoproteinaemia, hypertension, coronary heart disease (CHD) and stroke. The data clearly show that regular intake of fish, particularly fatty fish, has a positive influence on the blood lipoprotein profile and reduces risk of CHD mortality and ischaemic stroke. The results confirm the recommendation of the DGE to eat fish once to twice a week.

Keywords: fish intake, prevention, dyslipoproteinaemia, hypertension, coronary heart disease, stroke

Introduction

The intake of fish and its effect on human health have been subject of scientific studies for a long time. Regarding the intake of fish, health-promoting effects have been described that are primarily due to the content of long-chain n-3 fatty acids, which are particularly present in fatty saltwater fish [1]. In the evidence-based guideline "Fat intake and prevention of selected nutrition-related diseases" by the German Nutrition Society (DGE), the effects of fat and fatty acid intake including long-chain n-3 fatty acids on the prevention of nutrition-related diseases were investigated. However, studies on foods were not considered in the guideline. As intake of long-chain n-3 fatty acids is almost exclusively ensured by the intake of fish and other seafood, the following text amends the findings from the guideline by the preventive aspects of fish intake. The diseases considered in the following are dyslipoproteinaemia, hypertension, coronary heart disease and stroke, as they are of interest in connection with the findings of the DGE guideline on long-chain n-3 fatty acids [2].

In intervention studies, long-chain n-3 fatty acids are usually administered in pharmacological doses as supplements or enriched products, whereas in prospective cohort studies, the effects of long-chain n-3 fatty acids are investigated by questioning the intake of fish and other seafood. This may explain why the results of the studies vary depending on study design. Furthermore, there are indications that different effects are to be expected in different intervention studies with supplements of long-chain n-3 fatty acids, too, for example depending on the form in which the long-chain n-3 fatty acids are supplemented [3].

The study results presented in the following only refer to study results on the intake of fish as food and not on the intake of long-chain n-3 fatty acids. The latter aspects have recently been published in the Ernährungs Umschau (issue 9/2015) in the article of Fischer and Glei [4]. For an overall assessment of the preventive potential of long-chain n-3 fatty acids, please refer to the DGE guideline on fat intake [2].

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Methodological approach

The results described in the following are based upon an analysis of epidemiological studies on the influence of fish intake on certain diseases and on the review of study results obtained therein. The literature research was performed using the NCBI PubMed data base and captured the publications from 1975 to August 2014. The search strategy included the search terms "fish" and "fish intake" and the disease outcomes "dyslipoproteinaemia", "hypertension", "coronary heart disease" and "stroke". Additionally, the references in relevant publications were reviewed.

Results

Fish intake and risk of dyslipoproteinaemia

In a prospective cohort study including 903 adults, an increase in fish intake by 20 g/day led to a significant increase in serum HDL (high-density lipoprotein) cholesterol concentration within 10 years (ß ± standard error [SE] 0.010 mmol/L ± 0.004; p = 0.02) and a significant reduction in serum triglyceride concentration (ß ± SE -0.014 mmol/L ± 0.006; p = 0.02), while there was no association with serum total and LDL (low-density lipoprotein) cholesterol concentration (ß ± SE -0.013 mmol/L ± 0.013; p = 0.3 and ß ± SE -0.019 mmol/L ± 0.012; p = 0.1) [5].

In an intervention study with 118 healthy adults, mean intake of 317 g fatty fish per week over a period of 3 months in comparison to mean intake of 32 g fatty fish per week, resulted in a significant reduction in plasma triglyceride concentration (difference to control group = -0.12 mmol/L, standard deviation [SD] = 0.61), while no changes were observed in plasma concentrations of total, HDL and LDL cholesterol [6].

A significant reduction in plasma triglyceride concentration (mean difference = 0.13 mmol/l; 95 % confidence interval [CI] -0.25; -0.003) and a significant increase in plasma HDL cholesterol concentration (mean difference = 0.08 mmol/L; 95 % CI 0.008–0.16) as well as a reduction in the ratio of total to HDL cholesterol (mean difference = -0.24 mmol/L; 95 % CI -0.38; -0.11) was observed in an 8-week intervention with 48 subjects who consumed 125 g fatty fish daily, while there were no changes in the control group without intake of fatty fish. Plasma LDL cholesterol concentration was not influenced by the intake of fatty fish (mean difference = -0.13 mmol/L; 95 % CI -0.25–0.001) [7].

In the weight-loss intervention by Gunnarsdotter et al. [8] including 324 overweight or obese individuals, intake of 150 g fatty fish three times a week resulted in a small significant reduction in serum triglyceride concentration compared to a diet without fish after adjustment for weight loss (difference to control group = -0.0060 mmol/l; 95 % CI -0.101; -0.018). When instead of fatty fish, 150 g low-fat fish was consumed three times a week, no change in serum triglyceride concentration was detected compared to a diet without fish (difference to control group = -0.036 mmol/l; 95 % CI -0.079–0.006). Both intervention diets with fatty fish or low-fat fish did not influence the concentration of serum total, HDL and LDL cholesterol as well as the ratio of total to HDL cholesterol compared to the control group without fish intake.

In two intervention studies by Lindqvist et al. from 2007 and 2009 including 13 men and women and 35 men, respectively, intake of fatty fish (in each case 150 g herring fillet 5 days a week) resulted in a significant increase in plasma HDL cholesterol concentration in contrast to a control diet without fish. Total and LDL cholesterol concentrations as well as the triglyceride concentration in plasma remained unchanged [9, 10].

Two intervention studies did not find any influence regarding plasma concentrations of lipoproteins and triglycerides after intake of lean fish (200 g daily for 6 weeks) [11] or medium-fat fish (150 g daily for 8 weeks) [12] in comparison to a control diet without fish.

Another 24-week intervention study including 134 men and women investigated the effect of the intake of 2 portions of fatty fish per week on the concentration of blood lipids in comparison to consumption of low-fat fish. Intake of fatty fish (on average 43 g/day) compared to intake of low-fat fish (on average 59 g/day) resulted in a significant reduction in plasma triglyceride concentration, while the concentration of the other lipoproteins did not change [13].

In two intervention studies, the effects of a diet with fish or meat on plasma lipoprotein and triglyceride concentrations were compared. The study by Leaf et al. [14] with ten adults showed that a diet with low-fat fish in contrast to a diet with beef (276 g fish or beef/2,000 kcal per day) lead to a significant reduction in plasma triglyceride concentration, while plasma HDL concentration was significantly increased by the beef diet. In the intervention study by Wolmarans et al. [15] including 28 adults, a diet with fatty fish was compared to a diet with red meat. Compared to the diet with red meat (men: 300 g/day, women: 225 g/day), the diet with fatty fish (men: 280 g/day, women: 216 g/day) resulted in a significant reduction in plasma total and LDL cholesterol and triglyceride concentration.

The results regarding the prevention of dyslipoproteinaemia through intake of fish show that regular intake of fatty fish is associated with

a reduced triglyceride concentration and an increased HDL cholesterol concentration in plasma, while there is no influence on plasma total and LDL cholesterol concentration.
In addition, the results of a 6-week intervention study including 58 subjects with coronary heart disease showed that a significant reduction in serum triglyceride concentration and a significant increase in serum HDL cholesterol concentration was only observed in subjects who had consumed 700 g fatty fish per week that was fed with fish oil, but not in subjects who were given fish that were fed with rapeseed oil or a mixture of fish and rapeseed oil [16].
Regarding the effect of fish intake on the risk of dyslipoproteinaemia it has to be considered that it is not known to what extent the observed favourable effect on triglyceride and HDL cholesterol concentration is only due to the long-chain n-3 fatty acid content in fish. The total fat content or the content of other kinds of fatty acids such as saturated fatty acids in fish may also contribute to the observed effects.

Fish intake and risk of hypertension

For the evaluation of the association between fish intake and the risk of developing hypertension, the results of a prospective cohort study and of four intervention studies are available.

An observational study with 4,508 US-American citizens over a period of 20 years showed that high (> 1.26 portions of fish/day) compared to low (< 0.3 portions of fish/day) intake of non-fried fish was associated with a significantly lower systolic blood pressure (comparing extreme quartiles: hazard ratio [HR] = -0.63 mm Hg; 95 % CI -1.20; -0.06), but there was no association with diastolic blood pressure (comparing extreme quartiles: HR = -0.17 mm Hg; 95 % CI -0.65; 0.31). Furthermore, there was no association between intake of fish and incidence of hypertension (comparing extreme quartiles: HR = 0.85; 95 % CI 0.70–1.03) [17].
In an 8-week intervention including 48 healthy adults (20 to 55 years old), daily intake of 125 g of fatty fish significantly lowered systolic (mean difference = -4.6 mm Hg; 95 % CI -7.0; -2.1) and diastolic blood pressure (mean difference= -3.0 mm Hg; 95 % CI -5.0; -0.9) [7].
In the intervention study by Ness et al. [18] over 2 years on 2,033 men who had previously suffered a myocardial infarction, comparison between intervention group (recommendation to consume 2 portions of fatty fish per week and as much other fish as possible) and control group (no recommendation regarding fish intake) showed no difference regarding systolic (mean difference = 0.40 mm Hg; 95 % CI -1.33; 2.13) and diastolic blood pressure (mean difference = 0.19 mm Hg; 95 % CI -0.88; 1.26).
The 8-week intervention study by Ramel et al. [19] including 324 subjects with fish intake of 150 g three times a week, and the 12-week intervention study by Vandongen et al. [20] including 120 men with fish intake of 90 g/day to 160 g/day (both studies included subjects with moderate cardiovascular risk) revealed no influence of fish intake on systolic and diastolic blood pressure.

Current data regarding the influence of fish intake on risk of hypertension are inconclusive. Further prospective studies are required to allow a more accurate estimation of the possible preventive effect of fish intake.

Fish intake and risk of coronary heart disease (CHD)

CHD mortality

There exist five meta-analyses of prospective cohort studies on the association between fish intake and CHD mortality [21–25]. Due to their different times of publication as well as inclusion and exclusion criteria the meta-analyses consider different individual studies to some extent. However, many of the prospective cohort studies were included in several meta-analyses and were therefore considered several times.

The meta-analysis of 13 prospective cohort studies by He et al. [21] showed a significantly reduced CHD mortality when comparing fish intake of five times a week to fish intake of less than once a month (relative risk [RR] = 0.62; 95 % CI 0.46–0.82).
The meta-analysis of 13 prospective cohort studies by Whelton et al. [22] published in the same year (2004) also indicated a reduced CHD mortality (RR = 0.83; 95 % CI 0.76–0.90) when comparing fish intake (no information about quantity or frequency) with no or low fish intake.
The meta-analysis of seven prospective cohort studies by König et al. [23] published in 2005 showed, too, that fish intake (no information about quantity or frequency) reduced CHD mortality in comparison to no or low fish intake (ΔRR = -0.17; 95 % CI -0.25; -0.088).
The meta-analysis by Skeaff and Miller [24] investigated the association between intake of polyunsaturated n-3 fatty acids (n-3 PUFA) and CHD mortality in 20 prospective cohort studies that included studies on fish intake, studies on intake of n-3 PUFA and biomarker studies. In most of the studies, fish intake was recorded. Here as well, the comparison between high (0.37–2.5 g n-3 PUFA/day corresponding to 22–180 g fish/day) and low (0–0.3 n-3 PUFA/day corresponding to 0–23 g fish/day) intake of n-3 PUFA showed a reduced CHD mortality (RR = 0.82; 95 % CI 0.71–0.94).
The most recent meta-analysis by Zheng et al. [25] published in 2012 also investigated the association

between fish intake and risk of CHD mortality. Data from 17 prospective cohort studies were included. The intake of 1 portion of fish per week in comparison to less than 1 portion per month as well as the intake of 2 to 4 portions of fish per week in comparison to less than 1 portion per month significantly reduced the risk of CHD mortality (RR = 0.84; 95 % CI 0.75–0.95 and RR = 0.79; 95 % CI 0.67–0.92); intake of 5 portions of fish per week compared to less than 1 portion per month lowered the risk similarly, but the result was not statistically significant (RR = 0.83; 95 % CI 0.68–1.01).
Regarding the association between fish intake and the endpoint fatal myocardial infarction, there are more recent results from a cohort study with analysis of data from the German arm of the EPIC study (European Prospective Investigation into Cancer) [26] and a case-control study with analysis of data of the Northern Sweden Health and Disease Study [27]. Both studies did not show an association between fish intake and risk of fatal myocardial infarction.

Considering the published meta-analysis on the association between fish intake and CHD mortality, it can be concluded that a higher intake of fish reduces the risk of dying of CHD. Future meta-analyses will show the relevance of the two new cohort studies in the overall context of the available studies.

CHD risk

The following study results on the association between fish intake and risk of CHD (fatal and non-fatal combined) as well as non-fatal CHD events are more inconsistent than the results regarding CHD mortality.

The meta-analysis of seven prospective cohort studies by Whelton et al. [22] did not reveal a statistically significant association between fish intake and risk of CHD (RR = 0.93; 95 % CI 0.87–1.00).
The meta-analysis by Skeaff and Miller [24] investigated the association between intake of n-3 PUFA and risk of CHD in seven prospective cohort studies that included studies on fish intake, studies on intake of n-3 PUFA and biomarker studies. Most of the studies recorded fish intake. The comparison between high (0.37–2.5 g n-3 PUFA/day corresponding to 22–180 g fish/day) and low (0–0.3 n-3 PUFA/day corresponding to 0–23 g fish/day) intake of n-3 PUFA showed no significant association with risk of CHD (RR = 0.87; 95 % CI 0.71–1.10).
However, the meta-analysis of 27 prospective cohort studies by Mente et al. [28] showed a significant inverse association between fish intake and risk of CHD when comparing high to low fish intake (RR = 0.83; 95 % CI 0.73–0.93).

Regarding the association between fish intake and risk of non-fatal myocardial infarction, the meta-analysis of five prospective cohort studies by He et al. [21] showed that fish intake five times a week compared to once a month significantly lowered risk (RR = 0.79; 95 % CI 0.64–0.99).
In the meta-analysis of three prospective cohort studies by König et al. [23], fish intake (no information about quantity or frequency) compared to no or low fish intake was associated with reduced risk of non-fatal myocardial infarction (ΔRR = -0.27; 95 % CI -0.34; -0.21), but intake of an additional portion of fish per week in individuals who regularly consume fish showed no association (ΔRR = 0.083; 95 % CI -0.012; 0.028).
In the prospective cohort study analysing EPIC data from Germany by Kühn et al. [26], risk of non-fatal myocardial infarction was reduced by high intake of fish, but the result was not statistically significant (comparing the highest quintile with an average intake of 40.4 g/day and the lowest quintile with an average intake of 2.7 g/day, RR = 0.78; 95 % CI 0.59–1.03).

The results regarding the association between fish intake and risk of CHD as well as the risk of non-fatal myocardial infarction indicate a preventive effect of fish intake, but they are not entirely conclusive. Therefore, further studies are necessary.

Fish intake and risk of stroke

The association between fish intake and risk of stroke has been investigated in five meta-analyses [21, 29–32]. The majority of the respective prospective cohort studies were included in more than one of the five meta-analyses and were therefore considered several times.

In the meta-analysis of five prospective cohort studies and one case-control study by Bouzan et al. [29], fish intake (no information about quantity or frequency) compared to no fish intake was not associated with risk of stroke (ΔRR = -0.12; 95 % CI 0.25; 0.01).
The meta-analysis of 21 prospective cohort studies on the association between fish intake and risk of cerebrovascular disease by Chowdhury et al. [30] showed a reduced risk of cerebrovascular disease comparing the highest with the lowest fish intake (RR = 0.88; 95 % CI 0.84–0.93).
Regarding ischaemic and haemorrhagic stroke, too, a reduced risk was shown when comparing the upper third with the lower third of intake level (RR = 0.93; 95 % CI 0.87–0.94 for ischaemic stroke; RR = 0.81; 95 % CI 0.70–0.94 for haemorrhagic stroke; results based on data from six studies on these endpoints).
The meta-analysis of nine prospective cohort studies by He et al. [21] showed a reduced risk of stroke when comparing fish intake of five times a week to fish intake of less

than once a month (RR = 0.69; 95 % CI 0.54–0.88). Subgroup analysis revealed a reduced risk of stroke in women (RR = 0.64; 95 % CI 0.46–0.88), but not in men (RR = 0.77; 95 % CI 0.52–1.14). There also was an inverse association with risk of ischaemic stroke (RR = 0.65; 95 % CI 0.46–0.93), but no association with risk of haemorrhagic stroke (RR = 0.80; 95 % CI 0.44–1.47).

The comparison between highest and lowest intake of fish in the meta-analysis of 15 prospective cohort studies by Larsson and Orsini [31] also showed a reduced risk of stroke (RR = 0.88; 95 % CI 0.81–0.96). An increase in fish take by three portions per week was associated with a reduced risk of ischaemic stroke (RR = 0.90; 95 % CI 0.84–0.97), while there was no association with haemorrhagic stroke (RR = 0.90; 95 % CI 0.76–1.06).

The meta-analysis by Xun et al. [32] including 16 prospective cohort studies, 13 of which had also been considered in the meta-analysis by Larsson and Orsini, showed a reduced risk of stroke with fish intake of five times a week compared to fish intake of less than once a month (HR = 0.87; 95 % CI 0.79–0.96). Here as well, subgroup analyses demonstrated a reduced risk of ischaemic stroke (HR = 0.83; 95 % CI 0.75–0.92), but no association with haemorrhagic stroke (HR = 0.92; 95 % CI 0.80–1.07). Another subgroup analysis revealed that the inverse association between fish intake and risk of stroke was observed in North America (HR = 0.79; 95 % CI 0.65–0.96), but not in Europe (HR = 0.91; 95 % CI 0.76–1.08) or Asia (HR = 0.89; 95 % CI 0.72–1.10).

The results of the meta-analyses indicate that higher fish intake is associated with a reduced risk of stroke, especially regarding risk of ischaemic stroke.

A more recent prospective cohort study supports this evaluation: increased fish intake was associated with reduced risk of mortality due to ischaemic stroke (HR comparing extreme quintiles of fish intake = 0.63; 95 % CI 0.41–0.94) [33]. However, a more recent analysis of data from the German arm of the EPIC study showed no association between fish intake and risk of stroke (RR = 0.96; 95 % CI 0.73–1.26) [26].

Conclusions

The current data show that intake of fatty fish is associated with reduced triglyceride concentration and increased HDL cholesterol concentration in plasma, while there is no influence on plasma total and LDL cholesterol concentrations. Regarding risk of hypertension, the data are currently inconclusive. Intake of fish is associated with reduced risk of CHD mortality and lowers risk of stroke. This particularly applies to ischaemic stroke, but not to haemorrhagic stroke.

The favourable effect of fatty fish on blood lipids may partially explain the reduction in the CHD mortality as well as lowering the risk of ischaemic stroke, the most common type of stroke in Europe [34]. In order to be able to finally assess the effect of fish intake on blood pressure, further prospective studies are required. These studies should investigate the effect of fatty fish in particular and also consider the preparation methods, as a high intake of table salt may increase blood pressure and therefore risk of haemorrhagic stroke as well.

Based upon these findings, regular intake of fish is recommendable, particularly intake of fatty fish like salmon, mackerel or herring. Wild-caught fish should be preferred over fish from aquaculture, as the latter has a less favourable fatty acid composition [35].

Adverse effects of fish intake were not observed in the considered studies. According to the literature, at a fish intake of once to twice a week, the health benefits of fish intake outweigh the potential harm of the fish's pollution load [36–38]. This is confirmed by a systematic review by the National Evidence Library (NEL) of the US-American Dietary Guidelines Advisory Committee (DGAC) published in 2010, which concludes with probable evidence that in the amount of up to 340 g per week the advantages of fish intake overweigh the adverse effects of a potential contamination of fish with methylmercury and persistent organic pollutants [39].

However, it is not possible to derive a defined intake level based on the studies presented here, since most of the studies did not compare absolute quantities of fish but portions or frequencies. For the primary prevention of CHD-related deaths, an intake level of 250 mg eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) per day is stated in the literature. Regarding a food-based recommendation on fish intake, this intake level of EPA and DHA is covered by the intake of one to two fish meals per week, provided that this means an intake of for example 70 g of fatty fish. This is an approximate value, as the content of EPA and DHA depends on fish species, fishing zone, food/feed and preparation method [16, 40–42].

Independent of this, fish is a valuable source of protein, iodine, selenium and vitamin D. However, an intake of fish exceeding one or two portions a week should be viewed critically for reasons of sustainability [43].

Conflict of Interest
The authors declare no conflict of interest.

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