Role of Omega-3 Polyunsaturated Fatty Acids in Mental Health—Studies from Japan

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Abstract: Omega-3 polyunsaturated fatty acids is a generic term that encompasses eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are abundant in fish, and α-linolenic acid, which is abundant in perilla oil. These fatty acids became well known following an epidemiological study conducted in Greenland about 50 years ago. EPA formulations, with their putative prophylactic effect against cardiovascular disease, first became clinically available in the 1990s in Japan. There were reports of their association with mental health, especially depression, and from around the year 2000 several epidemiological studies and clinical trials were conducted. This article introduces the epidemiological studies and clinical trials conducted in Japan and the knowledge gained.

Key words: omega-3 polyunsaturated fatty acids, depression, epidemiological studies, clinical trials

1 Introduction

A case-control study conducted in the UK by Fehily et al. in 1981 was probably the first to report the association between omega-3 polyunsaturated fatty acids (PUFAs) and depression, finding reduced blood levels of omega-3 PUFAs in patients with endogenous depression compared with age- and sex-matched healthy individuals. Research evaluating this association expanded steadily until the findings of a multinational study by Hibbeln in 1998 prompted a marked increase in the number of epidemiological studies and clinical trials conducted. A meta-analysis published in 2010 evaluated the results of 14 case-control studies of the association of blood omega-3 polyunsaturated fatty acids with depressive symptoms or depression and reported significantly lower concentrations of omega-3 PUFAs in peripheral blood in patients with depressive symptoms or depression compared with controls. These differences were also clearer in a subgroup of patients with depression diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM), which was used in 6 of the 14 studies. A recent meta-analysis of prospective studies also reported that seafood consumption and/or dietary omega-3 PUFA consumption could prevent depression.

Historically, seafood consumption is high and the prevalence of depression is low in Japan. However, with the increasing popularity of a Western diet, meat consumption exceeded seafood consumption in 2006, and the gap continues to widen. This posed the question of whether the association between seafood consumption and depressive symptoms is also apparent in the Japanese population. This article reviews the findings of epidemiological studies and randomized controlled trials (RCTs) conducted in Japan.
2 Epidemiological studies in Japan

2.1 Studies in children

The youngest population investigated for the association between seafood or omega-3 PUFA consumption and depressive symptoms was 6,517 state-funded middle-school students (12-15 years of age) in the cities of Naha and Nago in Okinawa Prefecture. Significant associations were found between seafood consumption and depressive symptoms and between EPA consumption and depressive symptoms in male students only.

2.2 Studies in adolescents

A cross-sectional study of 4,190 undergraduate students (mean age, 20.5 years) that my colleagues and I recently conducted found a negative association between fish consumption and depressive symptoms. Subgroup analysis by sex showed that the association was stronger in female than in male adolescents. Surprisingly, 12.8% of the study population rarely consumed fish.

2.3 Studies in pregnant women

Five observational studies have investigated the association between consumption of fish or omega-3 PUFAs and perinatal depression in Japan. However, only 2 studies, and not the remaining 3, confirmed the association. My colleagues and I conducted one of the 2 studies with positive findings, in which data from approximately 70,000 pregnant women were examined. The association was weak during the first trimester, became stronger during the second and third trimesters, and was sustained, albeit slightly weakly, during the postpartum period. Also, fish consumption was more strongly associated with depressive symptoms than omega-3 PUFA consumption. The study also examined approximately 40,000 husbands of pregnant women and showed that the association of fish consumption with depressive symptoms was weaker in husbands than in their pregnant wives, while the association of omega-3 PUFAs with depressive symptoms was absent in husbands. The other study that showed positive finding was conducted by Miyake et al. Using a cross-sectional design, they found an inverse association between levels of fish, EPA, and DHA and depressive symptoms during pregnancy. Of the three studies that produced negative findings, two prospective studies examined the effect of n-3 PUFA intake during pregnancy on the risk of postpartum depression and found no clear inverse association. The other had a cross-sectional design and found no beneficial effects of n-3 PUFA intake on these symptoms. These mixed and inconclusive findings during the perinatal period may be attributable to differences in study design, sample size, duration of follow-up, participant background factors, and/or the instruments used to assess depression, suggesting that further research is required.

2.4 Studies in middle-aged individuals

The number of studies that examined middle-aged individuals is relatively large, with 6 reported to our knowledge thus far. Two of these were cross-sectional studies that examined individuals in certain occupations. One study involving 517 civil servants in the Kyushu region of Japan found no association between consumption of omega-3 PUFAs and depressive symptoms, whereas the other study involving 523 employees of 3 leading companies in an urban area did find an association between fish consumption and reduction in depressive symptoms. Among studies that examined community residents, one study in which I collaborated with Matsuoka’s group examined a cohort of 1,181 residents of Minamisaku District, Nagano Prefecture, who fell within the catchment area of Saku Public Health Center. Following screening, major depressive disorder was diagnosed in 95 residents by a psychiatrist using DSM-IV criteria. Reduced risk of major depressive disorder was found in the third quartile for consumption of fish, the third quartile for consumption of docosapentaenoic acid (which is an intermediate metabolite of EPA and DHA), but not in any quartiles for consumption of EPA and DHA. However, a later cohort study of 2,335 community residents in Aichi Prefecture showed an association between EPA and DHA consumption and reduced risk of depressive symptoms. A study conducted by the same research group 2 years earlier showed that serum levels of fatty acids were associated with depressive symptoms in residents of the same area. The association between serum fatty acids and depressive symptoms was also examined in a cross-sectional study involving 2,529 residents in the Hisayama Study. Arachidonic acid (AA)/EPA ratio and AA/DHA ratio were not associated with the presence of depressive symptoms in the overall study population; however, AA/EPA ratio, but not AA/DHA ratio, was associated with risk of depressive symptoms in a subgroup with inflammatory findings (C-reactive protein ≥ 1 mg/L, n = 581).
3 RCTs in Japan

To my knowledge, only 3 RCTs examining the association have been conducted in Japan\textsuperscript{20–22}, all of which I was involved in as a collaborator. This is in contrast to the many RCTs that have been conducted overseas\textsuperscript{23–32}. The first study was a multicenter RCT (with a factorial design) by Watanabe \textit{et al.} that examined the amelioration of anxiety and depressive symptoms in female nurses by intervention with either omega-3 PUFA supplementation (1.8 g/day for 90 days) and/or a stress management program and found no significant differences between the PUFA group and control group\textsuperscript{27}. The second RCT by Tayama \textit{et al.} examined 90 workers with mild to moderate depression who were assigned to receive either cognitive behavioral group therapy with omega-3 PUFA supplementation (1.8 g/day for 12 weeks) or cognitive behavioral group therapy only\textsuperscript{20}. They found no significant differences between the groups. The third RCT was conducted in collaboration with Nishi’s group and China Medical University, Taiwan. The study examined 108 pregnant women in Japan and Taiwan, and again no significant effect of omega-3 PUFA supplementation was confirmed\textsuperscript{21}. This is in clear contrast to the beneficial effect of omega-3 PUFAs found for depression during pregnancy in a similar RCT that was conducted by the same Taiwanese group 10 years earlier\textsuperscript{20}. The major difference between the 2 trials was the daily dose of omega-3 PUFAs (1.8 g/day in the former\textsuperscript{20} vs. 3.4 g\textsuperscript{26}), suggesting that a higher dose may be necessary for pregnant women.

4 Mechanism of action and recommended dose

It has been suggested that serotonin and dopamine in the brain are likely involved in the mechanism of action of omega-3 PUFAs. In an animal study, a diet deficient in omega-3 PUFAs increased 5-HT\textsubscript{2} receptor density but decreased dopamine D\textsubscript{2} receptor density\textsuperscript{25}. Also, in a human study, a positive correlation was found between plasma DHA level and serotonin metabolites in cerebrospinal fluid\textsuperscript{35}. Taken together, these findings indicate that omega-3 PUFAs likely affect serotonin metabolism, thereby ameliorating depressive symptoms.

The possible involvement of brain-derived neurotrophic factor (BDNF) has also been suggested. Blood BDNF level was low in patients with mood disorder and was negatively correlated with severity of the condition\textsuperscript{35}. However, increases in brain BDNF level due to omega-3 PUFAs have been demonstrated in an animal study\textsuperscript{36} and an interventional study in humans\textsuperscript{27}. Other likely mechanisms include the regulation of corticotropin-releasing hormone, inhibition of protein kinase C, modulation of heart rate variability, enhancement of dendritic branching and synapse formation, suppression of neuronal apoptosis, and improvement of cerebral blood flow\textsuperscript{38}.

In 2006, the Omega-3 Fatty Acids Subcommittee of the American Psychiatric Association modified the recommendations proposed by the American Heart Association as follows: (1) all adults should eat fish ≥ 2 times per week; (2) patients with mood, impulse-control, or psychosis disorders should consume 1 g EPA + DHA per day; and (3) a supplement may be useful in patients with mood disorder (1-9 g per day). Use of >3 g per day should be monitored by a physician\textsuperscript{39}. There are no guidelines in this field in Japan, but the Dietary Reference Intakes for Japanese (2015 version) show the recommended total consumption of omega-3 fatty acids (α-linolenic acid, EPA, DHA, and other omega-3 PUFAs) by age and sex. These are, for example, 2.1 g or 1.6 g daily consumption for men and women aged 30-49 years, respectively, and 2.4 g or 2.0 g daily consumption for men and women aged 50-69 years\textsuperscript{32}. This then raised the question of a possible optimal EPA:DHA ratio. EPA appeared to be more effective for depression based on the meta-analysis results\textsuperscript{40}. McNamara recommended an optimal EPA:DHA ratio of 2:1\textsuperscript{41}, which has been used in the RCTs conducted in Japan\textsuperscript{20–22}.

5 Closing remarks

Fish consumption is steadily declining in Japan, even while epidemiological studies show the likely association of fish (i.e., omega-3 PUFA) consumption with amelioration of depressive symptoms. Although it is only a matter of speculation, the association of n-3 PUFA and/or fish intake with depression might not have been this large in decades past when the consumption of fish was still high. Along with this decline in fish consumption, the association might be much stronger in the near future. Furthermore, this effect has not yet been confirmed by interventional studies in Japan because the number of such studies is too small to reach a definitive conclusion. Nevertheless, no serious adverse events have been reported in any studies, and with such a good safety record, omega-3 PUFAs should be readily administered to pregnant women and children. Furthermore, if nutritional intervention can ameliorate depression even slightly, it will be of great significance in health economics. Large-scale cohort studies and clinical trials in this field are anticipated in Japan in the future.

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