Fish Consumption: A Review of Its Effects on Metabolic and Hormonal Health

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ABSTRACT: Dietary habits are a major determinant of the risk of chronic disease, particularly metabolic and endocrine disorders. Fish as a food group are a unique source of nutrients with metabolic and hormonal importance including omega-3 fatty acids, iodine, selenium, vitamin D, taurine and carnitine. Fish are also a source of high quality protein and have in general low caloric density. The impact of these nutrients on cardiovascular risk has been extensively reviewed, but the impact of fish on the broader field of endocrine and metabolic health is sometimes not sufficiently appreciated. This article aimed to summarize the impact the effect of regular fish consumption on conditions like the metabolic syndrome, obesity, diabetes, hypothyroidism, polycystic ovary syndrome and the menopausal transition, which are in and of themselves significant causes of morbidity and mortality worldwide. The review revealed that scientific evidence from food science, translational research, epidemiologic studies and interventional trials shows that regular fish consumption has a positive impact on thyroid homeostasis, facilitates maintenance of a healthy body weight, reduces the magnitude of age-associated increases in blood pressure, improves glucose homeostasis helping prevent diabetes and the metabolic syndrome, and has a positive impact on muscle mass preservation among the elderly. These effects are mediated by multiple mechanisms, only some of which have been identified. For most of these effects it holds true that the potential benefits are more substantial when baseline fish consumption is low.

KEYWORDS: Fish, seafood, hormones, endocrine, metabolic syndrome

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Introduction

Hormonal and metabolic alterations are extremely frequent, carry a large morbidity and mortality burden and are profoundly influenced by diet quality.[1] One of the foods with a large potential for positive impact on hormonal and metabolic homeostasis, and usually recommended as part of a balanced healthy diet in most dietary guidelines is fish, but several factors have combined to make fish consumption relatively limited. In 2008, the world production of fish reached 140 million tons (115 for human consumption), for an average per capita consumption of 17 kg/person/year.[2] In Latin America as a whole, food consumption is remarkably low, compared to the rest of the world.[3] In Colombia, for example, fish consumption per capita only increased from 3.69 to 7.16 kg/person/year between the years 1980 and 2017.[3] As a reflection of this, fish represents only about 6% of all dietary protein worldwide,[4] despite being rich in high-quality protein. Fish was traditionally consumed in locations close to the sea or mayor water bodies, but recent advances in the processing, distribution, transport and storage have made it a safe, accessible and economic protein source for most people.[2] Even now, however, mistaken perceptions about the cost, accessibility or safety of fish consumption limit its consumption by many populations.

Some fish are richer in fat and other are higher in protein, in general fatty fish are sources of lipids with demonstrated positive effects on health, and lean fish contribute protein of high biological value.[5] However, the information available to the public on the health effects of fish consumption is insufficient, does not usually differentiate among fish types, and may be influenced by the media outlet where it is presented.[6]

Within this context, there is still uncertainty about the metabolic effects of usual fish consumption. Synthesizing and clarifying the existing evidence in this regard may serve to guide public health and food policy, and provide the public with up-to-date information in this regard.

The research question for this narrative review was: "¿What is the effect of the regular consumption of fish, or its nutritional constituents, on the risk of developing metabolic or endocrine disturbances in humans?." A bibliographic search was performed in PubMed and EMBASE for studies examining the association between the intake of fish or fish nutrients as exposure and various endocrine or metabolic conditions as outcomes, including metabolic syndrome, obesity, diabetes, hypothyroidism, polycystic ovary syndrome and menopause. The search terms included, in addition to the above-mentioned terms, "fish," "seafood," "omega 3," "fish oil," "intake," "consumption," and "dietary." The search was updated last time on October 30, 2020. Abstracts were reviewed in order to eliminate studies unrelated to the research question and duplicate studies. Then, the full text of articles was evaluated in order to assess their eligibility and 53 original studies were included in the review. Abstracts from scientific meetings, letters to the editor or prior reviews were not included, but the reference lists of the latter were reviewed in detail for other potentially eligible articles.

Nutrients of Endocrine and Metabolic Importance Present in Fish

Iodine

Iodine is the main constituent of tetraiodothyronine or thyroid hormone (65% of its molecular weight), and without it there is no possible thyroid hormone synthesis. Iodine is very scarce in the diet, for this reason iodine fortification of table salt is a mandatory public health measure in many countries. The iodine content of fish shows considerable variation, but in a Portuguese study in which iodine was directly measured in several specimens the results were the following (in mcg iodine/100 g of fish): 19 for canned tuna, 16.7 for fresh tuna, 10.5 for salmon, 40.5 for mackerel, 26 for sardines, and 56 for cod.[7] The Recommended Dietary Allowance (RDA) for iodine is 90 to 120 mcg for children, 150 mcg for the general adult population, 220 mcg for pregnant women, and 290 mcg for breastfeeding women.[8] Thus, assuming a portion size of 4 ounces (110 g), fish consumption may be a relevant contributor toward reaching the iodine RDA in many individuals.

Selenium

Selenium is another scant mineral in the diet, one that has an essential role in thyroid hormone *action*. After being synthesized in the thyroid gland and secreted into circulation, thyroid hormone (tetraiodothyronine-T4) reaches the target tissues and is deiodinated to T3, allowing it to bind its nuclear receptor with high affinity and elicit a plethora effects on cellular metabolism and energy production. This deiodination step is accomplished by a group of enzymes collectively named deiodinases, all of which contain the aminoacid selenocysteine and hence depend on sufficient selenium availability for their action.[9] The RDA for selenium is 20 to 40 mcg/day for children and 55 mcg/day for adults.[9] After Brazil nuts, fish are the food with the highest selenium content, ranging between 30 and 130 mcg/100 g depending on the fish species.[10] In consequence, a single serving of fish may provide an amount of selenium close to or above the RDA for large segments of the population.

Vitamin D

Vitamin D may be considered a steroid hormone, one required to guarantee the appropriate absorption of dietary calcium and phosphate, therefore it plays an essential role in the homeostasis of the musculoskeletal system. Besides its well-known role on the preservation of bone integrity, vitamin D could potentially have a function in metabolic, and immune physiology.[11] The RDA for vitamin D is 600 IU/day for individuals below 70 years of age and 800 IU/day for those older than 70.[12] Fish have a substantial content of vitamin D, with ample variations depending on the specific fish. For most species, vitamin D content fluctuates between 400 and 800 IU/100 g, but in trout and tilapia it may reach up to 1200 IU/100 g.[13] A recent systematic review of studies assessing the association between dietary intake of fish and bone health outcomes concluded that most of the body of evidence (at least 12 independent studies) found a negative association between a fish-rich dietary pattern and reduced risk of developing osteoporosis or clinical fractures, as compared to a dietary pattern in which beef was the main protein source.[14]

Table 1. Approximate content of total omega-3 fatty acids in several commonly consumed fish (mg/100 g). Constructed using data from Mozaffarian et al.[16] and Young.[17]

FISH	OMEGA-3 FATTY ACIDS (MG EPA + DHA/100 G)
Albacore tuna	862
Skipjack tuna	270
Tilapia	163
Trout	935
Farmed salmon	2648
Wild salmon	1043
Sardines	982
Snapper	321
Catfish	177
Cod	158
Tilefish	905
Halibut	465
Herring	2000
Mackerel	1200
Mahi-mahi	139
Pollock	468

Omega-3 fatty acids

Omega-3 (also called n-3) fatty acids are a type of lipid very unusual among terrestrial organisms, but quite abundant among marine animals. Omega-3 fatty acids are considered essential nutrients, as the human body is unable to produce them in order to fulfill physiological requirements. Part of their essential character derives from the fact that the areas of the cell membrane where hormonal receptors are more frequently located, tend to be richer in omega 3 fats.[15] Thus, hormonal action at the cellular level requires an adequate omega-3 content in cell membranes, particularly for hormones with membrane receptors. The main omega-3 fatty acids present in fish are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The approximate total content of omega-3 fatty acids in several commonly consumed fish are shown in Table 1.

Table 2. Taurine content of several dietary sources of animal protein. Constructed using data from Wójcik et al.[25] and Laidlaw et al.[26]

FOOD	TAURINE (MG/100 G)
Mussels	827
Clams	520
Oysters	396
Squid	356
Canned tuna	176
White fish	151
Pork	61
Ham	50
Beef	43
Shrimp	39
Light turkey meat	30
Light chicken meat	18
Dark chicken meat	15
Dark turkey meat	11

Taurine

Taurine is an unusual organic compound found especially in the muscle and bile of animals. An average human body contains approximately 70 g of taurine, most of which is provided by the diet.[18] Functions of taurine in the human organism include stabilization of the cell membrane and prevention of cardiac arrhythmias, regulation of platelet function, reduction of blood pressure and modulation of neuronal activity.[18] There are large inter-individual variations in the dietary intake of taurine, as large as between 10 and 700 mg/day.[19,20] Plasma taurine concentrations are usually low among individuals with diabetes, due to faster renal elimination and reduced intestinal absorption.[21] Several intervention studies in animal models and human patients with diabetes have documented reductions in glycemic levels with taurine supplementation,[21] apparently through a reduction of insulin resistance and slight improvements in beta cell function.[22] Accordingly, cross-sectional population studies have found that a higher urinary taurine excretion (indicating greater dietary intake) is associated with a smaller number of cardiovascular risk factors.[23] Fish is one of the foods with highest taurine content, as an example the taurine content is 176 mg/100 g for tuna and 60 to 94 mg/100 g for salmon.[24] In fact, when compared to other major protein sources, fish and seafood are the food group with the highest nutritional contribution of taurine (Table 2).

Fish Consumption and the Metabolic Syndrome

The metabolic syndrome is a group of commonly found alterations that are related to a defective response to the hormone insulin, or *insulin resistance*. Excessive body adiposity, especially abdominal obesity, is a determinant risk factor for the appearance of insulin resistance and the metabolic syndrome. Besides abdominal obesity, the clinical features of the metabolic syndrome include hyperglycemia, high blood pressure, hypertriglyceridemia, low plasma HDL cholesterol (HDLc) and high plasma uric acid. Having metabolic syndrome increases the risk of ischemic heart disease, stroke, and diabetes (including diabetic nephropathy, retinopathy, and neuropathy).[27]

Several studies have explored the influence of fish consumption on the risk of developing metabolic syndrome. One of the most important interventional studies in this regard is the SEAFOODPlus study,[28] in which 126 overweight individuals aged 20 to 40 were randomized to receive a diet with 30% caloric restriction with or without 150 g/day of fish (cod), 5 times a week, for 8 weeks. Participants who received fish as part of their dietary regime lost an extra 1.7 kg body weight compared to the control group in addition to a 3.4 cm reduction in waist circumference and a 5.2 mmHg reduction in systolic blood pressure. Another relevant study is the Spanish WISH-CARE trial, in which 273 patients with metabolic syndrome were randomly assigned to receive during 8 weeks 100 g/day of white fish (Namibia hake) plus dietary counseling, or the same counseling program without the addition of fish, in a crossover design. The fish group intervention was accompanied by larger declines in waist circumference, diastolic blood pressure, and LDL cholesterol.[29]

Several observational studies have documented similar findings. A cohort study of more than 3500 adults in South Korea found that an average daily fish consumption between 40 and 70 g/day was associated with a 57% reduction in the risk of developing metabolic syndrome, albeit only among men.[30] A study with a similar design undertaken in the United States and with a very prolonged follow-up (25 years), found that individuals who consumed fish at least 5 times a week had half the risk of metabolic syndrome compared to non-consumers.[31] The protective effect was most pronounced for participants who consumed fish in preparations other than fried. Even in countries whose population has a high baseline fish intake like Norway, every extra serving of fish was associated with a significant reduction in the risk of metabolic syndrome, especially among older adults.[32] In this same Norwegian cohort, frequent intake of lean fish was associated with smaller increments in waist circumference over time among men, while frequent intake of fatty fish was associated with reductions in plasma triglycerides and increases in protective HDL cholesterol among women.[33] A dietary survey in Finland found that the risk of metabolic syndrome was 40% lower for men who consumed at least 60 g of fish a day.[34] Outside the Scandinavian countries, a cohort study in France documented a reduction in the risk of metabolic syndrome of 39% for frequent fish consumers, in this case being significant for both sexes.[35] These findings have also been consistent in populations with a low baseline fish intake. In a study in Iran (mean fish intake 14 g/day), the negative association of fish consumption with the metabolic syndrome was even stronger: Being in the highest tertile of fish intake was associated with 65% lower prevalence of metabolic syndrome, even after statistical adjustment for multiple potential confounders.[36]

It is important to consider that most foods are not consumed in an isolated manner, but as part of a dietary pattern. Taking this into account, a very large study that pooled 3 cohorts from the United States examined how the intake of determined foods within a dietary pattern was associated with long-term changes in body weight.[37] Only 3 sources of animal protein were associated with long-term weight loss: fish, skinless chicken, and lean cheese.

Another aspect of the metabolic syndrome whose association with fish has been explored is hypertension. Blood pressure, especially systolic blood pressure, tends to increase with age, due to progressive loss of elasticity of the arterial wall associated with vascular aging. In a study of older adults (age 65-100) from several Mediterranean islands, ingestion of at least 300 g of fish per week was associated with significantly lower blood pressure.[38]

Among the many potential explanations for the observed influence of fish consumption on insulin resistance and the metabolic syndrome, one that has been explored in detail is its impact on appetite and satiety. In a classic proof-of-concept study, postprandial satiety, blood aminoacids, insulin and glucose were measured in healthy volunteers after the ingestion of the same amount of protein from a different source (beef, chicken or fish).[39] Postprandial satiety was highest after the ingestion of fish. The mechanisms responsible for this observation may involve larger increases in plasma concentrations of the aminoacid tryptophan (precursor of the neurotransmitter serotonin, which contributes to satiety), and a more prolonged digestion, as blood aminoacids took a longer time to reach a peak after the fish meal relative to the other protein sources. Not only is postprandial satiety higher, but also plasma glucose excursions are lower after a meal containing fish (tuna), compared to meals containing egg or turkey as their main protein source.[40]

Another plausible explanation of the effect of dietary fish on the metabolic syndrome is a direct effect on insulin resistance. One key study employed the gold standard technique (the hyperinsulinemic – euglycemic clamp) to measure insulin action in 19 overweight/obese individuals before and after 4 weeks of consuming a diet with identical amounts of Calories, carbohydrates, lipids and proteins, but in which the main protein source was fish *versus* other sources.[41] The fish protein diet induced a statistically significant 29% reduction in insulin resistance. The effect of fish on insulin resistance might be mediated by the anti-inflammatory effects of their omega-3 fatty acids. A recent meta-analysis of studies in patients with HIV showed that omega-3 fatty acid supplementation causes significant reductions in C-Reactive Protein (CRP), tumor necrosis factor-alpha (TNF-alpha) and interleukin 6 (IL-6).[42] Supplementation with omega-3 fatty acids also improves the antioxidant capacity of serum and glutathione peroxidase activity,[43] potential mechanisms for improved insulin sensitivity.

Fish Consumption and Sarcopenia

It is frequent to encounter that older individuals present a lower muscle mass, increased risk of falls and other serious accidents, a phenomenon known as sarcopenia. Sarcopenia is characterized by a progressive, generalized loss of muscle mass, muscle strength, and physical performance.[44] Sarcopenia happens more frequently with aging in both sexes, bringing with it physical disability, deteriorated quality of life, and increased mortality.[45] One of the features of muscular aging is a reduced capacity to respond to anabolic stimuli like dietary protein, exercise, or plasma concentrations of insulin-like growth factor-1 (IGF-1). On top of that, aging is accompanied by reduced secretion of testosterone among men, a deficiency that further prevents preservation of a normal muscle mass.[45]

Large studies from the USA, Europe, and Japan[46] have documented a worrisome prevalence of sarcopenia, with a projected increase of up to 70% over the next 2 decades.[47] There is also evidence from the developing world showing the high prevalence and relevance of sarcopenia. A meta-analysis of 31 studies performed in Brazil[48] found a 17% prevalence among adults older than 60, reaching 20% among females. Similarly, the Colombian study of Health, Aging, and Well-being (SABE – *Salud, Bienestar y Envejecimiento*), which included over 2000 older individuals, found a sarcopenia prevalence of 11.5%, being significantly higher among women and current smokers.[49] These studies highlight the importance of actively screening and diagnosing sarcopenia, and of providing interventions to ameliorate or mitigate its impact on patients.

Besides the normal aging process, a phenomenon that frequently accelerates and worsens sarcopenia is the insufficient protein intake of older adults with normal renal function. The minimal protein intake has been estimated at 1.2 g/kg body weight/day for healthy individuals, 1.5 g/kg/day for persons with chronic conditions that increase protein catabolism and 2.0 g/kg/day for persons under acute stress like severe infection, trauma or major surgery.[50] Fish is an excellent source of dietary protein with high biological value (abundance of essential aminoacids). The protein content of fish ranges between 16 and 28 g of per 100 g, and its biological value is higher than that of plant protein or even beef,[51] being slightly inferior only to milk and egg protein. Fish is particularly rich in the essential aminoacid lysine,[51] which is very scarce in cereals. This observation is particularly relevant in developing countries, where cereals constitute the basis for the nutrition of most of the population.

In addition, fish is rich in carnitine, an aminoacid derivative that plays a pivotal role in the intracellular transport of fatty acids to the mitochondrial matrix for their oxidation. This process is particularly active in muscle cells; hence carnitine is necessary for the use of energy stored as fat by the muscle. The desirable intake of carnitine for an omnivore like the human is between 50 and 300 mg/day,[52] and fish can provide 10 to 20 mg of carnitine in a 100-g serving.[53] A third nutrient with pertinence for muscle health is magnesium, a mineral required for the hydrolysis of ATP and the release of its chemical energy to propel muscle contraction. Several epidemiologic studies have documented an association between magnesium intake and muscle function. In a cohort of more than 2500 adult English women, dietary magnesium intake was positively associated with both general muscle strength and explosive strength of the legs, a measure of preserved muscle function.[54] The same research group performed a prospective study of 156 000 adults of both sexes, in which dietary magnesium correlated positively with handgrip strength and total body muscle mass.[55] A single 4-ounce serving of fish provides about 20% of the total recommended dietary intake of magnesium.[56]

One last nutrient with potential to preserve or improve muscle mass and functionality is fish-derived omega-3 fatty acids. A recent intervention trial evaluated the effect of supplementing the diet of 60 older adults with 4 g/day of omega-3 fatty acids or a control intervention (corn oil) over a 6-month follow-up period.[57] In the fish oil group, there was a 3.6% increase in muscle circumference, a 2.3 kg increase in handgrip strength and a 4.0% increase in the maximal number of isometric exercise repetitions. Similar results have been reported with omega-3 supplementation of the diet in postmenopausal women for 90 days, in this case the intervention improved performance in a chair-rising test, reflecting improved muscle functionality.[58] At the molecular level, proof-of-concept translational studies in humans have demonstrated that omega-3 fatty acids increase the uptake of circulating aminoacids by muscle tissue, as well as their incorporation into newly synthesized muscle proteins.[59]

Conclusions

Hormonal and metabolic diseases are highly prevalent and constitute a major source of disease and death worldwide. This group of conditions are highly susceptible of positive modifications through changes in dietary habits. Fish are a food source of several nutrients of central importance to hormonal and metabolic function, among them iodine, selenium, vitamin D, omega-3 fatty acids, taurine, and carnitine. Fish are also an outstanding source of high biological value protein, with a relatively low caloric density. Relative to other animal protein sources, fish provides high satiety, helps control appetite, and produces smaller glycemic excursions after a meal. These properties have been reflected by a negative association between fish consumption and components of the metabolic syndrome in observational studies, and by significant improvements in interventional trials. A recent focus of research has been the effect of fish consumption or supplementation with fish oil on age-associated sarcopenia and frailty. The evidence pointing to a positive effect in this aspect seems promising but further research on larger samples and over longer follow-up periods is warranted. Lastly, studies in countries with a low baseline ingestion of fish suggest that the health benefits from its consumption may be larger in such populations.

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