Nutrients in Fish and Possible Associations with Cardiovascular Disease Risk Factors in Metabolic Syndrome

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Abstract: Non-communicable diseases (NSDs) are responsible for two-thirds of all deaths globally, whereas cardiovascular disease (CVD) alone counts for nearly half of them. To reduce the impact of CVD, targeting modifiable risk factors comprised in metabolic syndrome (e.g., waist circumference, lipid profile, blood pressure, and blood glucose) is of great importance. Beneficial effects of fish consumption on CVD has been revealed over the past decades, and some studies suggest that fish consumption may have a protective role in preventing metabolic syndrome. Fish contains a variety of nutrients that may contribute to health benefits. This review examines current recommendations for fish intake as a source of various nutrients (proteins, n-3 fatty acids, vitamin D, iodine, selenium, and taurine), and their effects on metabolic syndrome and the CVD risk factors. Fatty fish is recommended due to its high levels of n-3 fatty acids, however lean fish also contains nutrients that may be beneficial in the prevention of CVD.

Keywords: fish consumption; lean fish; fatty fish; metabolic syndrome; cardiovascular risk; cardiovascular disease; diet; protein; amino acids; nutrients

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death worldwide [1], being responsible for more than 40% of the deaths from non-communicable diseases (NCDs) [2]. CVD includes coronary heart diseases (CHD), such as angina and heart attack, cerebrovascular disease (stroke) and peripheral arterial diseases. The underlying disease process of CVD is atherosclerosis, a complex pathological process in the walls of blood vessels.

Several risk factors promote the process of atherosclerosis, and both behavioral (e.g., tobacco, physical activity, diet, and alcohol) and metabolic risk factors (e.g., obesity, raised blood lipids, blood pressure, and blood sugar) play a key role in its etiology [1]. Some of these metabolic risk factors were described by Kylin as early as in the 1920s, as the clustering of hypertension, hyperglycemia, and gout [3]. Today, these metabolic risk factors are known as metabolic syndrome (MetS), and a clinical definition was agreed upon through a Joint Interim Statement (JIS) in 2009, after several attempts to unify the criteria for MetS [4]. In the JIS definition, a presence of any three of the five given risk factors (abdominal obesity, elevated triglyceride (TG), reduced high-density lipoprotein cholesterol (HDL-C), elevated blood pressure (BP), and elevated fasting glucose) constitutes a diagnosis of MetS [4] (Table 1).

Abdominal obesity appears to precede the appearance of the other MetS components [5], where an expansion of adipose tissue due to adipocyte hypertrophy leads to an inflammatory response in the fat tissue due to the infiltration of macrophages and other immune cells that release pro-inflammatory...
cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) \[3,6\]. TNF-α influence the immune system by increasing the permeability and adhesiveness of the blood vessels, while IL-6 stimulates hepatocytes to synthesize C-reactive protein (CRP) \[7\], which is a systemic inflammation marker.

Fish is recommended as a part of a healthy diet \[8\] and it is considered to be a key component of a cardio-protective diet \[9\]. Furthermore, fish is an important source of various nutrients, such as protein, \textit{n}-3 fatty acids, vitamin D, iodine, and selenium \[10\], which may contribute to a healthier metabolic profile \[11,12\].

**Table 1.** Criteria for diagnosing the metabolic syndrome (MetS) \[4\].

| Measure              | Cut Points               |
|----------------------|--------------------------|
| Waist circumference  | Men: ≥94 cm
|                      | Women: ≥80 cm            |
| serum-HDL cholesterol| Men: <1.0 mmol/L (40 mg/dL)
|                      | Women: <1.3 mmol/L (50 mg/dL) |
| serum-triglyceride   | >1.7 mmol/L (150 mg/dL)  |
| Systolic blood pressure | ≥130 mm Hg               |
| Diastolic blood pressure | ≥85 mm Hg                |
| Fasting serum-glucose | ≥5.6 mmol/L (100 mg/dL)   |

* Population- and country-specific definitions: Caucasian, Middle East, Mediterranean, Sub-Saharan African, Ethnic Central and South American. HDL: High-density lipoprotein cholesterol.

A recent meta-analysis from Iran found an inverse association between fish consumption and risk of all-cause and total cardiovascular mortality \[13\]. However, regional differences were revealed for this association, whereas higher fish intake was associated with higher risk of all-cause and cardiovascular mortality in Western countries, but not in Asians \[13\]. These findings may suggest that types of fish/species consumed, methods of fish preparation, and potential local contaminants should be considered in addition to other possible confounders, such as regular food items consumed together with the fish.

Consumption of fatty fish has been suggested to reduce the risk of CVD, which is mainly due to its high level of \textit{n}-3 fatty acids \[14\]. Beneficial effects of fish consumption (in general) on CVD have been revealed over the past decades \[14–16\], and several studies have suggested an inverse relationship between fish consumption and heart failure \[17\], cerebrovascular disease \[18\], coronary calcification \[19\], ischemic stroke \[20\], and sudden coronary death risk \[21\]. Other studies suggest that fish consumption prevent, or improve metabolic health and thus has a role in MetS prevention \[22\].

Targeting the modifiable risk factors of MetS is of great importance for public health. This review aims to examine current recommendations for fish intake as a source of various nutrients (proteins, \textit{n}-3 fatty acids, vitamin D, iodine, selenium, and taurine) and their possible effects on MetS and the CVD risk factors. To explore how fish intake affects CVD risk, we systematically reviewed prospective and intervention studies investigating the effects of fish consumption on the CVD risk factors of the MetS.

2. Method

Literature search was performed in PubMed to identify studies examining the associations between fish consumption and the possible effects on MetS and the CVD risk factors of the MetS. Combined search terms were: (1) fish consumption and metabolic syndrome; (2) fish consumption and each of the individual risk factors comprising MetS (e.g., waist circumference, lipid profile, blood pressure, and glucose); and (3) fish consumption and cardiovascular risk.

The search was restricted to papers that are written in English, and animal studies were excluded. The selection process is illustrated via a flow diagram (Figure 1). All intervention, prospective cohort, and cross-sectional studies (conducted among adults) investigating the association between fish consumption and MetS were included, however, only intervention and prospective cohort
studies investigating the effect of fish consumption on the CVD risk factors were included. Potential abstracts and full-text articles were screened and assessed for eligibility, and the included studies are presented (Tables 2–4). Abstracts, letters, or reviews were not included, but they were inspected for additional references that met the inclusion criteria. In addition, the reference lists of the included studies and relevant published reviews were examined to identify additional papers for possible inclusion. The review procedure was performed in accordance with the PRISMA statement for review reporting [23], and a protocol of the study selection was made. The last search was done on 8 December 2017.

### Figure 1. Flow diagram of the review process.

#### Table of Results

| Identification          | No of records identified through database search | n = 285 |
|-------------------------|-----------------------------------------------|---------|
|                         | No of records excluded                         | n = 194 |
| Screening               | No of abstracts screened                       | n = 91  |
|                         | No of abstracts excluded                       | n = 44  |
| Eligibility             | No of full text articles assessed for eligibility | n = 47  |
|                         | No of full text articles excluded              | n = 41  |
|                         | Main reasons for exclusion:                   |         |
|                         | - Duplicates                                  |         |
|                         | - Animal studies                              |         |
|                         | - Missing data                                |         |
|                         | - Missing criteria                            |         |
| Inclusion               | No of studies included                        | n = 21  |

3. Results

The literature search identified 285 citations, of which 108 were found in the first search (fish consumption and metabolic syndrome). In the second search (fish consumption and the individual risk factors comprised MetS), 120 studies were identified (e.g., waist circumference: 6, lipid profile: 28, blood pressure: 46, and glucose: 40). In the third search (fish consumption and cardiovascular risk), 57 studies were included (Table 3) and 15 studies (intervention and follow-up) examining the associations between fish consumption and the CVD risk factors comprised MetS were included (Tables 3 and 4).

3.1. Fish Consumption and Metabolic Syndrome

The included studies are one intervention study, two follow-up studies, and eight cross-sectional studies. The intervention study [24] (8-weeks, energy restricted (−30%): 150 g cod 3 times/week, 150 g cod 5 times/week, or no seafood) found no association between fish consumption and MetS, while...
an inverse association between fish consumption and MetS was identified in both of the follow-up studies [25,26]. In these two observational studies, the participants did not have MetS at the beginning of the study. Regarding the cross-sectional studies, six out of eight studies found an association between fish consumption and MetS [27–32]. However, for two of these [30,31], the association was found only for lean fish and men (Table 2). Few studies have investigated the possible differences between lean and fatty fish consumption and MetS. A recent meta-analysis found a significant inverse association between total fish consumption and the risk of MetS when pooling data from prospective cohort studies, however, no significant association was found after pooling the cross-sectional studies [33].

**Table 2. Studies on fish consumption and metabolic syndrome (MetS).**

| Reference               | Design                  | Results                                                                 |
|-------------------------|-------------------------|-------------------------------------------------------------------------|
| Ramel et al., 2009 [24] | RCT                     | No association (8-week intervention, energy restricted * (−30%): 150 g cod 3 times/week, 5 times/week, or no seafood as control) |
| Baik et al., 2010 [25]  | 3-years follow-up       | Men: Reduced risk of MetS with average daily fish consumption (40–70 g), when compared with less than once a week, OR 0.43 (95% CI 0.23 to 0.83). Women: No associations |
| Kim et al., 2016 [26]   | 25-years follow-up      | Men and women: Non-fried fish consumption inversely associated with incidence of MetS, age adjusted HR 0.51 (95% CI 0.40 to 0.64) from the highest quintile (≥5 week) |
| Karlsson et al., 2017 [27] | Cross-sectional     | Men and women: Total fish intake was inversely associated with MetS, adjusted OR 0.75 (95% CI 0.57 to 0.97). |
| Kouki et al., 2011 [28] | Cross-sectional        | Men: Fish consumption (10 g/day) associated with reduced risk of having MetS, OR 0.97 (95% CI 0.94 to 1.00) Women: No associations |
| Lai et al., 2013 [34]   | Cross-sectional        | No association                                                          |
| Pasalic et al, 2011 [35]| Cross-sectional        | No association                                                          |
| Ruidavets et al, 2007 [29]| Cross-sectional   | No association                                                          |
| Tørris et al., 2016 [31]| Cross-sectional        | Men and women: Fish consumption was associated with lower risk of MetS in the age group 60–70 years (OR 0.64, 95% CI 0.45 to 0.91), compared to the younger age groups. However, only lean fish consumption was associated with a reduced risk of having MetS, no association for fatty fish consumption. |
| Tørris et al, 2016 [30] | Cross-sectional        | Men and women: Fish consumption once a week or more was associated with lower risk of MetS, OR 0.83 (95% CI 0.74 to 0.93), compared to fish consumption less than once a week. Only lean fish was associated with lower risk of having metabolic syndrome, no association for fatty fish consumption. |
| Zaribaf et al., 2014 [32]| Cross-sectional       | Women in the highest tertile of fish consumption were less likely to have MetS, compared to those in the lowest tertile, OR 0.35 (95% CI 0.14 to 0.88). |

* −30% from calculated total energy expenditure, approximately 600 kcal/day. MetS: Metabolic syndrome.

### 3.2. Fish Consumption and the CVD Risk Factors of Metabolic Syndrome

The included studies comprised in 13 intervention studies (Table 3), and two follow-up studies (observational) (Table 4). All studies identified associations between fish consumption and CVD risk factors of MetS, however, none of the studies found association between fish consumption and blood glucose.
Table 3. Intervention studies on fish consumption and the metabolic syndrome risk factors.

| Reference/Country | Participants | Intervention | Results |
|-------------------|--------------|--------------|---------|
| Aadland et al., 2015 [36] Norway | 20 healthy adults (7 men, 13 women) | 4-week, crossover: 1: 60% of proteins lean-seafood 2: No seafood (lean meat and 3.3 g cod liver oil) | Lean fish reduced TG Change $-0.17 \pm 0.06 \text{ mmol/L}$ HDL no association |
| Bao et al., 1998 [37] Australia | 69 overweight nonsmoking men and postmenopausal women, using hypertensive | 16-week, parallel: 1: Fatty fish (3.65 g n-3 FA) & energy restricted ($-2\text{MJ/d}$) 2: Energy restricted ($-2\text{MJ/d}$) 3: Fatty fish (3.65 g n-3 FA) 4: Control | Fatty fish reduced BP SBP $-6.0 \pm 1.4 \text{ mm Hg}$ DBP $-3.0 \pm 1.4 \text{ mm Hg}$ |
| Erkkila et al., 2008 [38] Finland | 33 adults (27 men, 6 women) with coronary heart disease | 8-week, parallel: 1: Fatty fish (4 meals/week) 2: Lean fish (4 meals/week) 3: Control (lean meat) | Lean fish reduced BP SBP $-3.5 \pm 3.2 \text{ mm Hg}$ DBP $-4.6 \pm 3.6 \text{ mm Hg}$ |
| Hagen et al. 2016 [39] Norway | 38 healthy adults | 4-week, parallel 1: Fatty fish (750 g/w) 2: Lean fish (750 g/w) 3: Control (lean meat) | High intake of fatty fish, but not lean fish reduced TG and increased HDL |
| Hallund et al., 2010 [40] Denmark | 68 healthy men | 8-week, parallel: 1: Trout (marine diet) 2: Trout (vegetable diet) 3: Control (chicken) | No association (BP, TG, HDL, glucose) |
| Lara et al., 2007 [41] UK | 48 healthy adults (16 men) | 4 week: Salmon (4-weeks) followed by no-fish (4-weeks) | Fatty fish decreased TG $-0.13 (-0.24$ to $-0.01)$ Fatty fish increased HDL $0.09 (0.01$ to $0.15)$ Fatty fish decreased BP SBP $-4.6 (-7.1$ to $-2.0) \text{ mm Hg}$ DBP $-2.9 (-5.0,$ $-0.9) \text{ mm Hg}$ |
| Lindquist et al., 2009 [42] Sweden | 35 overweight men | 6-week, cross-over 1: Herring 5 day/week 2: Chicken and pork | Fatty fish decreased TG $-0.35 \text{ mmol/L}$ Fatty fish increased HDL $0.05 \text{ mmol/L}$ BP no association |
| Lindquist et al., 2007 [43] Sweden | 15 healthy obese adults | 4-week, cross-over 1: Herring 5 day/week 2: Chicken and pork | Fatty fish increased HDL $+0.09 \text{ mmol/L}$ TG no association |
| Ramel et al., 2010 [44] Iceland, Spain, Ireland | 324 overweight/obese healthy adults | 8-week, parallel Energy restricted * ($-30\%$): 1: Lean fish (cod) 3 times/week 2: Fatty fish (salmon) 3: $\times 150 \text{ g/week}$3: Fish oil (DHA/EPA) 4: Control (No seafood) | Fatty fish decreased DBP compared with lean fish, no association with control group |
| Ramel et al., 2009 [24] Iceland | 126 overweight/obese healthy adults | 8-week, parallel Energy restricted * ($-30\%$): 1: 150 g cod 3 times/week 2: 150 g cod 5 times/week 3: Control (no seafood) | Lean fish reduced WC Lean fish 5 t/week $-3.4$ Lean fish increased BP SBP: Lean fish 5 t/week $+5 \text{ mmHg}$ DBP: Lean fish 3 t/week $+3 \text{ mmHg}$ TG no association HDL no association |
| Telle-Hansen et al., 2012 [45] Norway | 30 healthy adults (7 men and 23 women) | 15 days, parallel 1: 150 g cod daily 2: 150 g salmon daily 3: Control (150 g potato daily) | Lean fish decreased TG $-0.1 (p < 0.05)$ HDL no association Fatty fish decreased TG $-0.2 (p < 0.05)$ Fatty fish increased HDL $+0.1 (p < 0.05)$ |
| Thorsdottir et al., 2007 [46] Iceland, Spain, Ireland | 324 overweight/obese healthy adults (138 men and 186 women) | 8-week, parallel: Energy restricted * ($-30\%$): 1: Lean fish (cod) $3 \times 150 \text{ g/week}$ 2: Fatty fish (salmon) 3: $\times 150 \text{ g/week}$3: Fish oil (DHA/EPA) 4: Control (no seafood) | Lean fish reduced WC Lean fish reduced WC Lean fish $-5.0 (2.9)$ (p $< 0.05$) Fatty fish $-5.4 (3.3)$ (p $< 0.05$) Fish oil $-5.1 (3.1)$ Control $4.0 (2.4)$ |
Table 3. Cont.

| Reference/Country       | Participants                          | Intervention                      | Results                                                                 |
|-------------------------|---------------------------------------|------------------------------------|-------------------------------------------------------------------------|
| Vazquez et al., 2014 [47] Spain | 273 patients with metabolic syndrome  | 8-week, cross-over: 100 g/day lean fish (Namibia hake) Control: No fish/seafood | Lean fish reduced WC: treatment effect \( p < 0.001 \) Lean fish reduced DBP: treatment effect \( p = 0.014 \) HDL no association TG no association |

* \( -30\% \) from calculated total energy expenditure, approximately 600 kcal/day. WC: Waist circumference, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, BP: Blood pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid.

Regarding waist circumference (WC), four of the intervention studies identified the associations between fish consumption and reduced WC, whereas three identified associations for lean fish [24,46,47] and one for fatty fish [46]. The greatest decrease in WC was found in overweight and obese adults, where a 3.4 cm reduction relative to the control group was found among those in the lean fish consuming group (cod 5 t/week) [24]. However, all of the participants in this study followed an energy restricted diet (\( -30\% \) from calculated total energy expenditure). Recently, a large Norwegian study (\( n = 23,907 \)), found that lean fish consumption was associated with a 1.15 cm decrease in WC among men, while the consumption of fatty fish was associated with an increased WC for both genders (women: 0.97 cm, men: 0.60 cm [48]. In contrast to this study, a European cohort study found no association between the consumption of lean fish and WC, but identified an annual decrease in WC with a \( -0.01 \) cm per 10 g higher fatty fish consumption daily [49].

Several, but not all, of the intervention studies revealed a decreased TG and an increased HDL associated with consumption of fatty, as well as lean fish. A decreased TG and an increased HDL was also reported in one of the follow-up studies, and here particularly lean fish was associated with a reduced TG and a healthier lipid profile [48].

For most of the studies, fish consumption decreased BP, but this finding was not consistent. In the intervention studies, lean fish consumption was associated with decreased BP both in cardiac patients randomized to lean fish, fatty fish, or lean meat (control) [38], and in patients with MetS randomized to lean fish or no fish/seafood [47]. On the other hand, one study found an increased BP after lean fish consumption [24]. However, fatty fish consumption decreased BP [37,41]. Lean fish consumption was additionally associated with lower BP in one follow-up study [48]. Also, a previous European cross-sectional study among elderly participants (aged 65 to 100 years) found reduced BP among those with a high intake of fish (>300 g/week), however only for SBP [15].

Fish consumption and possible associations with blood glucose have previously been investigated in cross-sectional studies, and both a reduction in fasting blood glucose [15] and a slightly higher non-fasting blood glucose level have been found among those with high fish consumption, as compared to those with a low intake of fish [31]. Still, improved glucose metabolism has been found in obese participants receiving a healthy diet containing fish [50,51].
Table 4. Follow-up studies on fish consumption and the metabolic syndrome risk factors, assessing lean and fatty fish separately.

| Reference/Country | Participants/Follow-Up Time | Results |
|-------------------|-----------------------------|---------|
| Tørris et al., 2017 [48] Norway | Investigating fish consumption (≥1 ×/week compared to <1 ×/week and change in MetS components by consumption of fish during the follow-up period, age adjusted) | Lean fish decreased WC<br>Men −1.15 (−1.96 to −0.35) <br>Fatty fish increased WC<br>Women 0.97 (0.29 to 1.65) <br>Men 0.60 (0.01 to 1.18) <br>Lean fish reduced TG<br>Women −0.04 (−0.08 to 0.00) <br>Men −0.11 (−0.17 to −0.06) <br>Lean fish increased HDL<br>Women 0.03 (0.01 to 0.05) <br>Men 0.04 (0.02 to 0.05) <br>Fatty fish increased HDL<br>Men 0.02 (0.00 to 0.03) <br>Lean fish decreased BP<br>SBP Men −0.86 (−1.66 to −0.06) <br>DBP Men −0.63 (−1.18 to −0.07) |
| Jakobsen et al., 2012 [49] Europe | 1-year change in WC | Fatty fish decreased WC<br>Annual WC change 0.01 cm/10 g higher fatty fish consumption per d (95% CI 0.02 to 0.01) <br>Lean fish no association with WC |

WC: Waist circumference, TG: Triglyceride, HDL-C: High-density lipoprotein cholesterol, BP: Blood pressure.

4. Nutritional Contribution of Fish

Fish is an important source of a variety of nutrients, such as n-3 fatty acids, proteins, selenium, iodine, vitamin D, and taurine [10] (Table 5). The current dietary recommendations from various governing bodies recommend the consumption of fish one to three times a week (Table 6). Fish can be classified as lean, medium-fatty, or fatty depending on the amount of fat in its body tissue, where fatty fish contains more than 8 g of fat per 100 g, medium-fatty fish contains 2–8 g of fat per 100 g, and lean fish contains less than 2 g of fat per 100 g [10]. While the amount of fat varies considerably in fatty fish, it is relatively stable in lean fish. The content and concentration of nutrients vary between the species, and the largest differences are between fatty and lean fish. Fatty fish has a higher level of n-3 fatty acids and the fat-soluble vitamin D, but in contrast lean fish contains more iodine and taurine [10].

Table 5. Nutritional profile of commonly consumed, whole, raw fish, per 100 g [52].

| Food Item, Raw | Energy (kJ) | Fat (g) | n-3 (g) | Taurine (mg) | Vitamin D (µg) | Selenium (µg) | Iodine (µg) |
|---------------|-------------|---------|---------|-------------|---------------|---------------|-------------|
| Haddock (Melanogrammus aeglefinus) | 290 | 0.2 | 0.05 | 28 b/57 c | 0.5 | 30 | 320 |
| Pollack (Pollachius pollachius) Saithe (Pollachius virens) Cod (Gadus morhua) Cod farmed (Gadus morhua) Plaice (Pleuronectes platessa) Trout (Salmo trutta) Mackerel May–June (Scomber scombrus) Trout farmed (Salmo trutta) Salmon wild (Salmo salar) | 279 | 0.2 | 0.05 | - | 2.2 | 30 | 143 |
| 292 | 0.3 | 0.1 | 162 c | 0.8 | 30 | 93 |
| 343 | 1.1 | 0.26 | 108 a/120 c | 2 | 22 | 119 |
| 358 | 0.5 | 0.16 | - | 0.7 | 30 | 300 |
| 382 | 2.6 | 0.66 | 146 b | 6 | 30 | 14 |
| 462 | 3.3 | 0.62 | - | 9 | 19 | 19 |
| 516 | 5.4 | 1.38 | - | 6 | 30 | 50 |
| 693 | 10 | 2.47 | - | 6.9 | 30 | 5 |
| 760 | 12 | 2.12 | - | 8 | 50 | - |
Table 5. Cont.

| Food Item, Raw            | Energy | Fat | n-3  | Taurine | Vitamin D | Selenium | Iodine |
|---------------------------|--------|-----|------|---------|-----------|----------|--------|
|                           | kJ     | g   | g    | mg      | µg        | µg       | µg     |
| Salmon farmed (Salmo salar) | 932    | 16  | 3.63 | 60       | /94       | 10       | 30     | 12     |
| Mackerel, autumn (Scomber scombrus) | 1214   | 25  | 6.35 | 78       | /4         | 5.4      | 60     | 63     |

a Taurine content (mg/100 g raw wet weight) in portions of four fish species purchased in a supermarket [53].
b Taurine content (mg/100 g raw wet weight) in portions of 14 fish species (spot samples) [53].
c Taurine concentrations (mg/100 g wet sample) in unprocessed fresh samples [54].

Table 6. Current dietary recommendations from various governing bodies.

| Organization/Diet           | Dietary Fish Recommendation                                                                 |
|-----------------------------|---------------------------------------------------------------------------------------------|
| Australian Dietary Guidelines 2013 [56] | At least two servings of fish/week                                                             |
| Dietary Guidelines for Chinese Residents (2016) [57] | The appropriate weekly intake is set at 280–525 g of fish                                       |
| European Guidelines on cardiovascular disease prevention in clinical practice 2016 [8] | Fish 1–2 times/week, one of which to be fatty fish                                            |
| Norwegian dietary recommendations (2014) [58] | At least 2–3 portions or 300–450 grams of fish weekly, including a minimum of 200 grams of fatty fish |

8 ounces = 224 g (REF EFSA) [59]. EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid.

4.1. Proteins and Amino Acids

Fish contains a unique combination of high-quality proteins. Both a greater satiety level and a slower decline in satiety have been observed among participants consuming fish (Mustelus antarcticus) when compared to participants consuming beef or chicken [60]. In contrast, a reduction in energy intake after a meal containing fish protein (cod) without a reduction in satiety has also been observed (2765 vs. 3080 KJ), with no later energy compensation after the meal [61]. Further, fish (tuna) has been found to be more effective than turkey and egg in reducing both appetite and food intake, and stimulating a greater insulin response as compared to turkey and egg [62].

Fish proteins have been found to have beneficial effects on lipid profiles. A Norwegian randomized controlled trial (RCT) reported a reduction in both fasting and postprandial circulating TG concentrations in participants consuming proteins from lean fish (e.g., cod, pollock, saithe, and scallops), when compared to the intake of non-seafood protein sources (lean meat: chicken, beef, turkey, pork, egg, and low-fat milk) [36]. Beneficial changes in lipid profiles have also been observed in animal studies, both in rabbits receiving fish protein (cod) when compared to casein or milk protein [63] and in rats receiving fish protein as compared to casein or soy protein [64–66]. In animal studies, dietary proteins have been suggested to regulate lipid metabolism and to slow both the absorption and the synthesis of lipids and to further promote lipid excretion [67]. The responsible mechanisms of fish protein on lipid metabolism has not been fully identified, however, both amino acid composition and bioactive peptides may play a role [67]. Furthermore, dietary proteins from cod have been found to improve insulin sensitivity in insulin-resistant individuals, when compared to those consuming other animal proteins [68].

Beneficial effects of taurine on cardiovascular risk factors have been proposed [69–72], and both a reduction in body weight [73], beneficial effects on blood lipids [73,74], anti-atherosclerotic, and anti-inflammatory effects have been observed [71]. The anti-obesity effects of taurine may partly be due to suppression of inflammation in adipose tissue [75]. Furthermore, taurine supplementation has been found to increase adiponectin levels, and decrease markers of inflammation (high-sensitivity C-reactive protein) [76]. Recently, taurine has been found to lower BP, both in humans where the
participants received either taurine supplementation (1.6 g/day) or a placebo for 12 weeks. Here, the mean SBP reduction for taurine/placebo was 7.2/2.6 mm Hg, and DBP was 4.7/1.3 mm Hg [77]. Such associations have also been found in rats [78]. This lowering effect may be due to the improved vascular function of taurine, possibly through antagonism of Angiotensin II action influencing the blood pressure [79]. Furthermore, taurine may affect the regulation of blood glucose, and it has a role in beta-cell function attenuating cell injury as induced by stress in the islets [80].

4.2. n-3 Fatty Acids

n-3 fatty acids are polyunsaturated fatty acids (PUFA) that are naturally found in plants (e.g., soybeans, mustard, walnut, linseed) and seafood, such as fish and algae. The marine long-chain n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are mainly present in fatty fish [81], however, lean fish is also a source to n-3 fatty acids as it contains approximately 260 mg n-3 per 100 g (Table 4). EPA and DHA are responsible for biological actions, such as maintaining the cell membrane, modulating inflammatory processes, and decreases the secretion of pro-inflammatory cytokines [82] affect both lipid metabolism and thrombosis [83]. Furthermore, n-3 fatty acids have been shown to regulate pathways controlling fat storage and fat mobilization and to decrease lipid accumulation processes [84].

An intake of two to three portions/week of a variety of seafood provide a recommended intake of EPA and DHA (250.0 mg/d) [55], however not all individuals fulfil the recommended intake [81].

Several decades ago, Bang and Dyerberg discovered the cardio-protective effects of n-3 fatty acids when they found that both the Greenland Eskimos food and blood contained a very high level of n-3 fatty acids, when compared with a Danish cohort with higher frequency of ischemic heart disease compared to the Eskimos [85]. Today, current evidence supports the beneficially effects of n-fatty acids on cardiovascular risk factors [86], where beneficial effects of n-3 fatty acids (fish oil) on WC [87], decreased TG [87,88], increased HDL-C [88,89], and reduced blood pressure [44,87] have been demonstrated. However, a recent meta-analysis of almost 80,000 patients (coronary heart disease, stroke, or diabetes) did not find any reduced risk of cardiovascular outcomes after intake of n-3 fatty acid supplements, indicating that the cardioprotective effects of n-3-fatty acids for these patients may have been overestimated. Whether or not fish oil supplements are beneficial for primary prevention of heart disease for healthy people, remains presently uncertain [90].

Beneficial effects of n-3 fatty acids on MetS and CVD have been proposed [91]. n-3 fatty acids have also been associated with reduced risk of MetS in follow-up studies [25,26], however not all found such association [34]. Potential anti-inflammatory effects of EPA and DHA have been revealed (in vitro studies), where n-3 PUFAs have been found to modulate pro-inflammatory cytokines, such as TNF-α and IL-6 in macrophages [92], and DHA, in particular, seems to decrease TNF-α levels [93]. Nevertheless, even though fish oil supplements are popular [94], n-3 fatty acids may be more efficacious when consumed in fish rather than equivalent amounts provided as fish oil capsules. A lower n-3 intake from fish resulted in higher increments in plasma EPA and DHA concentration when compared to capsules, where a two- to nine-fold higher dose of EPA and DHA from capsules was needed to give the same increments as fish [95]. n-3 FAs from fish and sea mammals have been associated with lower blood pressure, TG, 2-hour glucose and higher HDL-C, when high intake of n-3 FAs was compared to low intake of n-3 FAs [96].

4.3. Vitamin D

Vitamin D is a fat-soluble vitamin that is important for bone health and calcium homeostasis, and it may also have an anti-inflammatory effect on human immune cells [97]. Vitamin D is naturally found in fish, and it is also derived in the skin by the effect of ultraviolet rays from sunlight. Fatty fish is a major food source of vitamin D [98], however, the vitamin D content in farmed salmon seems to be declining, which is possibly due to changes in fish feeds over the years [99]. However, recommended levels of
fish consumption are usually not enough to optimize vitamin D status alone, and the fortification of different foods, such as margarine, is common in many countries [100].

The recommended intake of vitamin D in Europe is estimated to be 15 microgram/day, in order to achieve a serum 25(OH)D concentration near or above the target of 50 nmol/L [59]. However, not all individuals fulfill the recommended intake and high prevalence of vitamin D deficiency has been observed both in Europe [101,102] and in the United States [103].

Recently, low vitamin D level (<30 ng/mL) was associated with increased risk of MetS (OR 1.90, 95% CI 1.26 to 2.85), and several of the cardiovascular risk factors comprised in MetS; high TG levels (OR 1.55, 95% CI 1.13 to 2.35), and low HDL-C levels (OR 1.60, 95% CI 1.19 to 2.40) [104]. This has also been found in other studies; MetS [105], WC [106,107], HDL-C [107–109], BP [107], and glucose [110].

4.4. Iodine and Selenium

Both iodine and selenium are trace elements that are required for the thyroid function [111]. While iodine is important for the normal functioning of the thyroid gland [10], through the production of the hormones thyroxine (T4) and triiodothyronine (T3), the primary functions of selenium is to be a co-factor in antioxidant activities and thyroid hormone metabolism [112]. Diseases in the thyroid gland influence body weight, thermogenesis, and lipolysis in adipose tissue, thus hypothyroidism is often related to weight gain, decreased thermogenesis, and metabolic rate [113].

The highest levels of iodine are found in lean fish, whereas ten times more iodine is found in cod and haddock when compared to fatty fish, such as salmon and trout [52]. Among adults, the recommended daily intake (RDI) of iodine is 150 microgram/day, which is considered to be the appropriate amount to allow for normal T4 production without stressing the thyroid [112]. Several studies have reported low intake of iodine and iodine deficiency [114–118]. On the other hand, Iceland has been known for its population’s good iodine status, which is possibly due to their high intake of lean fish and here the most commonly consumed fish is haddock and cod [115,119].

Previously, higher thyroid volume has been found among patients with MetS, as compared to healthy controls without MetS [120]. Obesity may be an independent risk factor to iodine deficiency, and lower urinary iodine has been found in obese women, in comparison with healthy non-obese women [121]. Furthermore, low intake of iodine and no intake of iodine supplements have been associated with obesity in Denmark [117].

For selenium, the recommended daily intake (RDI) is 50 microgram/day for women, and 60 microgram/day for men [58]. Selenium intake and status have been reviewed, and found to be suboptimal both in Europe and in the Middle Eastern countries [122]. One exception is Finland where the selenium levels are now sufficient after a nationwide selenium fertilization programme initiated due to this country having the lowest levels in the world in the early 1980s [123]. In a Spanish population (n = 2009, 50% men), 25% did not meet the recommended intake [124], and as much as half of a group of postmenopausal women (n = 97) in New Zealand did not meet the recommended intake of 50 microgram/day [114].

A reverse association between blood selenium levels and blood pressure has been reported in men, but not in women [125]. Possible harmful effects of mercury on blood pressure may be attenuated by high levels of selenium [126].

5. Conclusions

This review has examined the state of knowledge on the current known beneficial nutrients in fish (n-3 fatty acids, proteins, selenium, iodine, vitamin D, and taurine), and their possible associations with the CVD risk factors comprising MetS.

In the recommendations, dietary advice emphasize intake of fatty fish due to its high levels of n-3 fatty acids. However, lean fish contains numerous nutrients that may be beneficial in the prevention of CVD, indicating that also lean fish should be included in the diet when targeting these modifiable risk factors that are comprised in MetS.
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