BMS

Review

Fish intake, mercury, and metabolic syndrome: a review of the literature

Biomedicine and Surgery

Soric Tamara (1), Dragičević Ivona (2), Coklo Miran (3)
(1) Psychiatric Hospital Ugljan, Ugljan, Croatia
(2) Omnipharma d.o.o., Zagreb, Croatia
(3) Institute for Anthropological Research, Zagreb, Croatia

ABSTRACT

It is already well established that mercury, as a toxic metal, may induce oxidative stress, inactivate several antioxidant mechanisms, and induce a chronic low-grade inflammation, eventually leading to increased risk for metabolic syndrome development. Even though fish intake is commonly associated with the beneficial effects on health, all fish species contain methylmercury, which may have a toxic effect on the human body. Several studies have reported a higher prevalence of metabolic syndrome among people living in the coastal areas, who usually consume more fish than their inland counterparts. Taking into account the impact of fish intake on mercury concentration, together with that of mercury exposure on metabolic syndrome, the aim of this research was to review the existing scientific data regarding the association of all three factors. To our knowledge, only four studies examined the association between mercury concentration and metabolic syndrome, taking fish intake into account. Three out of four studies indicated that exposure, even to low-dose of mercury is associated with metabolic syndrome or at least some of its components. Two of them determined that total fish intake or the intake of some species containing relatively high levels of methylmercury is a contributing factor for mercury concentration in human body. For better understanding of this association, it is necessary to obtain larger prospective cohort studies or randomized controlled trails. Further studies should be carried out over a wider geographic area and elucidate all significant contributing exposure sources for mercury levels.

KEY WORDS: fish intake; mercury; metabolic syndrome

Correspondence to: Tamara Soric, Head of Nutrition Department at Psychiatric Hospital Ugljan, Otockih dragovoljaca 42, HR – 23275 Ugljan, Croatia, novoselic.tamara@gmail.com, tel.; +385-91-565-6166

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INTRODUCTION

Although the term metabolic syndrome (MetS) has been relatively new (1), it has almost reached epidemic proportions in countries with overnutrition and insufficient physical activity (2). The constellation of metabolic risk factors, defined as MetS, includes abdominal obesity, elevated blood pressure, atherogenic dyslipidemia, and elevated plasma glucose and can lead to the increased risk of cardiovascular disease and type 2 diabetes mellitus (3). Many different organizations have developed their own criteria for defining MetS, which usually differ only in small details and defining values but impede determination of the true prevalence of MetS worldwide (4). In the past few decades, there has been an alarming increase in the prevalence of MetS throughout the world. In particular, for the adult population the prevalence is estimated to be approximately 20 to 25% (5).

It is well known that people living in coastal areas consume more fish than their inland counterparts (6). Despite the fact that fish intake may improve metabolic health (7), and reduce risk of chronic diseases (8), the prevalence of MetS in those areas remains high. Those people living on the coast and on the islands of Croatia have typical Mediterranean diet mainly based on fish and seafood, wine, grapes, olives, olive oil, sheep, goats, figs, wild herbs and spices (9). Although it is considered that a Mediterranean-style diet might be effective in reducing the prevalence of MetS (10), according to the data available, the prevalence of MetS among the island population of Croatia is higher than those estimated globally. Depending on the criteria used, the prevalence varies from 25% in the town of Rab up to 53% on Mljet island (11, 12). Similarly, a constant increase of fish and seafood intake occurs in Asian population (13), but epidemiological studies performed in South Asian countries have also reported a significant increase of MetS prevalence (14).

Even though fish intake is commonly associated with the beneficial effects on health, all fish species contain methylmercury, which may have a toxic effect on the human body (15). Chronic exposure, even to low concentrations of mercury, can cause a variety of adverse health effects, including cardiovascular, reproductive, and developmental toxicity, neurotoxicity, nephrotoxicity, immunotoxicity, and carcinogenicity (16).

Taking into account the impact of fish intake on mercury concentration, together with that of mercury exposure on MetS, the aim of this research was to review the existing scientific data regarding the association of all three factors.

FISH INTAKE AND MERCURY CONCENTRATION

The primary source of mercury exposure is diet, mostly fish and shellfish that mainly contain methylmercury. Furthermore, constant fish consumption, especially sea fish, and particularly large, predatory sea fish (shark, tuna, mackerel, swordfish) can lead to the increased levels of mercury in the human body (17 - 20).

Nutrients in fish, especially long-chain n-3 polyunsaturated fatty acids (PUFAs), are believed to be beneficial in prevention and treatment of several diseases. However, methylmercury that is also present in fish could counteract with beneficial effects and therefore the potential of fish as a healthy food has been called into question (21, 22).

Korean adults who consumed seafood 3 days prior to blood sampling had significantly higher levels of blood mercury than those who did not include fish in their diet. In addition, the study showed a trend of higher levels of mercury in the population living near the coast than in inland areas (23). Another Korean study showed that high consumption of both small marine fish and large predatory species, and shellfish leads to significantly higher levels of whole blood mercury concentrations (24). Park and Seo concluded that toenail mercury concentration, which reflects long-term dietary exposure (25), is higher in Korean population which traditionally consumes whale and shark meat (26). Higher toenail mercury level was also associated with higher fish consumption among health professionals (27). Moreover, Finish men who consumed lean local fish species had higher hair mercury levels (28, 29). Similarly, relation between fish consumption and high mercury levels has been confirmed in the population of the Brazilian Amazon (30, 31).

MERCURY AND METS COMPONENTS

It is already well established that mercury, as a toxic metal, may induce oxidative stress, inactivate several antioxidant mechanisms, and induce a chronic low-grade inflammation (32), eventually leading to increased risk for MetS development (33). Although multiple studies have reported a close association between mercury exposure and increased risk of MetS (23, 26, 34), a larger number of them examined the interrelation between mercury exposure and certain MetS component.

As for the relation between mercury exposure and blood pressure, the research conducted so far has shown contradictory results. In particular, the results of a cross-sectional study involving 101 participants confirmed the association between elevated blood and hair mercury with the increase of hypertension risk but on the other hand, elevated blood and hair mercury levels did not seem to influence vascular reactivity (35). Similarly, the results of KNHANES IV and V studies indicate that elevated serum mercury concentrations are related to hypertension risk in men (36). Furthermore, in several other studies, a positive relation between mercury levels and hypertension in adults has also been observed (23, 26, 37, 38). Frao islanders and inhabitants of Navuk, who traditionally consume fish, have shown an association between mercury concentration and blood pressure (39, 40). Sørensen et al. have found that prenatal exposure to methylmercury led to the increased blood pressure in children of a high-fish consuming population (41). At the same time, no association between mercury and hypertension was reported in Saudi women (42) and in an elderly urban population (43). Furthermore, on the representative sample of 6,607 U.S. adults, association between blood or urinary mercury and hypertension was examined, and the authors have found no association of hypertension with blood mercury but a suggestive inverse association between urinary mercury and hypertension (44).

Regarding the relationship between mercury exposure and dyslipidemia, more consistent data were obtained (32). A strong association between mercury exposure and LDL cholesterol (45 - 47), and serum triglycerides (48) has been revealed. Another recently published study has showed that toenail mercury levels are interrelated with the risk of dyslipidemia (49). Blood mercury showed positive relationship with cholesterol among U.S. children and adolescents (50). Park and Seo found a positive correlation with triglyceride levels (26), while the results from Park et al. in 2016 showed a significant positive association between higher mercury concentration and higher HDL cholesterol in MetS men (38). The negative association may be explained by the fact that fish contain high level of PUFAs, which may decrease triglycerides and increase HDL cholesterol, eventually attenuating the effects of low dose mercury on the lipid profile (51, 52).

A great number of conducted research demonstrated interaction between mercury levels with obesity and indices of obesity (24, 38, 53, 54). To our knowledge, the latest published scientific research on this topic, demonstrated significant relationships between metallic elements, including mercury, and obesity, among a population aged 6-19 years (50). According to Eom et al. body mass index (BMI) and waist circumference (WC) are increased in relation to blood mercury levels (23). In their study You et al. noticed that the blood mercury level in males living in coastal areas was significantly related to waist-to-hip ratio, an index of central obesity (46). In a Brazilian natives study, BMI was not associated with mercury exposure from fish consumption (55).

The influence of mercury on insulin resistance and type 2 diabetes mellitus is a subject of a large number of scientific researches. According to Schumacher and Abbott, methylmercury has been shown to have negative effects on the development and function of pancreatic beta cells that could lead to insulin resistance and finally to the development of diabetes mellitus (56). In the cross-sectional study of 2,640 Inuit living in the area characterized by traditional food consisting mainly of predator sea animals with high mercury content, statistically significant association between whole blood mercury level with fasting glycemia and type 2 diabetes mellitus has been found (57). Another large population-based study investigating the association between serum mercury and insulin resistance has concluded that blood mercury could be a potential risk factor for insulin resistance in nondiabetic Koreans (58). On the other hand, a cross-sectional study conducted among members of Korean population has shown no significant relationship between the levels of toxic heavy metals (lead, cadmium and mercury) and diabetes mellitus (59).

FISH INTAKE, MERCURY, AND METS

As aforementioned, numerous works examinated the role of mercury in the development of single MetS component, but a smaller number of research dealt with the influence of mercury on the MetS itself. As far as we know, only four studies examined the association between mercury concentration and MetS, taking fish intake into account. The main characteristics of the relevant studies are summarized in Table 1.

In the study of You et al. 477 adults participated in order to determine the relationship between blood mercury concentration and cardiovascular risk factors, including MetS. The information on demographic factors, smoking status, alcohol consumption, menopause and medical history were gathered throughout the questionnaire. Participants also underwent blood sampling and physical measurements. The mean blood mercury concentration of the participants was 7.99 μg/L, significantly higher in males when compared to females (9.74 μg/L, 7.21 μg/L). No differences in fish consumption between males and females were determined. Although the association between mercury exposure and the risk of cardiovascular disease was observed in males, according to the results MetS was not correlated with mercury concentration (46).

In another Korean study, Eom et al. recruited 2,114 healthy Korean adults who participated in a personal interview including questions about demographic characteristics, lifestyle, dietary habits, and past medical history, and underwent physical measurement and blood sampling. Total mercury concentration was significantly influenced by sex, age, residence area, smoking, alcohol consumption, and fish intake. The determined mean concentration of total mercury was 3.90 μg/L and was higher in subjects living near the coast (4.96 μg/L) than in the inland areas (3.61 μg/L), as well as in subjects who consumed seafood within 3 days prior to blood sampling. This study has shown increased prevalence of MetS within higher blood mercury levels. Obesity and increased fasting glucose, as components of MetS, were also significantly associated with blood mercury levels (23).

The third research on this topic has also been done in Korea and included 7,616 subjects who underwent blood sampling and physical measurements in order to examine the association between serum HDL cholesterol and blood mercury concentration in relation with MetS. Information on socioeconomic status, health-related behaviours, quality of life, and healthcare utilization were also collected. This study showed lower serum HDL cholesterol and higher blood mercury concentrations in MetS subjects than in a non-MetS group. Mean blood mercury concentrations were 6.5, 4.2 μg/dL in MetS men and women, and 5.3, 3.8 μg/dL in men and women in the non-MetS group. Based on the results, Park et al. concluded that elevated mercury concentration may be a factor to increase HDL cholesterol concentration in Korean men. Furthermore, the results have shown higher mercury concentration with lower fish intake in the MetS group in relation to the non-MetS group (38).

To our knowledge, the latest study that took into account mercury concentration and MetS together with fish intake was that of Park and Seo. The research included 501 participants who gave information about their lifestyle and dietary habits. In order to carry out the research, toenail clippings, anthropometric and metabolic biomarkers were collected from the subjects. The aim of this study was to examine the relation between toenail mercury levels and MetS, and to determine whether selenium in toenails would modify it. This study showed a mean level of toenail mercury of 0.40 μg/g together with the fact that the subjects in the highest tertile of toenail mercury concentration were 2.47 times more likely to have MetS when compared to those in the lowest tertile. As parts of the MetS, obesity markers, blood pressure, fasting blood glucose, and triglycerides, were all significantly in relation with mercury concentration. The authors concluded that there was no difference in toenail mercury concentration between levels of total fish intake, but found out that the concentration is higher in subjects who habitually eat shark and whale meat. Moreover, according to the results the possible negative effect of mercury on MetS may be reduced by high levels of selenium (26).

Table 1. Studies on the association between fish intake, mercury exposure, and MetS

Reference	You et al., 2011 (46)	Eom et al., 2014 (23)	Park et al., 2016 (38)	Park and Seo, 2016 (26)
Type of study	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
Population	Korea	Korea	Korea	Korea
Mean age	53.9 y	45.5 y	41.3 y	44.8 y
Exposure biomarker for mercury	Blood mercury	Total blood mercury	Blood mercury	Toenail mercury
MetS criteria	NCEP-ATP III	NCEP-ATP III	AHA/NHLBI	NCEP-ATP III
Conclusion	MetS was not correlated with mercury concentration. No difference regarding fish intake was observed.	Blood mercury level was associated with MetS and was influenced by dietary habits, including fish consumption.	Blood mercury was higher in MetS subjects. Higher mercury concentration was associated with lower fish intake in the MetS group.	Mercury level was associated with the prevalence of MetS. While the consumption of whale and shark meat lead to higher mercury levels, total fish intake had no association.

DISCUSSION

Three out of four above mentioned studies indicated that exposure, even to low-dose of mercury is associated with MetS or at least some of its components. Two of them determined that total fish intake (23) or intake of some species containing relatively high levels of methylmercury (26) is a contributing factor for mercury concentration in human body. According to Park et al. higher mercury concentrations, together with lower fish intake, were found in participants with MetS compared to those without MetS. Previously stated has not been in the focus of this research and therefore the results that would enable further analysis and discussions are not presented (38).

The results of recent studies have showed a significant relation between mercury levels and MetS (23, 26), whereas You et al. did not observe the correlation, but concluded that WC was the only associated component of the diagnostic criteria (46). Results of the analysis of hair tissue of 343 Korean adults showed a significantly higher concentration of mercury in MetS subjects when compared to the normal group (34). Moon also confirmed these positive associations in an adjusted model for age, sex, region, smoking, alcohol consumption, and regular exercise, suggesting that people with higher mercury concentration are more likely to have MetS (60). Although numerous studies have dealt with the association of mercury exposure and MetS, as well as with the association with a certain MetS component, the results and the mechanisms by which the association could be explained are still inconsistent and not fully elucidated.

It is well known that fish and shellfish, especially predatory fish, represent a main source of mercury exposure to humans. Being associated with the MetS, mercury exposure may play a role as a possible risk factor for cardiovascular disease (23, 61 - 63). In contrast to these findings, there were several reports that detected no harmful effects between mercury and cardiovascular disease, or beneficial effects of fish consumption on cardiovascular disease (64 - 70) recommending the intake of fish, which long chain n-3 PUFAs and essential minerals might alleviate the adverse effect of mercury, for all population groups. Therefore, it is difficult to understand possible adverse effects of mercury exposure on cardiovascular disease (38).

The association between fish intake and mercury levels has been found in several studies (18 – 20, 23, 71). In 2005, Mahaffey noticed that high levels of mercury in coastal areas were the result of ready access to fresh seafood (72). Kim et al. postulated in 2012 that mercury level in blood increased with the amount of seafood consumption (73). A recently study has showed that increased fish intake lowers the risk of MetS and its components (74). These results are contrary to those of Eom et al., who have found increased prevalence of MetS with higher blood mercury levels and higher mean blood mercury concentration in those who have consumed fish 3 days prior to blood sampling (23).

Blood mercury concentrations may represent short-term exposure to mercury, while hair concentration may be limited by possible contamination from the use of hair products (26) and differ with length of the hair (46). Urinary mercury is the best biomarker of long term exposure to elemental and inorganic mercury, while blood mercury has been used in epidemiological studies as a marker of recent methylmercury exposure by diet in general population (18, 75).

Mercury levels are affected by various factors, including demographic factors (age and sex), smoking status, alcohol consumption, fish intake, and air pollution. While there is a consistent difference in blood mercury levels depending on age (23, 26, 75), sex related differences are not consistent. Blood mercury level was significantly higher in either men or women in some studies, but no statistical gender difference was reported in others (23, 48, 76 - 80). One recent study, according to the authors first of its kind to assess sex differences in the association between blood mercury concentration and MetS risk in general population, came to the conclusion that there were significant sex differences in the association between blood mercury concentrations and the increased risk of MetS, which could be explained by sex differences in the mercury excretion and retention (faster whole body clearance of mercury in females) and also those in oxidative stress and antioxidant capacity (the activity of some antioxidant enzymes is higher in females; the effect of estrogen against oxidative stress in females) (79). Higher mercury concentrations were found in males than in females in three out of four studies that were of primary interest for our review. Only Park and Seo did not show results depending on sex so we could not discuss possible differences (26). Behavioural factors, including smoking, alcohol drinking habits, and dietary patterns, especially fish intakes (18, 20, 23, 71, 81) are significant determinants of blood mercury levels (23). Higher household income was also in correlation with mercury levels (6, 26). According to

Nair et al. women with higher household incomes and education consumed greater amount of fish higher in mercury (6). Therefore, when trying to examine the association between specific factor and mercury concentration in humans, and also between mercury concentration and MetS risk, all factors that have potential impact should be taken into account. If not adjusted for all relevant characteristics, we could not say with certainty to what extent does a specific factor affect the results.

LIMITATIONS AND PERSPECTIVES

Those studies of primary interest in this review have some limitations. As well as the largest number of previous observations, they were obtained by cross-sectional analysis, thus larger prospective cohort studies or randomized controlled trails are required to determine the exact causal relationship. Previous reports were mostly conducted in limited geographic areas and therefore the results could not be generalized into various ethnic groups. Furthermore, in most of the reports whole blood mercury has been used as a biomarker, so the measurements may not accurately reflect chronic exposure status. For future studies it is necessary that they are carried out over a wider geographic area and that they elucidate other significant contributing exposure sources for mercury levels.

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