Chapter 33
Variations in Selenium Metabolism in Males and Females

Lutz Schomburg

Abstract Selenium elicits its effects on human health mainly in the form of selenoproteins, even though some selenocompound-specific effects have been described. The physiological roles of certain selenoproteins have been characterized in transgenic mice, and epidemiological analyses have indicated associations of selenoprotein genotypes with common pathologies. Supplementation studies yielded promising results indicating that selenium can reduce cancer risk, autoimmune disease, subfertility, or mortality risk in severe illness. General conclusions are drawn and discussed vividly in science, health politics, and elsewhere. But studies in experimental rodents indicate that selenium metabolism and selenoprotein expression patterns differ between the sexes. Similarly, the selenium-dependent reduction of cancer risk, subfertility, or mortality in sepsis is mainly observed in males but not in females. Selenium-dependent health effects in thyroiditis are described in females only, and associations of selenium status and goiter, thyroid nodules or cardiovascular disease are sexually dimorphic. Even the major side effect, i.e., increased diabetes risk, appears to be male-specific. Therefore, selenium metabolism and selenium health effects differ between females and males, and generalizations should not be made across the sexes.

33.1 Introduction

Women and men differ. This notion which is well known, appreciated, and savored in everyday's life becomes underestimated and ignored all too often in medicine and medical sciences. Women are underrepresented in most clinical studies [1, 2],

L. Schomburg (✉)
Institute for Experimental Endocrinology, Südring 10 CVK,
Charité-University Medicine Berlin, Berlin 13353, Germany
e-mail: lutz.schomburg@charite.de

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and suffer in general a higher frequency of adverse drug reactions [3]. Moreover, pharmacodynamics and pharmacokinetics differ considerably between the sexes [4, 5]. Although the varying body sizes and body compositions are obvious and sometimes taken into account when dosages are determined in a personalized manner, other sex-specific characteristics are less-well considered including differences in intermediary metabolism, e.g., renal glomerular filtration and secretion or hepatic phase I metabolism and phase II conjugation rates. On top of these physiological characteristics, the way of living has gender-specific aspects including differences in physical activities, eating habits, and even frequency, choice and extent of dietary supplement intake with respect to vitamins, minerals, or secondary plant metabolites [6, 7].

Accordingly, the health outcome of a chosen personalized self-medication can not be predicted for a given individual but general trends have been deduced [8] including the disturbing notion that many antioxidant supplements are having an adverse effect on health instead of prolonging life expectancy [9]. Consequently, the current picture of nutritional supplements is changing from sheer enthusiasm to general skepticism and selenium is no exception to this trend. But this verdict is not justified in general, and we need to more carefully analyze out study results since many aspects of metabolism, regulation, and health effects of the essential micronutrient selenium display strong sex-specific differences. This section tries to summarize the respective state of research and knowledge on this emerging issue in selenium biology [10, 11].

33.2 Selenium Metabolism in Female and Male Animals

During the initial phases of selenium research, when a rat model of vitamin E deficiency-induced necrotic liver degeneration was studied, an emphasis was put on the characterization of different selenocompounds and their relative characteristics, bioavailabilities, and protective effects [12]. In these pioneering studies, female and male rats were used without discrimination and results were generalized since the selenocompounds afforded a comparable degree of protection in both sexes. But soon thereafter, samples of males and females were separately analyzed and sex-specific differences were observed, e.g., when growth of second generation selenium-deficient animals was compared [13], when plasma and cell selenium concentrations were determined in adult humans [14], or when retention of selenium isotopes was analyzed in the tissues of male and female rats (Fig. 33.1) [15].

Of all the human genes encoding selenoproteins [16], none is located on the Y- or X-chromosome. This notion excludes that number of selenoprotein genes is a major reason for sexual dimorphic selenium metabolism. Selenium is essential for reproduction, especially in males by affecting testes development and spermiogenesis [17]. When comparing selenium effects on the gonads, profound differences with respect

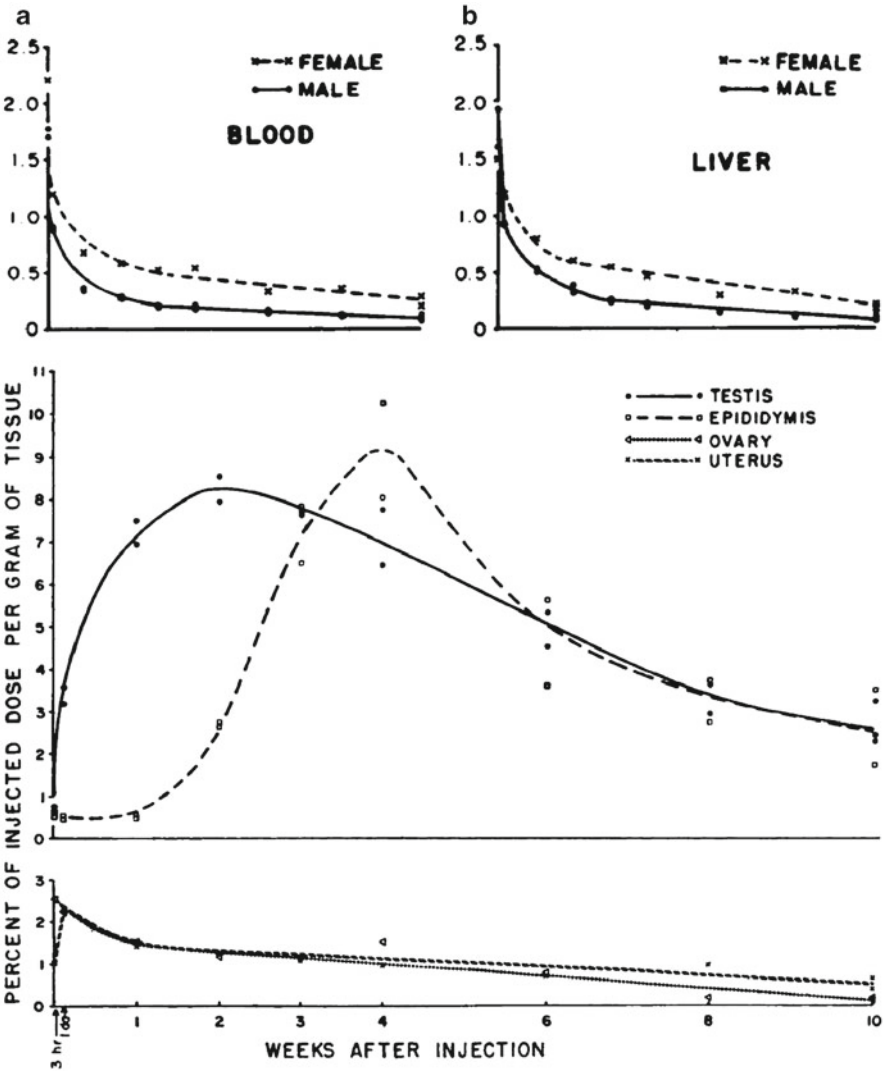

Fig. 33.1 Comparison of the retention of 75-selenium labeled selenite in male and female rats. Retention of 75-selenium was compared over 10 weeks after injection (i.p.) (reproduced from Brown and Burk [15] with permission from the "American Society for Nutrition"). Labeled selenium decreases faster in blood (**a**) and liver (**b**) of male compared to female animals. Gonads yielded a very dimorphic picture (*bottom*); the testes accumulated the radioactively-labeled selenium over an extended period of time, and apparently transferred the isotope to the epididymis, whereas the ovaries and uterus took up the 75-selenium selenite rapidly, and then lost the label as constantly as observed above in blood and liver. The underlying molecular pathways controlling this sexually dimorphic selenium metabolism involve transport via SePP from liver to the testes, specific uptake of selenium and use for GPx4 biosynthesis which becomes irreversibly converted into a structural component of the developing spermatids during spermiogenesis

to retention are observed (Fig. 33.1). Testes belong to the preferentially supplied organs residing high in the hierarchy of selenium supply among all the mammalian tissues [11, 18]. The kinetic profile of injected 75Se-SeO_3^{2-} highlights that selenium is taken up by the testes with a certain delay and then becoming transferred to the epididymis while the ovaries show a fast accumulation and an almost linear loss of the tracer [15]. The molecular mechanisms behind this male-specific metabolism of selenium in the reproductive tract have been intensively studied in recent years [19]. Our current picture comprises some detailed knowledge on the importance of certain selenoproteins for selenium transport to the testes, retention within testes, and functional importance of selenoproteins for spermiogenesis and sperm motility (for details please see Chap. 32).

Briefly, liver is the major organ for initial metabolism of dietary selenium, its uptake from the circulation and organification. Selenium becomes fast and efficiently converted into selenoprotein P (SePP), which serves as a transporter being taken up by other organs including brain and testes. Uptake is mediated by receptors of the lipoprotein receptor-related protein (Lrp) family, especially Lrp2 (megalin) in kidney [20, 21] and Lrp8 (ApoER2) in both brain [22] and testes [23]. SePP supply to testes is essentially needed for supporting the biosynthesis of testes selenoproteins and generation of vital and motile sperm [24]. Besides SePP, GPx4 has been identified as a second essential selenoprotein needed for male fertility [25], and the mitochondrial GPx4 isozyme is mainly responsible for normal spermiogenesis [26]. Accordingly, polymorphisms in the human GPx4 gene have been associated with male infertility [27]. In testes, Sertoli cells bind and internalize SePP [23], causing a strong selenium enrichment specifically in late spermatids, which apparently use SePP as a selenium source for GPx4 biosynthesis [28]. During spermiogenesis, GPx4 undergoes a functional metamorphosis from an active enzyme into a structural component needed for stability and motility of spermatids [29].

Accordingly, SePP and ApoER2 are abundantly expressed in male testes, but their expression is marginal or absent in female ovary or uterus. This pronounced sex-specific difference in selenoprotein expression may contribute to the differential selenium retention in males and females. But it is unlikely that sperm and seminal fluid are major factors controlling male-specific selenium metabolism and flux, for the total amount secreted with one ejaculation averages in humans at 100–250 ng selenium (mean volume: 2–5 mL, mean selenium concentration in seminal plasma: 50 μg/L) [30]. In comparison, the blood loss during menstruation is around 35 mL corresponding to an average loss of 1,750–3,500 ng selenium per month, i.e., in a similar range as the selenium loss via sperm in males. In vivo, thus, there must be other and more important pathways causing the sexual dimorphic kinetics of selenium uptake, retention, and selenoprotein expression patterns; unfortunately, the molecular details have not been fully characterized yet. But especially the growing number of sexual dimorphic effects observed in epidemiological studies and selenium supplementation trials highlighting sex-specific disease associations argue that these differences are real and of importance for human health.

33.3 Sex-Specific Regulation of Selenoprotein Expression

Like all other proteins, expression of selenoproteins is regulated at multiple steps, but the strict dependence on the limiting trace element selenium confers some specific oddities to the relative importance of the different regulatory levels [31]. The role of gender-specific circuits and sex steroid hormones controlling transcription of selenoproteins in the different tissues is a very complex and multilayer issue. In experimental animals, castration alters the expression of a number of selenoproteins in a sex-specific way [32]. The effects are not only exerted at the transcription level but involve posttranscriptional mechanisms giving rise to tissue-specific expression patterns in males and females which vary with the selenium status (Fig. 33.2) [33].

The following section illustrates the underlying complexity of trying to elucidate the mechanisms controlling selenoprotein expression in males and females, and highlights that different levels of regulation are involved which converge under physiological conditions ensuring a time-, tissue-, and cell-specific expression pattern of a given selenoprotein. The aforementioned multifunctional selenoenzyme GPx4 is chosen as a very instructive example, as it is ubiquitously expressed and of functional importance for diverse processes including brain development, arachidonic acid metabolism, and fertility. According to its sexual dimorphic importance in reproduction, GPx4 expression in testes depends on gonadotropin stimulation and increases after puberty in rat testes [34]. Surprisingly, testosterone or gonadotropins

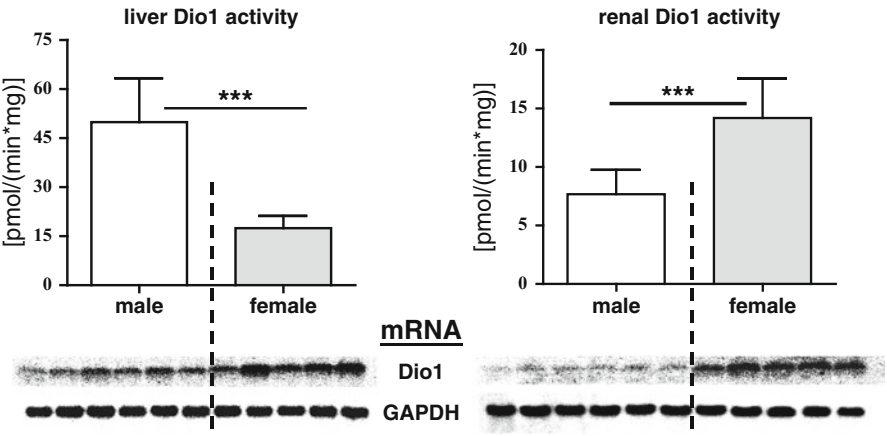

Fig. 33.2 Pre- and posttranscriptional mechanisms control sex-specific selenoprotein expression. Selenoproteins are sex-specifically expressed (*top*, activity; *bottom*, mRNA) in liver and kidney of adult mice (modified from Riese et al. [33]). Enzymatic activity of type 1 iodothyronine deiodinase (Dio1) is higher in male compared to female liver, whereas it is higher in female compared to male kidneys. This sexually dimorphic expression pattern is paralleled by respective differences in Dio1 mRNA concentrations in kidney but not in liver, where the differences in enzyme activity and mRNA levels do not correlate. Apparently, translational efficiency of Dio1 mRNA is higher in male compared to female hepatocytes by unknown molecular mechanisms

do not directly affect transcription of the GPx4 gene. The increased biosynthesis of GPx4 rather correlates to the maturation stage of spermatids, i.e., to a differentiation process which in turn is controlled by local testosterone from Leydig cells [35]. In addition, GPx4 is subject to dynamic alternative splicing and depending on environmental parameters, the cells synthesize different patterns of cytosolic, mitochondrial, and nuclear GPx4 isozymes [36, 37]. On top of this inherent transcriptional complexity, posttranscriptional mechanisms involving sequence-specific RNA-binding proteins recognizing the 5′-untranslated region of GPx4 mRNA control the translation efficiency, e.g., during embryonic brain development [38]. Finally, single nucleotide polymorphisms (SNPs) have been identified in the human GPx4 gene, which affect selenium-dependent GPx4 expression and turnover in a sex-specific way [39]. This gender effect may be of importance for sex-specific effects of selenium supplementation in clinical trials [11, 40].

Collectively, there are specific molecular mechanisms controlling the transcription, alternative splicing, translation, and posttranslational activity of selenoproteins in vivo, all of which may be subject to sex-specific modulation. These regulatory circuits ensure a gene-, cell-, age-, and selenium-status-dependent expression pattern in the tissues. Our molecular insights have mainly been obtained by comparing experimental animals. It has become obvious that the ratio of selenoprotein mRNA and corresponding protein amounts differs between the sexes and between different tissues [33], and that cell-type, age, and selenium status are three additional major regulators of sexual dimorphic selenoprotein expression patterns mainly controlling translational aspects [41]. We will have to take these confounding factors into consideration when clinical effects of selenium supplementation are analyzed and sex-specific differences are discussed.

33.4 Sexual Dimorphic Effects of Selenium in Clinical Studies

33.4.1 Cancer

Selenium belongs to the small number of trace elements and vitamins, which are taken as a nutritional supplement both in clinical studies and as an over-the-counter drug. The enthusiasm for supplemental selenium intake was supported by its alleged function as an antioxidative drug potentially slowing down degenerative processes and protecting genome integrity. Early analyses had indicated an inverse association of cancer prevalence and soil selenium concentrations [42], followed by a large number of respective experimental studies [43].

This general trend has been corroborated in the majority of clinical studies, and finally received tremendous support when the Nutritional Prevention of Cancer (NPC) trial was analyzed [44]. The NPC data indicated that a daily supplementation with 200 μg selenium in form of selenized yeast reduces the incidence of lung, colorectal, and prostate cancers, especially in those participants who entered into the study with relatively low baseline selenium concentrations [45]. Notably, this

conclusion was mainly drawn for males. Females were underrepresented in this important prospective cancer prevention trial and constituted only 25% of the enrolled participants. Nevertheless, the general conclusion was drawn that optimizing selenium intake by supplementation efforts confers chemoprevention and reduces cancer risk in all individuals. The sex-specific lack of information was not appreciated, and consequently the subsequent largest-ever chemoprevention trial testing selenium supplementation in a prospective setting, i.e., SELECT, was again initiated with males only, focusing on prostate cancer [46]. More detailed information on SELECT is found elsewhere in this book (see Chap. 23).

That such a generalization is not necessarily justified is indicated by several respective studies, e.g., the data from the European SU.VI.MAX trial (SUpplementation en VItamines et Mineraux AntioXydants). This randomized double-blind, primary-prevention trial indicated a significantly reduced total cancer incidence in men but not in women 7.5 years after initiating low-dose antioxidant supplementations including 100 μg selenium/day [47]. A detailed analysis of this surprising finding indicated that the baseline antioxidant status was sexually dimorphic, too, but proved insufficient to explain the full differences observed in the supplementation effect between the sexes. This trend of male-specific antioxidant effects is in agreement with two earlier reports from European epidemiological studies; increased cancer risk was associated with lower serum selenium levels in men but not in women in a Dutch [48] and independently in a Finish case–control study, in which the strongest association was observed for stomach and lung cancers [49].

Conversely, a recent meta-analysis indicated that the risk of bladder cancer is inversely associated with selenium concentrations in women but not in men [50]. Sex-specific differences in selenium metabolism and renal secretion are discussed as potential molecular reasons underlying this finding. The sex-specific trend of efficiency is in agreement with a case-control study in the US associating low toenail selenium concentrations with higher bladder cancer risk in women but not in men [51]. A more systematic comparison of sex-specific findings from several studies correlating selenium status and cancer risk has been compiled by Waters et al. [10]. Collectively, the available data indicate that the interactions are in general more pronounced in males (except for bladder cancer), but again, additional studies with both female and male participants spanning a large range of baseline selenium status are needed to get a better idea on the underlying mechanisms, i.e., whether the correction of a deficit ensuring maximal selenoprotein expression or selenocompound-specific, anti-tumor activities underlie the chemopreventive effects in females and males, respectively.

33.4.2 Infectious Diseases and Sepsis

Serum selenium and SePP are negative acute phase reactants and decline in response to inflammatory signals [52]. Plasma selenium concentrations are significantly lower in patients on the intensive care units than in controls [53]. Moreover and

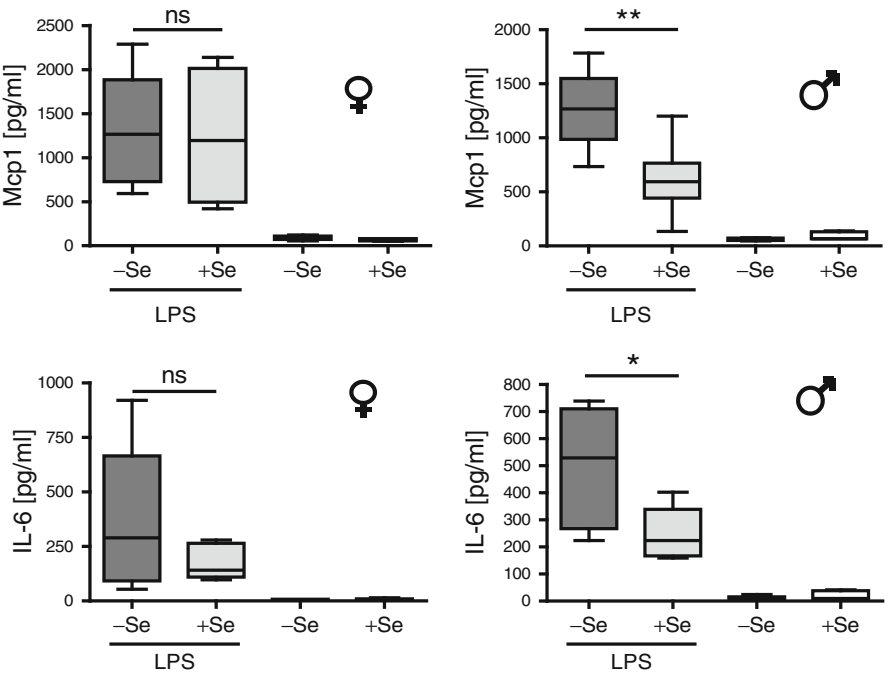

Fig. 33.3 Sexual dimorphic effects of selenite supplementation in a murine model of septic shock (modified from Stoedter et al. [60]). Male and female mice were raised on a selenium-deficient diet and then received regular tab water or water supplemented with selenite for 3 days. At 24 h before being sacrificed, a single injection (i.p.) of endotoxin (LPS) or saline was given. Circulating cytokines (IL-6, interleukin-6; Mcp1, monocyte chemoattractant protein 1) increased sharply upon LPS treatment. Notably, supplemental selenium had a mitigating effect on this acute phase response only in the male but not in the female mice

more importantly, low plasma selenium is associated with reduced survival odds of intensive care patients [54]. This association is valid for both females and males alike, and mortality risk can even be predicted from the minimal selenium levels observed in plasma [55]. Accordingly, clinical trials have been conducted trying to correct this trace element deficiency by a respective supplementation effort. The results are inconsistent, and different selenocompounds, chosen dosages, and application regimen have been discussed as potential reasons underlying this heterogeneity [56, 57].

A recently conducted large placebo-controlled multicentre study, i.e., the Selenium in Intensive Care study, has yielded positive supplementation effects reducing the 28-day mortality rate in patients with severe sepsis [58]. Unfortunately, female participants were again underrepresented, and the positive supplementation effect appeared to be confined to males [59]. This surprising finding was corroborated in a respective mouse study where LPS-induction was used as a model for septic shock. Short-term selenite supplementation efficiently reduced the overshooting immune response (Fig. 33.3) in male but not in female mice [60].

Again, the underlying reason for this sexual dimorphic supplementation effect is unknown, but since it applies to both rodents and humans, it appears to constitute a meaningful phylogenetically-conserved feature.

HIV infection is another strong inflammatory burden causing progressive weight loss and certain mineral and vitamin deficiencies. Part of this problem is given by reduced appetite and nutritional malabsorption, but the cytokine-dependent changes in the intermediary metabolism pose an additional problem to the patients. Serum selenium concentrations decline during HIV disease progression, and low selenium correlates again to poor survival odds [61]. A particular difference has been noted when comparing serum selenium concentrations before and after introduction of a highly-active antiretroviral therapy (HAART); among the most severely diseased individuals, males displayed the lower serum selenium concentrations compared to females before HAART [62]. Interestingly, the selenium status normalized during HAART along with improved weight stabilization, reaching serum selenium concentrations which no longer displayed a sex-specific difference. These findings indicate that the sexually dimorphic selenium status was dependent on the severity of the disease and activity of the immune system, especially in the male HIV patients.

33.4.3 Autoimmune Thyroid Disease

Among the autoimmune diseases, Hashimoto's thyroiditis (HT) is a relatively common destructive disorder of the thyroid gland eventually causing hypothyroidism, goiter, and loss of active thyroid gland tissue. This disease is probably the first one that has been identified as being caused by autoantibodies. It is highly prevalent affecting on average about 1 in 1,000 adults with a skewed sex ratio being about ten times more frequent in adult females than males [63]. Although there is no curative therapy targeting the thyroid destruction process at present, the accompanying hypothyroidism is corrected by a daily supplementation with thyroxin and a personalized dosage to establish euthyroidism and subjective well-being. HT patients are reported to have reduced serum selenium concentrations compared to controls [64]. This finding accords to the aforementioned negative regulation of serum selenium during sepsis and other inflammatory diseases in general.

Accordingly, supplementation trials have been conducted to analyze whether a correction of the selenium deficit improves health and clinical disease parameters [65]. A recent metaanalysis of randomized, placebo-controlled, blinded prospective studies with patients under thyroxin treatment highlights the prospect of selenium supplementation in reducing autoantibody load and improvement of general well-being [66]. This conclusion was based on the pooled analysis of four individual trials comprising in total 123 control and 136 treated HT patients. It is widely accepted as good evidence that selenium supplementation is a beneficial adjunct therapy option in HT. Albeit, in line with disease prevalence, the studies were conducted mostly with women, and only one particular trial enrolled males at all, which

constituted only 9 out of 65 patients [67]. A global statement on the effects of selenium on HT disease can thus not be given for the full population but for women only.

It might well be that the selenium effects will differ between male and female patients. The analysis of the baseline status in participants of the European SU.VI.MAX trial indicated that serum selenium inversely correlates to thyroid volume, risk of goiter, and hypoechogenicity in women [68]. None of these interactions was found in the male participants. We have independently determined the same sex-specific associations in a cohort of Danish adults [69]. Notably, all these sex-specific findings were observed in populations with mild iodine and selenium deficiency, i.e., in regular Europeans; it remains to be seen whether similar correlations are found in other countries with better iodine or selenium supply.

33.4.4 Cardiovascular System

The cardiovascular system is a prime target exposed to oxidative stress with the metabolically highly active myocardium and the widespread network of arteries, veins, and capillaries transporting a colorful cocktail of partly reactive and potentially damaging molecules throughout the body. Key events for development of arthrosclerosis comprise the activity of reactive oxygen species (ROS), especially during oxidation of LDL, triggering the development of proatherogenic foam cells in the vasculature. Selenoproteins of the GPx family are prime candidates for the physiological safe degradation of peroxides as potential precursors of ROS. Accordingly, GPx1 activity has been analyzed in red blood cells of patients with suspected coronary artery disease (CAD) and turned out as a very strong univariate predictor of risk for cardiovascular events [70]. Notably, sex was again an important modifier of the effects and young women expressed the highest GPx1 activities among the probands.

A straightforward test for the functionality, plasticity, and integrity of the cardiovascular system involves the simple measurement of systolic and diastolic blood pressure. In a Belgian cross-sectional and longitudinal analysis, a significant inverse correlation of these two parameters with blood selenium concentrations was found in men but not in women [71, 72]. Notably, the risk of hypertension correlated to baseline selenium status. In extrapolating the data, it appears that increasing the daily intake slightly to improve blood selenium concentrations by a margin of 20 μg selenium/L only might already suffice to lower CAD and myocardial infarction (MI) rates in European men by an impressive 7 and 10%, respectively. This male-specific trend was verified in a Finnish study but was not replicated in a similar French analysis [73].

CAD is the end result of a degenerative process affecting the coronary arteries finally impairing oxygen and nutrient supply to the heart and eventually causing MI. CAD is the leading cause of death of adults in the developed countries. The risk of acute MI is roughly twice as high for men than for women until 60 years of age; thereafter, the difference disappears and equal incidences on a higher level are

observed by the eighth decade of life [74]. The INTERHEART study determined that the median age of the first acute MI is on average 9 years earlier in men than in women [75]. In general, women share the same risk factors as men but their relative contribution to the overall risk differs between the sexes; weight and BMI are of high predictive value in men, while global baseline inflammatory status appears more important in women.

Results on the interaction of selenium status and disease risk differ between the studies, but a protective tendency of higher selenium status can be deduced from the observational studies [76]. In contrast, intervention trials yielded inconsistent results on the efficiency of selenium supplementation to prevent CAD endpoints [73]. A large observational analysis studying patients with stable angina pectoris and acute coronary syndrome, respectively, was conducted in Germany with participants of moderate selenium status [77]. Most patients were between 60 and 70 years of age, and again, only about 25% of the patients were female. Survival rates in stable angina pectoris patients were unrelated to serum selenium status while survival of acute coronary syndrome patients strongly correlated to serum selenium concentrations (hazard ratio of 0.38 (0.16; 0.91), $P=0.03$, for highest vs. lowest tertile of serum selenium) [77]. In this study, the influence of sex was of borderline significance on these associations highlighting the need for a more comprehensive analysis on the interaction of selenium, sex, and CAD.

33.5 Comparison of the Sex-Specific Risk–Benefit Ratio

In general, a low selenium status which is insufficient for full expression of selenoproteins seems to confer an increased risk for developing a number of diseases and impairing the convalescence process. Moreover, a selenium deficiency appears to aggravate during (inflammatory) diseases thereby closing a potentially dangerous feed forward cycle [78]. It is thus widely accepted that selenium supplementation and increased dietary intake offer some health benefits especially in poorly supplied individuals. As for every other medically active substance, an upper limit of intake should not be surpassed to avoid adverse effects. Selenium poisoning (selenosis) is regularly observed both in veterinarian medicine and as sporadic accidents in humans [79].

Besides the acute effects, the long-time intake of supplemental selenium even in the recommended dosages might increase disease risk under certain circumstances. Two independent reports from 2007 highlighted a potentially increased risk of developing type 2 diabetes mellitus (T2DM) upon high selenium intake, i.e., the follow-up analysis of the NPC trial [80] and an epidemiological cross-sectional analysis as part of the Third National Health and Nutrition Examination Survey (NHANES III) [81]. Notably, both studies were mainly conducted in the US and analyzed a population of relatively high baseline selenium concentration.

But most importantly, a detailed analysis of the primary data clearly indicates that the reported increased T2DM risk is confined to males; among the females of

the NPC trial, $n=8$ in the placebo and $n=9$ in the selenium arm developed T2DM, which is statistically insignificant [80]. Similarly, there was no significantly increased T2DM risk with high selenium status in post or premenopausal women of the NHANES III study [81]. While the former notion is somewhat limited due to the relatively low number of females enrolled in the NPC trial, the latter cross-sectional analysis needs to be interpreted in a sex-specific manner. The obvious sexually dimorphic risk of T2DM and selenium supplementation needs to be emphasized more actively, for it is not yet appreciated in the media or public. Similar sexual dimorphic data are available for the interaction of selenium and serum lipids, LDL- or HDL-cholesterol concentrations. At present, a U-shaped interaction curve with a minimal disease risk at an optimal selenium status is emerging, but it remains to be seen whether the optimal selenium status differ between the sexes.

33.6 Concluding Remarks

Even though there is some clear lack of mechanistic insights into the underlying molecular pathways, both animal experiments and clinical data highlight that the health effects of selenium, the associations of selenium intake and status with certain disease risks, and the side-effects from too high a daily selenium supply differ between the sexes. In general, males seem to be more dependent and more responsive to acute changes in the selenium supply, their status responds with faster kinetics and stronger amplitude to inflammatory stimuli, and likewise they are more likely to develop adverse health effects upon surplus intake. The current data do not yet allow for deducing sex-specific intake recommendations, especially with respect to the different health aspects of selenium, but the studies at hand which have compared males and females strongly argue for a more balanced study design in future trials. Wherever possible, we should not conduct studies with one sex only, if the funding allows a more complete approach. But more importantly, we should refrain from generalizations of the findings at hand when one sex only has been analyzed. Males and females differ considerably with respect to selenium metabolism, selenoprotein expression, and medical selenium effects, and these sex-specific differences appear to be conserved across the species and may thus be meaningful for health and disease.

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