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Review

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Gender medicine: a task for the third millennium

Abstract

Gender-specific medicine is the study of how diseases differ between men and women in terms of prevention, clinical signs, therapeutic approach, prognosis, psychological and social impact. It is a neglected dimension of medicine. In this review we like to point out some major issues in five enormous fields of medicine: cardiovascular diseases (CVDs), pharmacology, oncology, liver diseases and osteoporosis.

CVDs have been studied in the last decades mainly in men, but they are the first cause of mortality and disability in women. Risk factors for CVD have different impacts in men and women; clinical manifestations of CVD and the influence of drugs on CVD have lot of gender differences. Sex-related differences in **pharmacokinetics and pharmacodynamics** are also emerging. These differences have obvious relevance to the efficacy and side effect profiles of various medications in the two sexes. This evidence should be considered for drug development as well as before starting any therapy. Gender disparity in **cancer** incidence, aggressiveness and prognosis has been observed for a variety of cancers and, even if partially known, is underestimated in clinical practice for the treatment of the major types of cancer. It is necessary to systematize and encode all the known data for each type of tumor on gender differences, to identify where this variable has to be considered for the purposes of the prognosis, the choice of treatment and possible toxicity. Clinical data suggest that men and women exhibit differences regarding the epidemiology and the progression of certain **liver diseases**, i.e., autoimmune conditions, genetic hemochromatosis, non-alcoholic steatohepatitis and chronic hepatitis C. Numerous hypotheses have been formulated to justify this sex imbalance including sex hormones, reproductive and genetic factors. Nevertheless, none of these hypothesis has thus far gathered enough convincing evidence and in most cases the evidence is conflicting. **Osteoporosis** is an important public health problem both in women and men. On the whole, far more epidemiologic, diagnostic and therapeutic studies have been carried out in women than in men. In clinical practice, if this disease remains underestimated in women, patients' and physicians' awareness is even lower for male osteoporosis, for which diagnostic and therapeutic strategies are at present less defined.

In conclusion this review emphasizes the urgency of basic science and clinical research to increase our understanding of the gender differences of diseases.

Keywords: cancer; cardiovascular diseases; liver diseases; osteoporosis; pharmacology.

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Introduction

Gender medicine is a neglected dimension of medicine with respect to the study of sex influences on pathophysiology, clinical signs, prevention and therapy of diseases. In the last 30 years too many epidemiological and clinical studies reported results in only one sex.

In 1991, B. Healy described Yentle syndrome [1]. Yentl, the 19th-century heroine of Singer's short story, had to disguise herself as a man to attend school and study the Talmud. This Editorial of *New England Journal of Medicine* highlighted the discrimination of women in cardiology: women who were hospitalized for coronary heart diseases underwent fewer major diagnostic and therapeutic

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procedures than men [2, 3]. Those papers were a starting point for good work in the cardiology field. However, other fields of medicine did not improve in the same way. Male research continues to dominate in both animal studies and human clinical trials [4, 5] and an Editorial in *Nature* in 2010 recommended to 'Put gender in the agenda' [6].

Gender medicine is neither the medicine of gender-related diseases nor of diseases prevalent in a gender, mainly related to reproductive functions. Gender-specific medicine needs to focus the attention and efforts of the scientific community on understanding the differences of patho-physiology, clinical signs, prevention and treatment of diseases equally represented in men and women.

In this review we will present data and open questions on different fields of gender medicine in order to highlight the difficulties of clinical practice of the everyday work of a doctor in front of gender disparities in cardiovascular diseases, pharmacology, oncology, liver diseases and osteoporosis.

Cardiovascular diseases

Epidemiology

Coronary heart disease (CHD) is widely perceived to be less of a public health problem for women than for men. However, CHD is the leading killer of women by 65 years of age. Mortality for cardiovascular diseases and in particular for CHD has not decreased in the last 30 years in women as it has in men [7, 8]. The in-hospital mortality of an acute myocardial infarction (AMI) is higher in women than in men up to 70 years of age and survival after 6 months of AMI is lower in women [9]. Clinical trials on prevention and treatment of cardiovascular diseases have been conducted either exclusively in males or in populations with very low numbers of females [10, 11].

Clinical aspects

Women are less likely than men to have typical angina and are more likely to have atypical or non-anginal pain [8]. Thus very often CHD in women is under recognized particularly at younger ages or in patients with diabetes, and the disease is more severe and complicated (AMI, hearth failure, sudden death). Moreover, compared to men women are less likely to undergo cardiac monitoring, enzyme measurement, recovery in coronary care unit, coronary angiography, and revascularization [12].

Coronary angiography in women may show no evidence of atherosclerotic coronary artery disease because of the frequent involvement of microvascular circulation. Far more rarely women can have a Tako Tsubo cardiomiopathy or a coronary dissection [13].

Moreover, women have a higher resting heart rate, longer QT interval, increased risk for drug-induced torsades de pointes (TdP). Women with atrial fibrillation are at high risk of stroke, and they are less like to receive anticoagulation and ablation procedures compared to men. Stroke of any origin is more frequent in women than in men [14, 15].

Risk factors

Many risk factors for CHD and strategy for preventing disease in men are also important for women; however, the magnitude of their effect may differ depending on sex [7, 16–18].

Smoking is associated with a 70% increase in CHD mortality. This risk is similar in men and women, or somewhat more pronounced in women. However, smoking rates are declining more slowly for women than for men. Hypertension has an age-related increase and is more prominent in women [19]. In the Women's Health Study [20] only systolic blood pressure predicts cardiovascular outcomes in women and isolated systolic hypertension, a marker of loss of large-artery elasticity, is more common in women than in men. With the menopause transition low density lipoprotein (LDL) cholesterol increases in women and small dense LDL particles, with greater susceptibility to oxidation, increase. Much of the seminal research on dyslipidemia and CHD has involved middle-aged men and none or very few women. However, in a meta-analysis of observational cohort studies of 86,000 women high level of total and LDL-cholesterol strongly predicted CHD in women [7]. High density lipoprotein (HDL) cholesterol level is associated with CHD in both young and old women. Women with HDL levels under 50 mg/dL experienced a doubling of risk of CHD mortality. Triglycerides may be particularly important coronary risk factors in women, especially in the presence of low HDL cholesterol levels: a meta-analysis found that hypertriglyceridemia was associated with significant risk increase of CHD of 37% and 14% in women and men, respectively (after adjustment for HDL cholesterol and other risk factors) [21]. Higher lipoprotein(a) quintiles are strongly associated with CHD mortality in women. Type 2 diabetes is a potent coronary risk factor in women, increasing their risk of developing or dying from CHD by three- to seven-fold, as compared with a two- to three-fold risk increase in men. Adverse cardiovascular profiles are more common among diabetic

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women than among men [22]. Type 2 diabetes may be associated with greater endothelial dysfunction and inflammation in women than in men and with increase of androgen. Moreover, in women psychosocial factors such as depression, anxiety, and chronic psychosocial stress have adverse effects on heart rate, blood pressure, visceral obesity, endothelial dysfunction, inflammatory activation and may raise CHD risk [7, 17, 18].

Pharmacology

Gender differences in drug pharmacokinetics (PK) and pharmacodynamics (PD) have been recognized to play a key role in drug efficacy and safety profile [23, 24]. Ample evidence suggests that gender can influence several aspects of PK (Table 1) [25].

It has been shown for many cardiovascular drugs that there are important differences in the PK profile including different absorption/bioavailability, volume of distribution, protein binding, metabolism and excretion [23–26]. For example, Greenblatt and von Moltke [27] evaluated the role of gender on the disposition of drugs exclusively metabolized by CYP3A4 including calcium antagonists, opioids and benzodiazepines but not substrates for Pgp. The mean for female/male ratio of clearance was significantly different and 20%–30% higher in young women than young men. These results suggest that gender has a small but significant influence for CYP3A4.

The clinical impact of these differences still remains to be fully addressed. Weight-normalized verapamil clearance (CYP3A4 metabolized but also Pgp substrate/inhibitor) is as much as 50% greater in older women than in older men [28]. Another interesting example is the case of β-blockers. CYP2D6 is particularly relevant in the metabolism of β-blockers, such as metoprolol, timolol and propranolol, and displays an increased activity rate in males compared to females [25]. Gender-related differences in the PK of metoprolol enantiomers result in greater drug exposure in females (greater Cmax and AUC) without gender differences in elimination half-life [29]. Females had a greater reduction in exercise heart rate and systolic blood pressure; however, concentration-effect relationships did not differ between men and women. The differences were the result of gender-specific differences in metoprolol PK [29]. Regarding phase II glucuronidation, some findings support gender differences [30] but not others [31] thus leaving open the question on the involvement of gender in phase II metabolism [25]. Renal excretion is also potentially affected by gender as shown for digoxin clearance that has been reported to be 12%–14% lower in women than in men [25]. Nevertheless, additional investigations on sex differences in renal excretions are requested [24].

While gender-related pharmacodynamic data are limited, evidence suggests that women are more prone to the development of side effects and different pharmacological response to drug treatment that could translate into a different clinical outcome. Examples of the class of cardiovascular drugs that have shown differences between men and women are described below.

Statins

Statins decrease cardiovascular events and all-cause mortality in both women and men. The effect on cardiovascular

Mechanism	Gender-specific differences
General differences	
Lean/fat mass ratio	Lower lean/fat mass ratio in female
Distribution volume	Increased volume for lipophilic drugs in women
Drug binding	Smaller and fluctuating distribution volume in females
	Increased volume for hydrophilic drugs in males
	Hormonal influences on drug binding
Gastrointestinal differences	Longer gastric emptying time in women due to slower motility
	Higher pH
Metabolic differences (phase I)	
CYP	CYP1A2, CYP2E1, CYP2D6 all have higher activity in men
	CYP3A4 higher activity in females (maybe rate limiting step is P-glycoprotein)
Metabolic differences (phase II)	Not enough information available
Excretion differences	Females generally have lower GFR, mostly due to body size
	Active secretion might be reduced in females

Table 1 Gender differences in pharmacokinetics (modified from [25]).

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events is present in both primary and secondary prevention trials [32–34]. These results are in agreement with a similar LDL-cholesterol lowering efficacy achieved by statins in both women and men [32–35].

However, the issue of safety and drug tolerance is particularly important in primary and secondary prevention of CVD, where the risks of long-term therapy must be considered in the context of achievable benefits. Statins are frequently associated with a variety of skeletal muscle complaints including myalgia with or without serum CK elevations, cramps and weakness [36]. Female gender is one of the major risk factors that predispose patients to myopathy [34, 36]. Muscular symptoms were reported in 10% of statin-treated patients and led to discontinuation in 30% of the symptomatic patients [37]. Ho et al. [38] assessed the impact of medication discontinuation 1 month after MI on 12-month mortality. The findings of this study clearly show that patients who discontinue statins are at increased mortality risk. In addition, a significant interaction was found between age and sex, whereby the effect of increasing age on medication therapy discontinuation was greater for women (OR 1.77; 95% CI 1.34–2.34; per 10-year increment) than men (OR 1.23; 95% CI 1.02–1.47; per 10-year increment).

ACE inhibitors/angiotensin receptor blockers

Meta-analysis of the major randomized clinical trials of ACE inhibitors (ACEis) in patients with heart failure (HF) and left ventricular (LV) systolic dysfunction indicate that these agents reduce all-cause mortality in men, Whites, diabetics, and non-diabetics [39]. ACE inhibitors are also effective in women with symptomatic HF, but the data are inconclusive on the value of ACEis in women with asymptomatic LV dysfunction. Side effects of ACEis, i.e., cough, are reported significantly more frequently in the female population [40].

Angiotensin receptor blockers (ARBs) are effective in women and men [25]. Aldosterone antagonists are nowadays used in add-on strategies in the treatment of HF, showing equal effectiveness in women and men [41, 42].

β-Blockers

The classical β-blockers propranolol and metoprolol reach higher plasma concentrations in women than in men [29] that could lead to frequent reports of greater drug toxicity in women [25]. Accordingly, women suffer from increased β-blocker side effects when dosage is not adequately adjusted. A meta-analysis of β-blocker trials enrolling women with clinically stable HF, showed similar and statistically survival benefits in women and men [43]. These findings have been confirmed in another meta-analysis. Five studies on the effects of β-blocker treatment on mortality stratified data by gender. In aggregate, the pooled studies included 2134 women and 7885 men. The data confirmed that women and men with symptomatic HF have reduced mortality when treated with β-blockers [43].

Calcium antagonists

The increased bioavailability and decreased clearance of oral verapamil in women compared to men caused a greater reduction in blood pressure and heart rate in women compared to men [44]. However, another study that examined sex-based pharmacokinetic differences for oral verapamil showed that the reduction in mean arterial blood pressure owing to the drug was closely correlated with its plasma concentration, although without any interaction by sex [28]. Women had a higher response rate and a major decrease in blood pressure with amlodipine, compared with men [45].

Aspirin

The Women Health Initiative (WHS) study involved 39,876 healthy women (aged 45 years or more) that received 100 mg ASA on alternate days or placebo and were monitored for 10 years for a first MACE (non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes). In this trial, the results showed that among women low dose of aspirin lowered the risk of stroke without affecting the risk of myocardial infarction or death from cardiovascular causes, thus leading to a non-significant finding with respect to the primary end point. In a post hoc analysis of women ≥65 years of age, there was a significant reduction in the risk of ischemic stroke and a small reduction in risk of the MI; among women ≤65 years of age, there was no MI benefit and a small benefit in the reduction of stroke risk [24]. In analyses stratified according to sex, combined data on women from the WHS, HOT and PPP indicate that aspirin therapy was associated with a significant 19% reduction in the risk of stroke with no reduction in the risk of myocardial infarction [46]. By contrast, the aggregate data on men from the Physicians' Health Study, the British Doctors' Trial, the Thrombosis

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Prevention Trial, the HOT study, and the Primary Prevention Project indicate that aspirin therapy was associated with a significant 32% reduction in the risk of MI and a non-significant increase in the risk of stroke (RR 1.13) [46].

The gender differences in benefits associated with aspirin may reflect the later onset of CVD in women, the greater proportion of ischemic strokes among women compared with men, the relatively small incidence of MI among women and stroke among men, the gender differences in aspirin metabolism, and the fact that aspirin resistance is more common in women than men [47].

– Representation into phase I–II clinical trial
– Pharmacogenetics/pharmacogenomics variability gender-related
– The prevalence and characteristics in certain types of cancer
– The efficacy/toxicity of chemotherapy drugs and biological targeted therapy
– Diversity-related symptoms and their treatment (e.g., pain)
– Impact of comorbidities
– Impact of cancer on relational, social, and family role and caregiver

Table 2 Gender and cancer: the involved areas.

Antiarrhythmics

Women have a longer corrected QT time than men and suffer from greater QT prolongation on drugs that inhibit potassium inward channels [48]. Consequently, they tend to develop severe arrhythmia more frequently on QT prolonging therapy than men, potentially leading to a fatal arrhythmia known as TdP [25].

Altogether, the present evidence support that differences in PK and PD between sexes should be considered for drug development as well as before starting any therapy.

Cancer

Gender disparity in the incidence of cancer, aggressiveness and disease prognosis has been observed for a variety of cancers [49, 50], but relatively little is known and assessed about the impact of these differences, as it was underlined in the First National Congress on Gender and Cancer in Padua 2011. We can distinguish various aspects ranging from the different representation of women in clinical trials, the efficacy of diversity of anticancer drugs in man and women, the difference in clinical features of some kind of cancer at the same histology and stage (Table 2).

The low representation of women in clinical trials is a crucial point, beginning from animal models, where female guinea pigs make up only 20% of the total of experimental animals. Already in 1977 the Food and Drug Administration excluded women from phase I–II clinical trials. This means that results (in terms of efficacy and toxicity) obtained only in men were transferred to the entire population suffering from the same type of cancer, including women [51]. This aspect is very important for the implications of both difference in drug-related toxicity and efficacy, according to gender. Sex differences in drugs metabolism and PK have long been recognized [52].

Herein, we want to focus on how two major kinds of cancer, colorectal cancer and non-small cell lung cancer (NSCLC), can be influenced by gender variability.

Colorectal carcinoma is the second leading cause of cancer death in both sexes in Europe and in the USA. A retrospective study in over 147,000 patients (SEER data) has shown that colorectal cancer occurs in women on average 5 years later than in men, and has therefore shifted mortality to older females in the population group [53]. For this reason in the female population, it would be more appropriate to extend screening to the over 70 years of age group. Differently from men, women are at a more advanced stage when diagnosed, tumors are mainly located in the right colon, the histology of the cancer is mucinous, grade of differentiation 3, and more frequently colorectal cancer is diagnosed in an urgent/emergency situation [54]. Nevertheless, the survival of female patients is better than that of men. The colorectal cancers arising in women more frequently express microsatellite instability. This feature results in a lower sensitivity to fluoropyrimidines, cornerstone drugs for the treatment of colorectal carcinoma.

Significant differences in the pharmacogenetic basis of toxicity of fluoropyrimidines are found in women, and a lower toxicity is shown by targeted therapies, such as anti-EGFR drugs [55]. All these characteristics influence the choice of cancer treatment and they should be considered for protocols of therapy [i.e., 5-fluoruracil may be replaced by capecitabine, the toxicity of which is not related to the expression of dihydropyrimidine dehydrogenase (*DPD*) gene in women; greater prevention of skin toxicity is required for anti-EGFR therapy]. It is also important to consider the different impact on quality of life for men and women related to surgery for colon rectal cancer due to their diverse sexual apparatus. At the Medical Oncology Unit of the Venetian Oncologic Institute, in collaboration with the Aviano Cancer Institute, the association between

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specific genetic polymorphisms and the development of colorectal cancer was analyzed in a cohort of 2449 subjects (including 1106 patients with colorectal cancer and 1343 controls). This study has highlighted greatly significant gender-related differences in the expression of these polymorphisms [56]. These genetic variations between genders may provide reasons for different risk of age-related colorectal cancer, but may also explain the increase in side effects of chemotherapy in female patients [57]. Further studies are underway to clarify whether polymorphisms differently expressed among men and women can affect prognosis or risk of relapse for colorectal cancer.

As for colon cancer, gender seems to also influence the development of **non-small cell lung cancer** (NSCLC) and the effectiveness of treatments. From 1950 to 1994 the mortality from lung cancer in American women has increased by 500%. Since the 1960s there was a continuous increase of cases of NSCLC in women, and mortality for NSCLC is now higher than breast cancer. Evidence suggests that the development of lung cancer is different in women compared with men. The non-smoking women showed greater propensity to become ill: they in fact run a 2.5-fold higher risk than men to develop lung cancer, usually an adenocarcinoma, and at a younger age, but they respond better to treatment [58]. Smoker women develop greater susceptibility to the damage caused by cigarette smoking, probably related to polymorphisms of glutathione-S-transpherase M1, that play a role in detoxifying environmental carcinogens [59]. Women with lung cancer live longer than men with lung cancer, regardless of therapy and stage.

Gender differences in tumor development are linked to physiological factors, such as hormonal influence, or to behavioral and environmental factors, such as smoking habits, as well as to genetic factors that control the metabolism of carcinogens contained in tobacco.

Mutational analysis also shows that the origin of lung cancer is different between smokers and non-smokers, as it is also different between men and women. Sex seems to influence both the development of lung cancer and the effectiveness of treatments, especially biological ones. Recent studies have shown, in particular, the role of estrogen as a risk factor for NSCLC [60]. Women receiving estrogen replacement therapy show an increased risk of NSCLC and an additive effect to cigarette smoking. In addition, the lung tumor expresses estrogen receptors, and in vitro studies have demonstrated the effect of growth of tumor cells induced by the addition of estrogen in the culture medium. The role of estrogen in the onset of NSCLC has not yet been completely elucidated, but the expression of estrogen receptors defines a subset of NSCLC with distinct features associated with EGFR mutation [60]. In particular, different studies showed that in patients affected by NSCLC treated with EGFR tyrosine kinase inhibitors, female sex is predictive of response [61]. The correlation between estrogen receptor expression and EGFR mutation in NSCLC suggests that it might be important to target both pathways simultaneously for lung cancer chemoprevention and therapy. A recent meta-analysis, that evaluated 39 articles published involving 86,800 patients, confirmed that female gender is an independent prognostic factor in multivariate analysis, correlated with a better prognosis [62]. At the present time we do not have specific therapies/approaches for women with lung cancer. A better understating of the genetic, metabolic and hormonal factors in NSCLC represents a research priority. Future studies should better clarify the differences in genetics, the natural history of NSCLC by gender, and the implications in the choice of treatment.

Female **melanoma** patients generally exhibit significantly longer survival than male patients. In a retrospective study in which 11,774 melanoma cases extracted from the Munich Cancer Registry (Germany) diagnosed between 1978 and 2007 has been evaluated, females were at a lower risk of progression and of metastases. The largest gender difference was a higher than 50% risk reduction of visceral metastases. They also retained a significant survival advantage after the first progression [63]. Women suffer a less aggressive disease with better prognosis and increased survival even at first relapse [64]. Interactions with the immune system and the role of female hormones are currently under study.

Differences by gender have recently been described in thyroid cancer [65], esophageal adenocarcinoma [66], hepatocellular carcinoma [67] and gastric cancer [68]. In these types of tumors, sex-related differences are in part directly related to the presence of hormone receptors or dependent on glucose and lipid metabolism-related hormones. For metastatic gastric cancer, a recent retrospective SERR evaluation showed that gender is a significant independent prognostic factor for overall survival [68]. Another important area of research is the different impact of comorbidities gender-related in patients with cancer [69]. A recent retrospective study reviewed 10 years of hospitalized patients (36,457 female and 50,004 male cancer patients): 5992 females and 8345 males were diagnosed as type 2 diabetes mellitus (DM). Mortality rate of females with type 2 DM was higher than that of males. Type 2 DM increased mortality of cancer patients of both genders, with higher increase in gender-specific than in non-gender-specific cancers [69].

Difference by gender have also been shown in **chemotherapy-related toxicity**. In particular, females

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are more at risk of LVD after anthracycline chemotherapy administered in childhood. In childhood cancer survivors a recent study showed a risk for CVD two-to four-fold greater in females than in males in later years [70]. The reason may be an increased exposure of tissues 'noble' to anthracyclines in women, associated with a high percentage of body fat compared to male. By contrast, the women show increased sensitivity to the protective effect of dexrazoxane.

Another interesting difference by gender is on cancer-related **pain**. Numerous studies reported an increased perception of painful stimuli as well as reduced response to opioids in women [71]. In addition, males and females have different PK and efficacy of analgesics. To achieve the same effect in women with the same intensity of pain, doses of morphine should be increased by 30% [72]. Despite this, usually women receive lower dose of opioids than males with the same intensity of pain. The emotional state seems to correlate more with the intensity of pain in male than female [73].

In conclusion, gender differences, even if partially known, are deeply underestimated in clinical practice for the treatment of the main types of cancer. It is necessary to encode and improve the knowledge about tumor variability based on gender differences, in order to identify all the variables that can influence prognosis, choice of treatment and possible related toxicities.

We hope that the new oncological drugs consider gender as one of the possible variants, both in terms of efficacy and toxicity. It is also important to orient new clinical trials taking into account the gender diversity currently known. Nowadays, it is necessary to open a new era of studies and evaluations of gender differences, which may lead to better understanding and treating cancer patients.

Liver disease

Clinical data suggest that men and women exhibit differences regarding the epidemiology and the progression of certain liver diseases such as autoimmune conditions, genetic hemochromatosis, non-alcoholic steatohepatitis and chronic hepatitis C. The best example for gender differences is primary biliary cirrhosis (PBC) which is a progressive autoimmune liver disease, characterized by a very specific immunologic hallmark, i.e., antimitochondrial antibody (AMA) [74]. PBC manifests a female preponderance (10:1); numerous hypotheses have been formulated based on intuitive scientific backgrounds to justify this sex imbalance including the effects of sex hormones in lymphocyte maturation/activation and the synthesis of antibodies and cytokines, the immune-modulatory effects of estrogens during the reproductive life, fetal microchimerism, a skewing of the X-chromosome inactivation pattern, and defects in sex-chromosome [75]. Nevertheless, none of these hypotheses has thus far gathered enough convincing evidence and in most cases are conflicting with the X-chromosome vulnerability. Why not men in PBC? Up until now, this question has been one of the most fascinating mysteries waiting to be solved in medicine. However, at least three examples should be pinpointed to address the issue of gender differences in liver diseases: iron overload, non-alcoholic fatty liver disease, and chronic hepatitis C.

Iron overload

Genetic hemochromatosis is a common genetic disturbance caused by several genetic variants; the main cause is mutations in the *HFE* gene. GH is not a gender-specific disease, but its prevalence is higher in males than in females; generally the onset of the disease is usually later in females than in males, probably due to the protective effect of the menstrual period. Usually, clinical symptoms of iron overload are more frequent in males than in females, in particular, as hemochromatosis affects the hypothalamic-pituitary axis, symptoms of hypogonadism can be more evident in men, including erectile dysfunction, loss of secondary sexual characters, and infertility [76].

Interestingly, the main mutation of HFE, the C282Y, inhibits the heterodimer formation of HFE with the β_2 microglobulin chain. In contrast with humans, mice deficient in β_2 microglobulin expression exhibit lesser hepatic iron overload than females with the same deficiency [77]. As female laboratory mice do not experience menstrual bleeding, it should be hypothesized that a protective effect of Y chromosome or hormonal differences could explain the gender differences in mice [77].

Non-alcoholic fatty liver disease (NAFLD)

NAFLD is the main cause of increased aminotransferase levels in adults [78]. It is an emerging condition including a wide spectrum of liver diseases ranging from pure fatty liver to non-alcoholis steatohepatitis (NASH) which eventually progress to liver cirrhosis and hepatocellular carcinoma (HCC) [79]. NAFLD is actually considered the hepatic

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expression of the metabolic syndrome. Data collected from epidemiological studies show that NAFLD is more prevalent in men than in women. A cross-sectional multicenter study from Spain found a prevalence of fatty liver in 25.8% of men and in 20.3% in females [80]. Interestingly, in the POLISTENA Italian study which enrolled unselected consecutive subjects referred by GPs for evaluation of a 'bright liver' at ultrasound [81] the mean age of males with fatty liver was 43.3±1.2 years versus 56.5±1.1 in women. Carulli et al. [81] speculated that the circulating levels of estrogens might be responsible for a protective effect on the development of hepatic steatosis. These figures contrast with a recent paper in which the prevalence of NAFLD was explored in 1170 community-based adolescents in the Western Australian Pregnancy cohort [82]. Females compared with males had a significantly higher prevalence of NAFLD (16.3% vs. 10.1%, p=0.004). In this study, the gender differences in NAFLD prevalence were associated with significant differences in adipose distribution and metabolic parameters, including adipocytokine levels. Substantially, interactions between sex hormones, adipocytokines, insulin resistance, and adipose distribution may explain the differences in the gender-specific differences of NAFLD. It is also possible that bad nutritional habits can be acquired in young life, and then males, more than females, may develop additional risk factors for liver disease, e.g., an excessive alcohol intake.

Another interesting observation is that fatty liver is more prevalent in middle age and in early geriatric age, whereas there is a trend in decreasing prevalence in very old subjects. This trend has been observed by Frith et al. in Northern England [83], although in the English study only a few subjects above 75 years of age were enrolled. One explanation may be that old subjects with fatty liver may be exposed to a high co-morbidity for cardiovascular events which can lead to an increased mortality early in geriatric life.

Chronic hepatitis C

Hepatitis C (HCV) infection is the main cause of chronic liver disease, especially cirrhosis and hepatocellular carcinoma, and a leading reason for liver transplantation in industrialized countries. There is an interesting observation reported by the European Pediatric HCV network from a multicenter prospective study of HCV-infected pregnant women and their infants [84]. In this study girls were twice as likely to be infected as boys. This sex association is an intriguing finding that probably reflects biological differences in susceptibility or response to infections. However, when HCV infection is acquired in young people through the route of needle injections, still females experience a higher risk for acquiring HCV infection compared to males. In fact, in a study performed in 584 males and 260 injection drug users females in San Francisco, the females were more likely than males to share needles and equipment [85].

Current data suggest that long-term benefits of estrogen exposure (premenopausal women) have a slow progression in liver fibrosis. In an interesting study involving 376 women who had been infected with HCV 17 years earlier, almost all women had histological evidence of inflammation, but only about 50% had some degree of fibrosis and only 2% had probable definite cirrhosis [86]. Moreover, the histological progression of liver fibrosis was assessed in a cohort of 2235 HCV-positive French patients [87]. The results of this study demonstrated that three independent factors were associated with an increased rate of fibrosis progression: age at infection older than 40 years, daily alcohol consumption of 50 g or more and male sex [87]. The reduced rate of fibrosis among women disappears after menopause; in fact, post-menopausal women have accelerated progression of fibrosis compared with men that is slowed by long-term estrogen exposure with hormone replacement therapy [88]. The fertile age is indeed a crucial point when a female patient with chronic hepatitis C is treated with antiviral therapy. The sustained virological response (SVR) rate is significantly higher in women than in men, and women in fertile age with easy genotypes have a 100% chance of obtaining a SVR [89]. Data from another Italian study strongly suggest that early menopause is associated with a low likelihood of SVR, probably because of inflammatory factors that change at menopause [90]. Another explanation for the high rate of SVR in female patients in fertile age may be the effect of the depletion of iron as a result of menstruation. This is an interesting but not completely explored field. It is well known that iron accumulation negatively affects the SVR rate in HCV-positive patients treated with combination therapy [91]. Thus, menstruation can play an important role in reducing the toxic effect of iron accumulation.

Bone metabolism and osteoporosis

Osteoporosis

Osteoporosis is defined as a skeletal disease characterized by low bone mass and microarchitectural deterioration, resulting in bone fragility and susceptibility to fracture. In clinical practice, osteoporosis is diagnosed if bone mineral density (BMD) is at least >2.5 SDs (T-scores) below

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the mean peak BMD of young healthy adults. However, many patients with fractures do not have osteoporosis in terms of BMD, and BMD alone cannot capture other components that contribute to fracture risk. Therefore, a more appropriate definition of osteoporosis is a disease characterized by decreased bone strength in general, resulting in an increased risk of fractures. Consequently, for clinical purposes, some algorithms, like FRAX, have been developed to better assess fracture probability based on the combination of BMD testing with clinical risk factors for fracture [92].

Fractures

The burden of fractures in adults increases with age. The estimated number of hip fractures will increase worldwide from 1.7 million in 1990 to 6.3 million in 2050, mostly in Asia, the US and Europe. The estimated incidence of fractures worldwide in the year 2000 was nearly 9 million, with a similar female-to-male ratio. Interestingly, several recent studies, carried out in different Western countries, seem to show that a trend toward a possible decrease in hip fracture incidence is becoming evident [93].

Disability and mortality

Hip fracture is associated with an excess mortality of 10%–20% in the first year, with mortality being maximum with the first 6 months and decreasing thereafter. Of those who survive, half experience significant and permanent degrees of self-insufficiency. Vertebral fractures increase mortality as well, which is not confined in the first year after the event, but rather extends far beyond. In addition, once a fracture has occurred, the risk for future fractures is doubled even in the very short-term. The socioeconomic costs of osteoporosis and fractures are high and are expected to increase remarkably over the next decades due to increasing life expectancy. In a study in Sweden in 1996, more hospital bed days were due to osteoporotic fracture than to breast and prostate cancer combined, also approaching the number of bed days due to ischemic heart disease and stroke.

Differences by gender

Epidemiology of fractures

Several epidemiologic studies have been carried out to assess fracture incidence and prevalence in men and women. However, while hip fracture incidence has been extensively studied in both sexes, non-vertebral fracture incidence is poorly documented in men, in spite of the marked contribution of these fractures to the general burden of osteoporosis. Fracture prevalence and incidence differ between the sexes and, in addition, these differences are age-dependent. Boys and young men tend to sustain far more fractures than girls and young women, because of the more common incidence of high-trauma fractures in males at these ages. Thereafter, fracture incidence starts to increase earlier in women than in men. In adulthood, fracture risk in women increases from 40 years of age onward, and after the age of 50 years, hip and vertebral fractures increase exponentially. In men, vertebral fracture risk increases after 50 years of age and hip fracture risk increases after 65 years of age. In adulthood, lifetime risk of any fracture is two to three times higher in females than in males. For example, at age 50, lifetime risk is approximately 50% in women and 20% in men and at age 70 is 11% in men and 37% in women. After the age of 50 years, the incidence of vertebral fractures in men is about one third to one half of that in women [94].

Fractures outcome

Mortality rates after hip fracture are higher in men than in women. During hospital stay after hip fracture, mortality is two-fold higher in men than in women (approx. 10% vs. 5%) and after 1 year, mortality rates may reach 30%–48% in men as compared with 18%–25% in women. This difference is mainly due to pre-fracture comorbidity status, which is in general worse in men than in women [94]. Few data are available to compare disability rates in men and women after fractures. However, due to the higher morbidity of men sustaining a fracture, it seems likely that a full health status recovery is more common in women than in men after hip fracture.

Risk factors for fractures

Fractures may arise from several factors, among which bone strength and additional clinical conditions, such as neuromuscular ability and fall propensity play a key role. BMD is a very strong determinant of fracture risk both in men and women. However, the pattern of use of bone densitometry differs in men as compared to women, BMD testing being used at least four-fold more in women than in men [95, 96]. This clearly suggests

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a gender-specific lack of awareness for osteoporosis being a largely under diagnosed disease in men. Structural differences exist between men and women in bone growth, catabolism and size. Men have bigger bones than women and these larger dimensions are responsible for increased resistance to breaking forces. In addition, aging men have more periosteal apposition, less cortical porosity and endocortical resorption than aging women do. All these changes are responsible for increased bone strength in aging men. Moreover, older community-dwelling women experience significantly more falls than older men [97]. Even after correcting for physical and social factors, women are 1.5-fold more likely to fall than men are.

Pathogenesis

Estrogens have several well-documented protective effects on bone in women; the reduction in their synthesis after the menopause increases bone remodeling that, together with the age-dependent imbalance between formation and resorption, reduces bone density and strength. In men, androgen levels do not show the same pattern of rapid fall in middle-age, but rather tend to progressively decrease with age and testosterone deficiency is only variably present in older men. Moreover, the role of aging associated gonadal insufficiency has not been unequivocally documented in the pathogenesis of male osteoporosis, in which estrogen deficiency seems to be relevant as well. Secondary osteoporosis is far more common in men than in women, accounting for approximately 50% of all cases. Glucocorticoid use, excessive alcohol consumption, smoking and drug-associated androgen deprivation for prostate cancer are the more frequent pathogenetic factors [94]. Idiopathic hypercalciuria has also been reported in up to 20% of males with osteoporosis.

Treatment

Several drugs have been studied for the prevention of vertebral, non-vertebral and hip fractures in women [98]. The bisphosphonates alendronate, risedronate and zoledronic acid, as well as denosumab, a RANK-ligand inhibitor, all reduce the risk of these three types of fractures by 30%–65%. Ibandronate, strontium ranelate and teriparatide seem to act only on vertebral and non-vertebral fractures, while the SERMs raloxifene and bazedoxifene and PTH 1–84 act on vertebral fracture risk. In contrast, very few data are available for pharmacologic fracture prevention in males. Relatively small studies on alendronate, risedronate, calcitonin and teriparatide variably demonstrated some effects in reducing vertebral and hip fractures. However, few of these studies have been designed to specifically demonstrate fracture prevention. In clinical practice the pattern of treatment significantly differs between the sexes. Indeed, if most osteoporotic women are not currently treated for their disease, several findings indicate that the proportion of osteoporotic men undergoing therapy does not reach 1% [99]. In conclusion, osteoporosis is an important public health problem both in women and men. On the whole, far more epidemiologic, diagnostic and therapeutic data are currently available for women. In clinical practice, if this disease remains underestimated in women, patients' and physicians' awareness is even lower for male osteoporosis.

Final conclusion

In this review we focussed the attention on five very relevant fields of medicine for the everyday clinical work of a doctor and for the basic scientist. During the last decades, clinical trials and research in animal models have been gender unbalanced. Gender-specific medicine needs to reconstruct an equilibrium in order to understand how different clinical signs, diagnostic procedures and therapeutic needs of diseases are in men and women. This new dimension of medicine needs new investment in research but also reorganization of medical teaching and health policy.

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Annarosa Floreani is an Associated Professor of Gastroenterology at the University of Padua, Italy. Professor Floreani graduated in Medicine from the University of Padua in 1976. In 1979 she obtained the Specialization in Geriatrics, and in 1983 the Specialization in Gastroenteronterology from the University of Padua. She was Research Associate at the Liver Unit of Newcastle upon Tyne, UK in 1986, Assistant Professor in Gastroenterology at the University of Padua from 1980 to 2000, and since 2000 has been an Associate Professor in Gastroenterology. She was Visiting Professor at the University of Newcastle upon Tyne between 1979 and 2000. Over the last 20 years the focus of her research group has been chronic cholestasis, liver disease in the elderly, in particular, hepatitis C virus infection, and liver disease in pregnancy, supported by grant funding from University of Padua and the Ministry of Education. She is the Director of a Master's course in Hepatology and Biliary Disease System, University of Padua. She has been the beneficiary of several honors, scholarships and fellowships. She has authored or co-authored 152 peer reviewed publications (total IF=706.099), 10 book chapters, and has delivered over 200 invited lectures. Professor Floreani is a reviewer for several scientific journals including *Hepatology, Lancet, Gut, American Journal of Gastroenterology, Alimentary Pharmacology and Therapeutics, Digestive Liver Disease, European Journal of Epidemiology, British Journal of Obstetrics and Gynaecology, Liver International, European Journal of Gastroenterology and Hepatology, Journal of Viral Hepatitis,* and *Molecular Biology Reports.* Additionally, she is a member of several academic societies, including the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of Liver Diseases (EASL), the Italian Association for the Study of Liver Diseases (AISF).

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Dr. Sandro Giannini is an Assistant Professor of Internal Medicine at the University Hospital of Padova, Italy. He graduated in Medicine from Padova University in 1984. He was on the Board in Nephrology in 1988 and Internal Medicine in 1996. He was also awarded a Ph.D. in Pathophysiology of Metabolic Bone Diseases and Calcium-Phosphate Equilibrium in 1991 from the University of Parma, Italy. Currently, he works at Padova University Hospital as an Assitant Professor in Internal Medicine and is Chief of the Regional Center for Osteoporosis and Metabolic Bone Diseases. His main research interest is dealing with skeletal and calcium metabolism. In particular, he is involved in several studies on skeletal and non-skeletal effects of vitamin D, on mesenchimal stem cell differentiation toward osteoblastic lineage and post-transplantation bone disease. He is author or co-author of more than 150 peer-reviewed publications, including original papers, reviews and book chapters. He serves as a reviewer of several international journals involved in bone metabolism research.

Dr. Vittorina Zagonel is Chief of the 1st Medical Oncology Unit at the Istituto Oncologico Veneto, IRCCS, in Padua. Dr. Zagonel took her degree in Medicine at the University of Padua cum laude in 1978. She specialized in Oncology at the University of Padua in 1981 and in Clinical Hematology at the University of Bologna in 1985. From 1983 to 1989 she was an Associated Director in the Medical Oncology Unit of Aviano Cancer Center; from 1990 to 1999 she was the Medical Director of the Hematology Unit, Department of Oncology, Aviano Cancer Center; from 2000 to 2009 she was Chief of the Oncology Unit and of the Department of Oncology 'S.G. Calibita' Hospital, Tiberin Island, Rome and from 2009 to the present she has been Chief of the 1st Medical Oncology Unit, Istituto Oncologico Veneto, IRCCS, Padua. She coordinates several clinical trials aimed at optimizing the treatment of hematologic malignancies in the elderly, and to developing new strategies to prevent treatment-related toxicity. She has participated at several international and national cooperative trials in GCP, particularly for colon cancer, breast, lymphomas, lung and ovary carcinoma. Dr. Vittorina Zagonel has authored or co-authored 175 papers on international scientific journals (H index 36), of 32 book chapters, three books and 385 congress abstracts.

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