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LETTER TO THE EDITOR

Sex-based differences in nuclear medicine imaging and therapy

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Dear Sir,

Sex-based differences in diseases are those related to biological and physiological factors (chromosomes, gonads, and hormones). Gender-based differences are those related to sociocultural, behavioural, and psychological factors. Sex-based differences affect the kinetics of drugs, the natural behaviour of a disease, prognosis, treatment response, and outcome in management. To realize optimal healthcare, a sex and gender approach needs to be integrated in all lines of health research and clinical practice. An important domain in healthcare is medical imaging. Molecular imaging, a fast-growing field, is able to visualize biological characteristics of diseases and molecular features of a disease can be noninvasively assessed with novel imaging technology. In the field of nuclear medicine, radiolabelled pharmaceuticals are used to specifically image and quantify the uptake and binding of metabolism of the pharmaceutical compound. It provides effective tools for precision medicine particularly with positron emission tomography (PET) and radioligand therapy.

The nuclear medicine practice should be approached as sex-based medicine, particularly in the management of specific diseases and when a practitioner wants to apply personalized interventions, targeted therapies, and individualized preventions. Several sex-based factors in nuclear imaging and radionuclide therapy may influence the image quality and quantitative measurements, the kinetic behaviour of radiopharmaceuticals, and dosimetry.

Preclinical, radiopharmacy, and kinetics

From preclinical data, we know that sex difference influences the finding on PET imaging. For example, preclinical PET studies with [^{18}F]atorvastatin demonstrated faster and higher hepatic uptake and clearance in female compared to male rats, probably due to higher efficiency for exchange between arterial blood and hepatic tissue [1] (Fig. 1).

Data in mice indicate that sex differences in myocardial perfusion are primarily driven by testosterone [2]. Radiopharmaceuticals for drug research with respect to sex-type may, therefore, differ. Most radiolabelled pharmaceuticals are exogenous intravenously administered compounds that are subject to distribution, metabolization, and excretion. The organs responsible for these kinetic processes are all subject to sex hormones [3]. Most importantly, sex differences in physiological characteristics (e.g., body mass index, muscle mass) influence the distribution of radiolabelled pharmaceuticals throughout the body, sex differences in metabolizing enzymes (CYP450) effect clearance, while differences in renal function lead to altered excretion characteristics of radiolabelled pharmaceuticals. As such, the kinetic behaviour, i.e., the concentration–time profile and thus radioactivity-time profile of radiolabelled pharmaceuticals, will differ based on sex. For instance, the dose-limiting organ for toxicity during peptide radioreceptor therapy (PRRT) is the kidney [4, 5]. Preclinical data suggest

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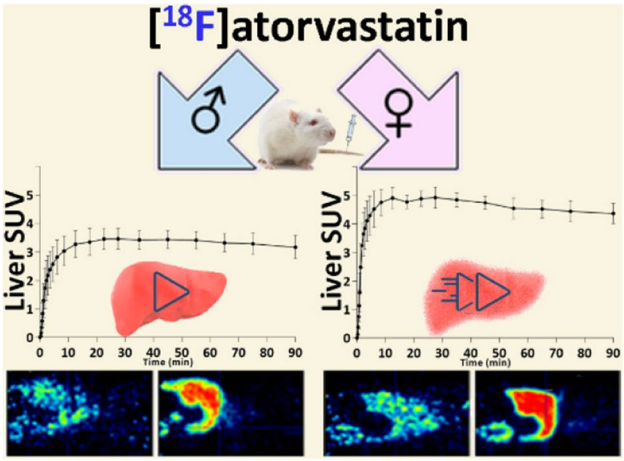

Fig. 1 [^{18}F]Atorvastatin PET showed faster pharmacokinetics in female rats compared to males, which may be related to higher exchange between arterial blood and hepatic tissue. With permission (1): *Mol Pharm* 2021;18(9):3378–3386

that both male rats and mice presented an increasing renal uptake of different peptides. However, while renal uptake of [^{111}In-DTPA]octreotide in rats showed no sex-based difference with constant renal uptake over time, female mice presented significantly higher renal uptake than males, rapidly decreasing over time with a different localization pattern [6]. Patient-specific dosimetry are able to improve therapeutic efficacy by optimizing effective tumour absorbed dose while limiting treatment-related radiotoxicity [4, 7], taking in account that male sex seems to be associated with shorter progression-free survival following PRRT retreatment [8]. This may very well require an alternative optimal dose, time of scanning, or sampling regimens, both in healthcare and in clinical research.

Dosimetry, size, and sex-type

In the last decade, more and more information has become available about the importance of accurate and patient-specific dosimetry. Since the late 1970s, simplified population-based anatomical models of average human have been used to conduct organ-level dosimetry during diagnostic imaging using ionizing radiation or radionuclide therapy. These models are continuously developed and maintained by the International Commissions on Radiation Protection (ICRP). Their accuracy and complexity are ultimately limited by three factors: image quality of diagnostic imaging modalities, detection efficiency of the measurement equipment (e.g., PET or SPECT cameras), and computational limits at the time. With the natural development of imaging technology and computing power, more previously unknown factors are revealed. For example, we now know that anatomical

Table 1 Reference values of height, mass, and surface area of the total body, used for 89 phantoms (ICRP 2002) (11)

Age	Height (cm)		Mass (kg)	
	Male	Female	Male	Female
New-born	51	51	3.5	3.5
1 year	76	76	10	10
5 years	109	109	19	19
10 years	138	138	32	32
15 years	167	161	56	53
Adult	176	163	73	60

variation, even within one sex and age group, can cause 20 to 60% difference in the calculated effective dose [9]. In contrast, the very first dosimetry model [10] did not even include differentiation based on size or sex-type between the patients.

Since the 1990s, simplified voxelized phantoms are used to represent the fundamental differences at the population level between a "typical" male and female adult, children at different stages of growth (e.g., new-born, 5, 10, 15 years), and a pregnant female [11, 12]. Initially, this represented a huge leap forward in radiation dosimetry, allowing the recording of realistic anatomical features and relevant reproductive organs. On a negative point, these models cannot be flexibly adjusted to reflect patient-specific size or, rarely, anatomical variations. The population-based (Table 1) "average human" also often corresponds very poorly to the actual size of the local population, especially in Asia. Additionally, while organ size and mass are specified in an ICRP reference phantoms, organ shape, depth, and position within the body are not defined by reference values.

Since the early 2000s [13], hybrid mesh–based phantoms have been increasingly developed, allowing extensive anatomical complexity and patient-specific dimensions to be incorporated into any sex-type category. Depending on a specific patient's BMI and international size percentile, one of nine size-specific male or female patients can be selected. Using these hybrid mesh phantoms, it was illustrated that the calculation of the effective dose of patients falling below the 10th or above the 90th percentile deviated 40% from the reference "average" patient [14] (within one sex category), clearly illustrating the high importance of personalized dose calculations.

Last but not least, the continuous advancements in artificial intelligence create more and more opportunities in nuclear medicine. Alternative algorithms for image reconstruction, artifact, attenuation and scatter correction, and more extensive dosimetry and quantitative analysis become possible [15, 16]. At the same time, with the increasing availability and understanding of AI technology, we are also discovering multiple unintended biases related to race

and sex that these algorithms can contain. Multiple studies [17, 18] have clearly shown that training deep learning or machine learning models based on sex- or race-unbalanced datasets often leads to unintentional, but even greater, discrepancies between these groups. Therefore, bias mitigation strategies should become a new standard as we move forward with the implementation of AI in the everyday practice of nuclear medicine [19, 20].

Clinical considerations

In the clinical setting, difference in amygdalar activity due to sex-type reveals that women are presenting a different pattern of cardiovascular disease than men, with higher prevalence of non-obstructive causes of (stress-related) ischemia [21]. Previous literature confirms this, including higher incidence of stress (Takotsubo) cardiomyopathy in women, a higher rate of ischemic responses to mental stress in female patients, and a significant increase in events according to higher psychosocial distress in women, forcing us to focus with particular attention to cardiovascular disease in women [22–24], due to crosstalk between the heart and brain [25]. A recent review paper of Makail and colleagues summarized major female characteristics in pathophysiology and clinical presentation of the most frequent cardiovascular conditions and discuss the limitations of cardiac imaging in women [26]. It was stated that despite shared imaging features and strategies between both sexes, there are critical sex disparities that need careful consideration, related to the selection of the most optimal imaging techniques, to technical limitations, and to specific diseases that are overrepresented in the female population. Potential specific diagnostic flowcharts for cardiovascular imaging in women are recently described in literature [27].

Furthermore, for the imaging specialist who often has to perform oncological staging and treatment response monitoring scans, it is relevant to realize that both the localization of metastatic tumour sites and the efficacy of immunotherapy can be sex-dependent.

There is also growing evidence that sex-driven dimorphism in immune functions and responses exist, which can show differences between men and women in autoimmune diseases and response to infectious agents. Such sex-related immune dimorphism also influences the efficacy of immune checkpoint inhibitors. Data from 20 randomised trials, performed on over 11,000 patients with different types of advanced cancers, showed that treatment with immune checkpoint inhibitors is significantly more effective in male than in female patients [28].

Concerning metastatic sides, a nationwide Swedish cancer registry study performed in 17,431 deceased lung cancer patients found that women (43% vs. 35%) more frequently showed nervous system metastases [29]. Another nationwide study from the Dutch cancer registry performed in 806 patients with umbilical metastases found that in male patients these metastases most frequently originated from the colon in 43.8% and in female patients from the ovaries (38.8%) [30].

Women also have a higher rate of radiation-induced side effects such as mucositis, dermatitis, presence of thrush in head and neck cancer, and radiation-induced coronary artery disease (CAD)–related cardiovascular events/mortality and all-cause mortality compared to men among radiation-treated patients with Hodgkin's lymphoma [31], suggesting the need for specific vigilant screening program for CAD among cancer patients and survivors who have received mediastinal radiation as suggested by the recent European Society of Cardiology (ESC) guidelines and EANM recommendations on cardio-oncology [32, 33]. Women are often underrepresented in clinical trials and are less participating due to factors such as contraceptive restrictions, resulting in the majority of subjects in randomised controlled trials being male [34, 35]. To date, literature is lacking regarding randomised controlled trials specifically designed to examine sex differences in radionuclide therapy. Currently, available evidence is based on observational studies or post hoc analyses from clinical trials.

In summary, there is a strong need for imaging guidelines that are tailored to sex-type differences. Some attempts have been made in this direction, but substantial knowledge gaps still exist. Future imaging recommendations require the integration of sex-type as an algorithm-modifying variable. In the final step of precision medicine, sex-type and disparities will be crucial to provide the best possible healthcare.

Data Availability No original data was used in this editorial.

Declarations

Studies with human participants or animals This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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