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The Journal of
Bone and Mineral Research

ISSN 3064-6979

Case Report

Factors Influencing Drug Metabolism

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Abstract

Efficacy of drugs depends on many factors; the most concerning one is gender-based drug metabolism. The metabolic differences found within a species are believed to be due to variations in age, sex, genetics and diseases. The male and female bodies behave differently when it comes to the manifestations and treatments of various diseases. Therefore, some conditions are more favourable in women than in men, and vice-versa for drug metabolism. For decades, drug trials were performed almost exclusively on men. Women were eliminated for drug trails because of every month they undergo menstrual cycle, occasionally become pregnant, during these periods their physiology and endocrinology change.

Keywords : Biological factors, sexual dimorphism, menstrual cycle, pregnancy, hormonal changes, change in composition of microbiota.

INTRODUCTION

Many drugs can lead to more serious health risks rather treating the disease for which it was prescribed. It can alter a person's thinking and judgment, including addiction, infectious disease, and adverse effects on pregnancy. Therefore, drug metabolic studies are carried out to determine drug safety and effectiveness (1). There are many factors involved in drug metabolism, starting from genetics to the environment.

BIOLOGICAL FACTORS AFFECTING METABOLISM

To understand how to optimize the use of drugs in order to minimize therapeutic adverse effects and enhance therapeutic potentials, both can be achieved by understanding the pharmacokinetics and pharmacodynamics in the diverse populations in which the drugs use is intended. The metabolic differences found within a species are believed to be due to variations in age, sex, genetics and diseases. Since, men and women have several biological differences, and their systems react differently to certain chemicals and stimuli. The male and female bodies behave differently when it comes to the manifestations and treatments of various diseases. These differences are due to biological and genetic reasons. For example, Sex chromosome genes and sex hormones, including estrogens, progesterone and androgens, contribute to the differential regulation of drug metabolism. Therefore, some conditions are more common in women than in men, and vice-versa (2). The female body metabolizes and responds to medications differently than the male body due to various physiological and hormonal differences. Some sex related differences in the metabolism of anxiolytics, hypnotics and a number of other drugs have been observed (3)

Earlier, for decades, drug trials were performed almost exclusively on men. In some cases, most research was performed on male subjects, leading to a misunderstanding of how women would react to certain types of medication. It is only recently that medical science started paying attention to the different reactions men and women have to certain types of medication. Medicines can affect and metabolize differently in the female body compared to the male body due to various physiological and hormonal differences, more so, at different physiological conditions in the same individual (4). Individual variability for drug response is a major cause of adverse drug reactions and prolonged therapy resulting in a substantial health problem (5). There are several reasons why men and women have different reactions to certain types of medications:

1. Physical size and anatomy: Even though women are often physically smaller than men, they receive the same dosage. This means that they have a higher concentration of the medicine in their body, which could explain the differences

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Email: pdg2000@hotmail.com.
Received: 02-June-2025, Manuscript No. TJOBMR - 4912 **; Editor Assigned:** 05-June-2025 **; Reviewed:** 16-July-2025, QC No.TJOBMR - 4912 **;**
Published: 21-July-2025.
Citation: P D Gupta. Factors Influencing Drug Metabolism. The Journal of Bone and Mineral Research. 2025 July; 12(1).
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in how the body reacts to it. At the same time, anatomical differences between genders can lead to increased sensitivity to certain types of medication in women (6).

2. Differences in how the body processes medication: Our kidneys play a vital role in clearing toxins and other waste products from the blood and excreting them through urine. This process, known as kidney detoxification, helps maintain the body's fluid and electrolyte balance. Both men and women rely on their kidneys for detoxification purposes. Glomerular filtration rate (GFR) in women tends to have a lower GFR than men, which can affect the elimination of medications that are primarily excreted by the kidneys. It is important to note that there is limited research on sex-based variations in kidney detoxification. However, it is believed that the overall process is similar between genders. The main differences may lie in the hormonal and metabolic factors that could potentially affect kidney function. Additionally, enzymes in the stomach lining and the liver,"P450" that also helps remove excess medicine in the body, behave differently in men and women (7) Women tend to have lower activity of certain cytochrome P450 enzymes, which can affect the metabolism of medications(8).

3. Stomach acidity levels: The digestive system in men and women works differently; so medication taken orally can affect each gender differently. In women, stomach acidity is lower than in men, leading to a slower emptying process. This means that the active ingredients in the medicine absorb in the stomach for longer periods, which affects women more than men.

4.Gastrointestinal Differences: Women may have higher activity of glucuronyltransferase enzymes, which can influence the metabolism of medications that undergo glucuronidation (9). Women tend to have slower gastric emptying than men, which can affect the absorption of medications and hormonal fluctuations during the menstrual cycle can influence intestinal motility and medication absorption (10).

The body fat percentage women have a higher percentage of body fat than men, which can affect the distribution and metabolism of lipophilic (fat-soluble) medications. More so, women tend to have a higher percentage of body water than men, which can influence the volume of distribution of water-soluble medications (11).

While both genders experience adverse effects from drugs and medications, it seems that women more often see a more severe side of this. In the case of drug dependency, this can become incredibly dangerous as the dependency leads to addiction. When certain drugs are more effective, higher doses quickly become more lethal. This appears to be doubled the case for women.

Hormones specifically can also greatly influence how a drug is metabolized. Because women hormones fluctuate during the menstruation cycle or menopause, during they can often experience different reactions than men to certain types of drugs. Due to different hormonal milieu women undergo menstrual cycles and pregnancies, that may be the reasons that women were prevented from participating during the study. This also led to neglect in studying the effects of medicine on women during their menstrual cycle. Estrogen and progesterone: Fluctuations in estrogen and progesterone levels throughout the menstrual cycle and during pregnancy can affect drug metabolism and efficacy. Pregnant women will also exhibit changes in the rate of metabolism of some drugs. These differences in enzyme concentration and activity result in individuals exhibiting different metabolic rates and, in some cases, different pharmacological responses for the same drug(12) in humans, aiming to find better ways to prevent, screen, diagnose, or treat diseases.

Illnesses that affect both genders are still studied on male subjects, and most experimental drugs are tested on men (13, 14). The emergence of gender-based medicine occurred during the 1970s, but only during the 90s were these issues discussed in a wider forum. When it came to conditions that were considered "women only", such as breast cancer and osteoporosis, men were not included as test subjects (15). The result was that it became much harder to diagnose these conditions in men, despite the fact that they do appear in them, as well as providing appropriate treatment for each gender. At this time, medical science is finally aware of the different effects medication has on men and women.

Males and females differ in their immunological responses to foreign and self-antigens and show distinctions in innate and adaptive immune responses. Certain immunological sex differences are present throughout life, whereas others are only apparent after puberty and before reproductive senescence, suggesting that both genes and hormones are involved.

Environmental factors, including nutrition status and the composition of the microbiome, also alter the development and functioning of the immune system differently in males and females (16-18). Oftentimes, the extreme cases of gender bias show a lack of women involved in drug trials and drug studies. This has damaging effects for a variety of reasons. A major reason is a lack of understanding of how drugs may affect women differently from men.

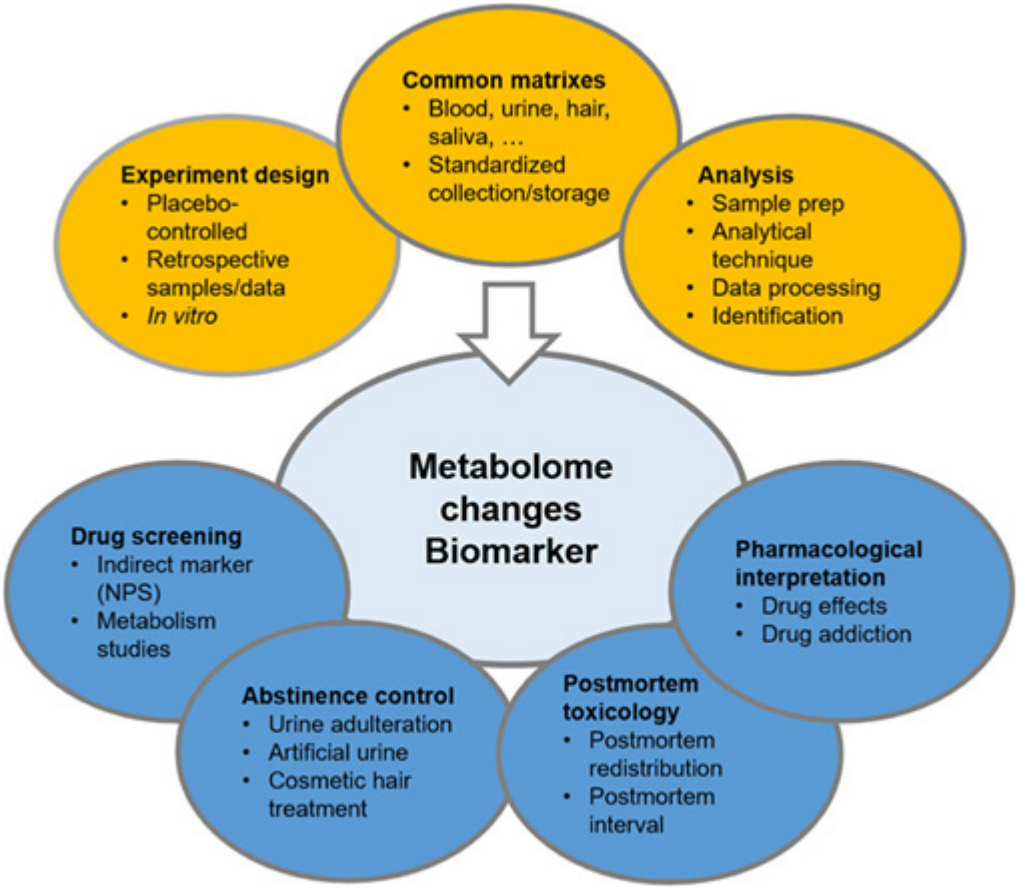
MICROBIOTA COMPOSITION

Recent research uncovers the involvement of gut microbiota in the metabolism of numerous pharmaceutical drugs. The human gut microbiota harbours 10–100 trillion symbiotic gut microbial bacteria that use drugs as substrates for enzymatic processes to alter host metabolism. More so, males and females are known to have gender-specific differences in their immune system and gut microbiota composition (19).

Thus, microbiota-mediated drug metabolism becomes more

complicated and can change the conventional drug action course completely and cause inter-individual differences in efficacy and toxicity (**Fig.1**), making it vital for drug discovery and development (20).

Figure 1. Microbiota changes biomarkers also due to the factors described.



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