Unveiling gender differences in caffeine metabolism and its long-term cardiovascular and neurological impact

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ABSTRACT

Introduction: Caffeine is one of the most widely consumed psychoactive substances globally, commonly ingested through coffee, tea, soft drinks, and energy beverages. Its stimulant effects are primarily mediated through the antagonism of adenosine receptors, leading to increased alertness, focus, and sympathetic nervous system activation. However, growing evidence indicates that physiological and behavioural responses to caffeine vary significantly between genders due to differences in metabolism, hormonal influence, and body composition. Understanding these variations is critical for developing gender-sensitive recommendations for safe and effective caffeine consumption. **Materials and Methods:** This review employed a comprehensive literature search using databases such as PubMed, ScienceDirect, NCBI, and Google Scholar. Keywords used included "caffeine," "gender differences," "metabolism," "cardiovascular effects," "neurologic disorders," and "positive and negative effects." The selected studies were analysed to compare caffeine's metabolic pathways, physiological outcomes, and long-term health implications across genders. Special emphasis was placed on the role of enzymes such as CYP1A2, NAT2, and XO, and the influence of hormonal states like pregnancy and oral contraceptive use on caffeine metabolism. **Results:** Findings reveal that men generally exhibit higher CYP1A2 enzyme activity, resulting in faster caffeine metabolism and lower plasma caffeine levels. In contrast, women especially those who are pregnant or using oral contraceptives experience slower caffeine clearance due to reduced enzyme activity, increasing their susceptibility to caffeine's adverse effects. Gender also influences subjective and physiological responses as men report more positive effects such as increased alertness and vigour, whereas women are more prone to side effects such as anxiety, insomnia, and diuresis. Additionally, long-term caffeine consumption shows differential impacts on cardiovascular and neurological health. Men consuming over three cups of coffee per day demonstrated increased risk of myocardial infarction, while women showed potential protective effects, such as reduced coronary artery calcification. Neurologically, moderate caffeine intake was associated with a decreased risk of Alzheimer's and Parkinson's diseases, particularly among women. However, excessive caffeine consumption has been linked to increased white matter hyperintensities in older women, suggesting potential cerebral risk of stroke and dementia. **Conclusion:** Gender significantly affects caffeine metabolism, physiological effects, and long-term health outcomes. Men tend to metabolize caffeine more efficiently and tolerate its effects better, while women are more vulnerable to adverse outcomes, especially under hormonal influences. These differences underscore the need for personalized caffeine consumption guidelines based on gender, hormonal status, and individual sensitivity. Moderate intake, adjusted for body weight and personal tolerance, remains the safest approach. Further research is needed to refine sex-specific recommendations and minimize health risks associated with excessive caffeine use.

Keywords: Caffeine, gender differences, metabolism, cardiovascular health, neurological effects