

VOLUME 10 ISSUE 1 2024

ISSN 2454 – 3055



**INTERNATIONAL
JOURNAL OF
ZOOLOGICAL
INVESTIGATIONS**

*Forum for Biological and
Environmental Sciences*

Published by Saran Publications, India



International Journal of Zoological Investigations

Contents available at Journals Home Page: www.ijzi.net

Editor-in-Chief: Prof. Ajai Kumar Srivastav

Published by: Saran Publications, Gorakhpur, India



ISSN: 2454-3055

Effect of Obesity on Liver Cytochrome P450 in Human Models: A Narrative Review

Abishek D. and Priyadarshini A.*

Department of Pharmacy Practice, SRM College of Pharmacy, SRMIST, Kattankulathur-603 203, Chengalpattu District, Tamil Nadu, India

*Corresponding Author

Received: 2nd December, 2023; Accepted: 22nd February, 2024; Published online: 4th March, 2024

<https://doi.org/10.33745/ijzi.2024.v10i01.038>

Abstract: This review investigates the intricate relationship between obesity and the cytochrome P450 (CYP) system, insight on the multiple impact of excessive adiposity on drug metabolism. Beginning with a global perspective on obesity's rise and its alarming health implications, the review finds into the complex of CYP enzymes, emphasizing their crucial role in metabolizing drugs and xenobiotics. Focusing on pharmacokinetic changes in obesity, the review shows alterations in drug absorption, distribution, metabolism, and elimination, underscoring the challenges in predicting drug clearance in obese individuals. Pharmacodynamic variations, encompassing changes in drug efficacy and toxicity, are explored with a specific focus on the intravenous anesthetic propofol. This review highlights the delicate balance in drug toxicity in obesity, where increased metabolism may lead to higher rates of transformation into harmful metabolites. An in-depth examination of specific CYP enzymes, including CYP1A2, CYP2B, CYP3A4, CYP2E1, CYP2D6, and CYP2C19, reveals alterations in their activity within the context of obesity. It concludes by advocating for a personalized approach to drug therapy in obese patients, emphasizing vigilant monitoring and further research to understand the complex interplay between obesity and the liver's CYP system, crucial for enhancing drug safety and efficacy in this expanding patient demographic.

Keywords: Obesity, Cytochrome P450, Pharmacokinetic, Pharmacodynamic, Drug toxicity

Citation: Abishek D. and Priyadarshini A.: Effect of obesity on liver cytochrome P450 in Human Models: A narrative review. Intern. J. Zool. Invest. 10(1): 339-344, 2024.

<https://doi.org/10.33745/ijzi.2024.v10i01.038>



This is an Open Access Article licensed under a Creative Commons License: Attribution 4.0 International (CC-BY). It allows unrestricted use of articles in any medium, reproduction and distribution by providing adequate credit to the author (s) and the source of publication.

Introduction

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) over 25 is considered overweight, and over 30 is obese (Anon, 2020). World Health Organization (WHO), predicted that by 2025, nearly 167 million individuals,

comprising both adults and children, may face poor health due to being overweight or obese (Anon, 2022). Obesity is closely related to serious health hazards, including hypertension, coronary artery disease, stroke, type 2 diabetes, osteoarthritis, depression, and various cancers

(Haslam and James, 2005). Particularly, 90% of type 2 diabetes cases are related to excessive body weight (Hossain *et al.*, 2007). Obesity is a global health concern impacting both developed and lower- and middle-income countries, with predictions that up to 58% of adults worldwide may be overweight or obese by 2030 (Yach *et al.*, 2006; Kelly *et al.*, 2008).

Cytochrome P450 (CYP), a heme protein, is vital for metabolizing drugs and xenobiotics, influencing drug concentrations and overall efficacy. Cytochrome P450 pathways are classified based on similar gene sequences, involving a family number (e.g., CYP1, CYP2), a subfamily letter (e.g., CYP1A, CYP2D), and a specific number for the isoform or individual enzyme (e.g., CYP1A1, CYP2D6). Among the numerous CYP enzymes involved in drug metabolism, key players include CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5, each contributing to various aspects of drug processing and bioavailability (Guengerich, 2003; Zanger and Schwab, 2013). Most CYP enzymes in the human organism find their primary expression site in the liver, where they play a crucial role in metabolizing a wide range of substances, including pharmaceutical drugs.

Inhibition of CYP pathways can result in drug toxicity, while induction may decrease drug levels, leading to treatment failure. Particularly, CYP3A4/5, CYP2C9, CYP2D6, and CYP2C19 collectively account for approximately 79% of drug oxidation (Zanger and Schwab, 2013).

Pharmacokinetic Changes in Obesity:

The impacts of obesity on the physiological factors influencing drug absorption, distribution, metabolism, and elimination (ADME), as well as pharmacokinetic implications (Cheymol, 1993) are as follows:

Absorption:

The oral absorption of certain drugs, such as midazolam, propranolol, and dexfenfluramine, appears largely unaffected by obesity. Obese

individuals are likely to have a modified diet and altered blood flow, the real influence of obesity on absorption has not yet been fully explained (Cho *et al.*, 2013).

Distribution:

Distribution is also dependent on plasma protein binding and tissue perfusion, both of which are altered with obesity. It changes in body composition and contributes to an increased volume of distribution (Vd) for lipophilic drugs in the obese population (Cho *et al.*, 2013).

Metabolism:

Obesity can influence phase 1 (CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4) and phase 2 (UGTs and GSTs) drug-metabolizing enzymes, drug transporters. Liver plays a major role in drug metabolism. Obese individuals often have fatty liver or non-alcoholic fatty liver. Impact on the expression and activity of drug-metabolizing enzymes leads to changes in pharmacokinetics of drugs (Cheymol, 1993; Cho *et al.*, 2013).

Elimination:

Most drugs are primarily cleared by renal elimination and/or biotransformation by liver enzymes. As such, drug clearance is largely determined by organ size, blood flow and functional capacity. Obesity predisposes individuals to hypertension and diabetes, which makes assessment of the independent effects of obesity on GFR difficult. It is generally accepted that for a range of drugs that undergo metabolism, clearance is altered in the obese (Cheymol, 1993; Cho *et al.*, 2013). However, it should be noted that current evidence indicates clearance for several drugs with high hepatic extraction remains unchanged between normal weight and obese subjects.

Pharmacodynamic Changes in Obesity:

Pharmacodynamic changes, which refer to differences in drug efficacy or toxicity even when accounting for pharmacokinetic variations, are increasingly recognized as playing a crucial role in the context of obesity. It is well known that obesity

causes an increase in gut permeability and an acceleration of gastric emptying; it may also have an impact on CYP-mediated gut and/or liver metabolism (Smit *et al.*, 2018).

In adults with normal body fat, blood flow to the fat only amounts for 5% of cardiac output (compared with 20% in lean tissue). However, in obese persons, blood flow to fat is diminished and the post prandial adipose blood flow is further reduced as compared with non-obese people (Goossens and Karpe, 2008). probably associated with insulin resistance as well as increased vascular resistance.

Pharmacodynamic alterations is seen with the intravenous anesthetic propofol. Research shows that although morbidly obese people exhibit higher clearance of propofol, their sensitivity to the medicine remains similar to that of lean persons. However, a more recent study revealed a reduction in the dose at which propofol reaches half of its maximum effect (E50) in obese persons, potentially due to increased brain sensitivity or differences in co-medication. This underscores the need of addressing lean body weight (LBW) for propofol dose (Smit *et al.*, 2018).

Drug Toxicity in Obesity:

Obesity can alter the toxicity of substances, influencing the metabolism of medications through systems like the CYP system. Increased metabolism in obesity may lead to higher rates of transformation of drugs into harmful metabolites, but conversely, toxic medications can also be converted to inactive metabolites at elevated rates. Changes in clearance, volume of distribution, bioavailability, or pharmacodynamics can all contribute to the hazardous potential of a drug.

Predicting toxicity related to obesity is a challenging task, if not outright impossible. When administering medications with a low therapeutic index to obese patients, vigilant monitoring becomes essential to ensure their safety (Smit *et al.*, 2018).

Changes of Cytochrome Enzyme Activity in Obesity:

CYP1A2:

The human CYP1A subfamily encompasses two primary members, CYP1A1 and CYP1A2. CYP1A1 is expressed in the placenta and fetal liver and may be reduced in obese women and non-human primates (Zanger and Schwab, 2013).

CYP1A2 metabolism contributes to a relatively small portion (approximately 5%) of total phase I drug metabolism. The act of smoking has been observed to induce CYP1A2 activity (Schrenk *et al.*, 1998).

Both caffeine and theophylline have been identified as specific probes for assessing CYP1A2 and have been the subjects of research comparing obese and non-obese populations. The observed trends, showing higher clearance values in obese individuals compared to non-obese subjects, suggest a slight increase in CYP1A2 activity. When adjusted for body weight, the clearance values indicate both higher and lower values for obese patients compared to non-obese individuals (Rasmussen and Brøsen, 1997).

CYP1B1:

CYP1B1, a member of the cytochrome P450 enzyme family, has been implicated in the metabolism of endogenous compounds, including steroid hormones and lipids, with potential consequences for adipose tissue regulation. Particularly, CYP1B1's involvement in arachidonic acid metabolism, a key fatty acid in cell membrane glycerophospholipids, suggests a potential link to obesity and insulin resistance. The metabolites produced by CYP1B1 in this process may influence cell membrane composition, impacting cellular functions and signaling pathways related to metabolic regulation. Another example Leptin, a key factor in obesity-related breast cancer that influence the balance of E2 metabolism, was demonstrated to upregulate CYP1B1 by binding to the CYP1B1 promoter (Roe *et al.*, 1999),

CYP2B:

Obesity-related diseases can impact the characteristics of CYP enzymes, which are crucial in drug metabolism. Particularly in animal models,

the role of the CYP2B6 enzyme in obesity is not significant, it significantly contributes to drug metabolism. This enzyme metabolizes ~8% of clinically used drug. Bupropion, pethidine, propofol and ketamine are drugs metabolized by CYP2B6. It is also partly involved in the metabolism of nicotine. This enzyme accounts for ~3-6% of the total CYP content in the liver (Turpeinen and Zanger, 2012). The use of rat models of obesity often leads to results different from those in mouse obesity models. In a study focused on determination of CYP2B2 mRNA expression in an obese Zucker rat model, decreased mRNA levels of this gene in the liver were observed (Xiong *et al.*, 2002).

CYP3A4:

The human CYP3A subfamily encompasses CYP3A4, CYP3A5, CYP3A7, and CYP3A43. Among these, CYP3A4 and CYP3A5 are the most abundant enzymes found in the human liver and gastrointestinal tract (Zanger and Schwab, 2013). CYP3A4, crucial for detoxifying xenobiotics and metabolizing numerous drugs, constitutes approximately 30% of liver CYP and is involved in clinically significant drug-drug interactions. Obesity appears to be associated with lower clearance rates for most CYP3A4 substrates, possibly due to reduced enzyme activity or increased protein binding (Brill *et al.*, 2012). CYP3A4 plays a crucial role in the phase I metabolism of about 50% of all drugs. This statement provides an overview of studies comparing the clearance of CYP3A4-metabolized drugs in both obese and non-obese individuals (Guengerich, 2007). For example the clearance of triazolam was significantly reduced in obese patients, and similar findings were reported for midazolam, alprazolam, and ciclosporin, where clearance values were lower in obese individuals compared to non-obese individuals.

CYP2E1:

CYP2E1, a key enzyme in the human CYP2E subfamily, constitutes approximately 3% of total hepatic CYP content and plays a crucial role in

metabolizing ethanol, acetone, and other CYP2E1 inducers (Tomankova *et al.*, 2017). Obesity is considered an inducer of CYP2E1, with increased CYP2E1 activity and elevated expression at protein and mRNA levels in obese individuals.

The metabolism of CYP2E1 accounts for approximately 5% of phase I drug metabolism. CYP2E1's role in the metabolism and toxicity of paracetamol is particularly significant, especially when considering its importance in pediatric therapeutics, both in obese adults and children.

Clinical trials have investigated the pharmacokinetics of chlorzoxazone, a drug specifically selected to probe CYP2E1 metabolism (Lucas *et al.*, 1999). Among women, the research demonstrated that morbid obesity is linked to an elevated level of 6-hydroxylation of chlorzoxazone, indicating the induction of CYP2E1 (O'Shea *et al.*, 1994). In obese patients, both with and without non-insulin-dependent diabetes mellitus, CYP2E1 activity was found to be 40% higher when compared to non-obese individuals (Lucas *et al.*, 1999).

CYP2D6:

The human CYP2D subfamily comprises a single protein-coding gene, CYP2D6, predominantly expressed in the liver, metabolizing about 20% of therapeutic agents (Martignoni *et al.*, 2006). The impact of obesity on CYP2D6 expression and activity produces mixed results (Zanger and Schwab, 2013).

CYP2D6 metabolism constitutes roughly 10–15% of phase I drug metabolism in humans (Evans and Relling, 1999). The activity of this particular CYP isoform can vary significantly among individuals due to genetic polymorphisms.

Several studies have shown trends pointing toward increased CYP2D6-mediated metabolism in obese individuals compared to their non-obese counterparts. For instance, drugs like dexfenfluramine and nebivolol have been the focus of pharmacokinetic investigations involving both obese and non-obese subjects.

CYP2C19:

The CYP2C subfamily, comprising CYP2C8, CYP2C9, and CYP2C19, constitutes approximately 20% of hepatic CYP content in humans. While CYP2C8 has limited significance in drug metabolism, CYP2C9 and CYP2C19 play crucial roles in metabolizing various clinically important medications (Zanger and Schwab, 2013). Studies examining the impact of obesity on CYP2C enzymes yield varied results, with a human study indicating slight increases in CYP2C9 and CYP2C19 activities in obese individuals, particularly with specific substrates (Zanger and Schwab, 2013).

CYP2C19 biotransformation participates in roughly 5% of all phase I drug metabolism. Similar to CYP2D6 and CYP2C9, the activity of this isoform can significantly vary depending on genetic polymorphism (Abernethy *et al.*, 1982).

For example, in the case of diazepam, the clearance was higher in the obese group, while there was no discernible difference in desmethyl diazepam clearance between obese and non-obese individuals.

Conclusion

Obesity has significant implications for the liver's cytochrome P450 system, impacting various aspects of pharmacokinetics, pharmacodynamics, and drug toxicity. The altered expression and activity of specific cytochrome P450 enzymes in obese individuals can lead to changes in drug metabolism, potentially influencing the rates of activation or inactivation of drugs. These alterations can affect the clearance, bioavailability, and distribution of drugs, thus complicating the prediction of drug responses and toxicities in obese patients. Therefore, a personalized approach to drug therapy in obese patients, coupled with vigilant monitoring and consideration of individual drug characteristics, is crucial to ensure optimal therapeutic outcomes and minimize the risk of adverse drug reactions. Further research is warranted to comprehensively understand the intricate interplay between

obesity and the liver's cytochrome P450 system to improve drug safety and efficacy.

Acknowledgements

The authors would like to acknowledge the technical support and facilities provided while preparing this manuscript by SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu district, Tamil Nadu, India.

References

- Abernethy DR, Divoll M, Greenblatt DJ and Ameer B. (1982) Obesity, sex, and acetaminophen disposition. *Clinical Pharmacol Therapeut.* 31: 783-790.
- Brill MJE, Diepstraten J, van Rongen A, van Kralingen S, van den Anker JN and Knibbe CAJ. (2012) Impact of obesity on drug metabolism and elimination in adults and children. *Clin Pharmacokinetics* 51: 277-304.
- Cheyamol G. (1993) Clinical pharmacokinetics of drugs in obesity. An update. *Clin Pharmacokinetics* 25(2): 103-114.
- Cho SJ, Yoon IS and Kim DD. (2013) Obesity-related physiological changes and their pharmacokinetic consequences. *J Pharmaceut Invest.* 43: 161-169.
- Evans WE and Relling MV. (1999) Pharmacogenomics: Translating functional genomics into rational therapeutics. *Science* 286: 487-491.
- Flockhart DA. (1995) Drug interactions and the cytochrome P450 system. *Clin Pharmacokinetics* 29: 45-52.
- Goossens GH and Karpe F. (2008) Human adipose tissue blood flow and micromanipulation of human subcutaneous blood flow. *Methods Mol Biol.* 456: 97-107.
- Guengerich FP. (2003) Cytochromes P450, drugs, and diseases. *Molec Interventions* 3: 194-204.
- Guengerich FP. (2007) Cytochrome P450 and chemical toxicology. *Chem Res Toxicol.* 21: 70-83.
- Haslam DW and James WPT. (2005) Obesity. *Lancet* 366: 1197-1209.
- Hossain P, Kawar B and El Nahas M. (2007) Obesity and diabetes in the developing world -- A growing challenge. *New England J Med* 356: 213-215.
- Kelly T, Yang W, Chen CS, Reynolds K and He J. (2008) Global burden of obesity in 2005 and projections to 2030. *Int J Obesity* 32: 1431-1437.
- Lucas D, Ferrara R, Gonzalez E, Bodenez P, Albores A, Manno M and Berthou F. (1999) Chlorzoxazone, a

- selective probe for phenotyping CYP2E1 in humans. *Pharmacogenetics* 9: 377-388.
- Martignoni M, Groothuis GMM and de Kanter R. (2006) Species differences between mouse, rat, dog, monkey and human CYP-mediated drug metabolism, inhibition and induction. *Expert Opin Drug Metabol Toxicol* 2: 875-894.
- Obesity (2020) <https://www.who.int/health-topics/obesity>.
- O'Shea D, Davis SN, Kim RB and Wilkinson GR. (1994) Effect of fasting and obesity in humans on the 6-hydroxylation of chlorzoxazone: A putative probe of CYP2E1 activity. *Clin Pharmacol Therapeut*. 56: 359-367.
- Rasmussen BB and Brøsen K. (1997) Theophylline has no advantages over caffeine as a putative model drug for assessing CYP1A2 activity in humans. *British J Clin Pharmacol*. 43: 253-258.
- Roe A, Howard G, Blouin R and Snawder J. (1999) Characterization of cytochrome P450 and glutathione S-transferase activity and expression in male and female ob/ob mice. *Int J Obesity* 23: 48-53.
- Schrenk D, Brockmeier D, Mörike K, Bock KW and Eichelbaum M. (1998) A distribution study of CYP1A2 phenotypes among smokers and non-smokers in a cohort of healthy Caucasian volunteers. *European J Clin Pharmacol*. 53: 361-367.
- Smit C, De Hoogd S, Brüggemann RJM and Knibbe CAJ. (2018) Obesity and drug pharmacology: a review of the influence of obesity on pharmacokinetic and pharmacodynamic parameters. *Expert Opin Drug Metabol Toxicol*. 14: 275-285.
- Tomankova V, Anzenbacher P and Anzenbacherova E. (2017) Effects of obesity on liver cytochromes P450 in various animal models. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 161(2): 144-151.
- Turpeinen M and Zanger UM. (2012) Cytochrome P450 2B6: function, genetics, and clinical relevance. *Drug Metabol Drug Interact*. 27: 185-197.
- World Obesity Day (2022) Accelerating action to stop obesity <https://www.who.int/news/item/04-03-2022-world-obesity-day-2022-accelerating-action-to-stop-obesity>.
- Xiong H, Yoshinari K, Brouwer KLR and Negishi M. (2002) Role of constitutive androstane receptor in the *in vivo* induction of Mrp3 and CYP2B1/2 by Phenobarbital. *Drug Metabol Disposition* 30: 918-923
- Yach D, Stuckler D and Brownell KD. (2006) Epidemiologic and economic consequences of the global epidemics of obesity and diabetes. *Nature Med* 12: 62-66.
- Zanger UM and Schwab M. (2013) Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Therapeutics* 138: 103-141.