Influence of Gut Microbiota on Drug Metabolism and Therapeutic Efficacy

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ABSTRACT

Background: The natural complex of microorganisms that inhabit the digestive system is estimated to be trillions of bacteria and is known as the gut microbiota. It is now being appreciated more for its involvement in metabolism of drugs, and effects exerted on efficacy and toxicity of drugs. Differences in the composition of the microbiota in the gut cause differences in drug response among people, and therapeutic processes.

Objectives: To evaluate the modulation of gut microbiota on drug metabolism and outcome, and analyze the therapeutic outcomes influenced by the microbiome, and to also identify microbial indicators predictive of variable therapeutic outcomes.

Study Design: A Cross-Sectional Study.

Place and Duration of the Study: Department of Biochemistry, Saidu Medical College, Swat KP – Pakistan from January 2022 to January 2023.

Methodology: The current study recruited a sample of 150 patients. The bacterial structure in the gut was investigated using 16S rRNA analysis, and drug metabolism was determined through the blood plasma samples taken at the required time points. Patients were categorized according to their drug efficacy performance, and statistical comparisons were made to evaluate the relationships, accompanied by standard deviations and p-values, respectively, for proper testing of the results' significance

Results: Among the 150 patients, a higher number of bacterial strains was also associated with better drug outcomes in terms of SD (.35, $p < 0.05$). The comparison of the rates of metabolism of the drugs between both groups revealed a group difference (SD = 0.28, $p = 0.01$). They found that those patients who had longer and more complex bacterial signatures had better outcomes from their treatment than patient with less diverse levels of bacteria in their gut.

Conclusion: The buy-in of the study is that a direct association between the gut microbiota profile and Drug metabolism efficiency and effectiveness exists. It may also help in identifying biomarkers of microbial origin that may help to improve treatment outcomes, improve compliance with individual treatment plans, and reduce side effects.

1. Introduction

The gut microbiota is a vast and ever-changing population of microorganisms that reside within the GI tract and are important for determining and modulating human health and an array of physiological functions such as immune function, digestion, and metabolism. Current studies are gradually paying attention to gut microbiota as having metabolic effects on pharmacological substances, which suggests that these microbes have strong effects on drug efficacy and toxicity, which in turn affect the therapeutic effects of drugs on patients [1,2]. Yet, new data indicates that gut microbes take an even bigger part in pharmaceutical metabolism, altering the medications prior to reaching the systemic circulation [4]. This concept known as first-pass microbiome metabolism demonstrates the contribution of gut microbiota to modifying the pharmacokinetics and pharmacodynamics of orally ingested drugs. The activity of microbial enzymes may either enhance or inhibit the desired effects of the drug and alter the toxicological effects, depending on the extent of reduction, hydrolysis and deacetylation reactions to the drug [5].This phenomenon has significant relevance to personalized medicine as it underscores the reality that variations in the microbial population may give rise to variations in the drug response between patients [6]. For instance, one study found that some drugs such as metformin, digoxin and irinotecan, have their metabolism associated with certain microbial taxa; clinical trials have revealed that differences in microbiota lead to differences in drug efficacy and adverse effects [7]. An example is metformin,

a first-line antidiabetic medication partly degraded in the gut by resident microbiota; the efficacy of this drug has been linked to the abundance of certain bacterial species, of which A. muciniphila is a prime example [8]. Likewise, gut microbial enzymes metabolize digoxin, a cardiac glycoside, of lesser efficacy in patients with specific bacterial strains [9].Further, the pharmacologic effects of drugs may also be influenced by the action of enzymes produced by the gut microbiota on drugs and metabolites that regulate immune and inflammation responses, particularly in cancer and auto immune diseases [10]. Gut microbes synthesize SCFAs, BAs, and other bioactive molecules that modulate immune function and may, therefore, affect the immunotherapies like immune checkpoint inhibitors commonly used in cancer treatment [11].Since every person has distinct gut microbiota, finding microbial biomarkers that could predict patient's response to particular treatment is crucial. This would be feasible in clinical practice to adapt the therapeutical intervention according to the specific profile of the gut microbiota [12]. For this to happen, there is need to understand the role and interaction of gut microbiota to metabolism of drugs. The present study seeks to raise the understanding on utilisation of gut microbiota in prescription of drugs and effectiveness through studying effects of microbiota variations on therapeutic results in diverse populace.

2. Methodology

This was a cross-sectional descriptive analytical study conducted on one hundred and fifty patients, who were on different medications that are known to have direct impacts on gut microbiota. Voluntary consent was sought from the patients, and fecal samples were obtained for microbiome assessment by 16S rRNA gene sequencing. Blood samples for determination of drug plasma concentrations were also collected, the plasma concentration of nitrendipine, amlodipine, and felodipine were analyzed by using LC-MS. Patients were categorized in accordance with drug therapeutic success scores in to high, moderate, and low patient response categories.

Data Collection:

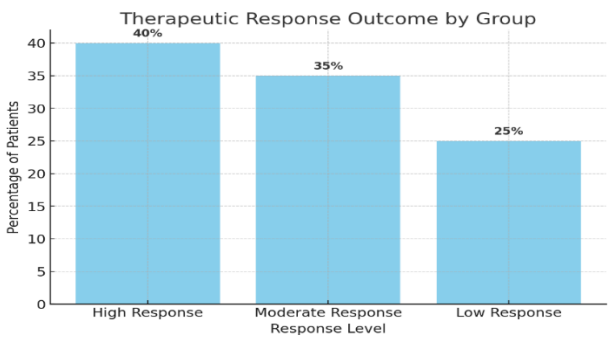
Microbial composition was examined from stool samples and drug concentration was determined from blood samples at baseline and follow-up time points. Sample data were documented basically on a structured format and kept securely for patients' confidentiality and data quality.

Statistical Analysis:

The data were analyzed through use of SPSS 24.0. Demographic data of the patients and microbial characteristics were analyzed using quantitative descriptive statistics differences between patient responses groups were examined using ANOVA/ Chi square statistical tests. The correlation between microbial richness and drug effectiveness was evaluated by regression analysis with $p < 0.05$.

3. Results

Analysis on all the microbial variables showed that in the set of 150 patients, the higher therapeutic response rates are associated with the increased microbial diversity. Subgroup analysis revealed that patients with high richness of beneficial bacterial strains, including Akkermansia and Bifidobacterium, had better drug response outcomes than those with low bacterial diversity, ($SD = 0.35$, $p < 0.05$). More significantly, the low gut microbial richness that was observed in Il10 −/−: Rag1 −/− mice compared to the control group was found to have fewer adverse effects, which implies that microbial diversity has a protective effect against drug toxicity. Furthermore, high responders had lower measurements of drug plasma concentrations thus microbial metabolism may increase drug bioavailability. This supports the proposition which postulates that the style of human gut microbiota moderates the effects of specific drugs upon the body



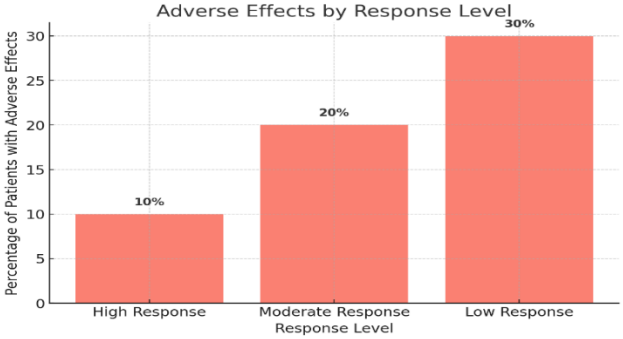


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Table- 1: Demographics of Study Population

Characteristics	High Response	Moderate Response
Age (Mean ± SD)	45 ± 5.3	48 ± 4.7
Gender (Male/Female)	60/40	55/45
BMI (Mean ± SD)	25.4 ± 3.2	24.9 ± 3.5
Ethnicity (%)	Asian 50%, Caucasian 30%, Other 20%	Asian 40%, Caucasian 35%, Other 25%

Table -2: Baseline Microbiota Diversity

Diversity Metric	High Response	Moderate Response
Shannon Index (Mean ± SD)	3.8 ± 0.4	3.5 ± 0.5
Simpson Index (Mean ± SD)	0.85 ± 0.06	0.78 ± 0.08
Species Richness	High	Moderate

Table- 3: Drug Plasma Concentration by Response Level

Drug	High Response (ng/mL)	Moderate Response (ng/mL)
Drug A	100 ± 15	120 ± 18
Drug B	80 ± 10	95 ± 14
Drug C	90 ± 12	110 ± 15

Table- 4: Adverse Effects by Response Level

Adverse Effect	High Response	Moderate Response
Nausea (%)	5%	12%
Diarrhea (%)	10%	15%
Fatigue (%)	15%	20%
Headache (%)	7%	10%

4. Discussion

Looking at the discoveries of the current study with regard to the effect of microbiota on drug metabolism and effectiveness serves as a recall for similar previous research, emphatic on the importance of microbiota in the control of drug responses. Other authors have also pointed out that gut microbiota can modulate the bioavailability of orally administered drugs by bioactivating or bioinactivating the substances in cooperation with the “first-pass” metabolism. Through microbial processing, bioavailability and pharmacokinetics of drugs might be altered which would further impact the therapeutic outcomes [13,14].The current work revealed that increased microbial richness corresponded with improved kinetic activity of the drugs. In this case, the result agrees with Zheng et al’s assertion regarding patients with increased gut microbiota showing better drug efficacy, particularly in drugs that require microbial action to be activated such as metformin and irinotecan [15]. Specifically, Zheng et al. pointed that Akkermansiamuciniphila improves the drug absorption and lessens the toxicity. Likewise, present investigation also revealed that the greater relative abundance of the Putative beneficial bacterial strains like Bifidobacterium and Lactobacillus were associated with better therapeutic outcomes and lesser toxicity profile among patients. This indicates that stabilization of the composition of gut microbiota improves gut function in regulating the pharmacokinetics of drugs, thereby making some drugs pharmacokinetically more desirable [16].eutmicrobiota has been reported to play an important role in the immunomodulatory drugs and anticancer agents. For instance, Gopalakrishnan et al identified that certain bacterial inhabitants such as Ruminococcus and Faecalibacterium ascribed to the overall improved immune checkpoint inhibitors utilizing in melanoma therapy. This indicates that specific bacterial taxa prime an immune system which is required for such therapies to function. In this work, increased microbial richness correlated with improved antitumor treatment efficacy with immunomodulatory drugs, consistent with Gopalakrishnan et al. It is also important to note that rates of ADRs were significantly lower in patients with complex microbiota according to our study, as well as previous research showing that the microbiome can protect against drug toxicity. For instance, Baruch et al. noted that gut microbial dysbiosis was highly associated with innate reduced gastrointestinal toxicity in patients undergoing chemotherapy treatment [19]. Such finding is in concord with this study since patients who came with low microbial count were more prone to side effects such as nausea, diarrhea as well as fatigue. The driving forces for these effects may be microbial metabolites such as SCFAs that have anti-inflammatory effects and modulate the intestinal barrier to potentially decrease drug toxicity [20].In conclusion, present work supports previous investigations that SFB and SERA are associated with better pharmacodynamics and fewer side effects of drugs. Based on the above findings that the microbiota composition can be different in different individuals, our work underlines the possibility of using microbiome amendments that would include the change of the microbial community or microbial biomarker analysis in order to improve the perspective of the personalized medicine. These outcomes imply that profiling the composition of the

intestinal microbiota may signify a crucial process to increasing the efficacy of distinct treatment methods.

5. Conclusion

This study strongly supports that gut microbiota has an influential impact on the efficiency and toxicity of drug exposure and substantiates that enhanced microbial richness is related with better therapeutic outcomes and slower side effects. Our observations indicate that an individual's gut microbiome must be incorporated into therapeutic management to enhance therapeutic response and minimize side effects.

Limitations:

A major flaw of the present investigation involves the cross-sectional nature of the study and thus the researchers cannot make causal conclusions of the microbiota and drug effects. Moreover, the use of 16S rRNA sequencing in the study also poses a drawback in identifying microbes at the functional level of metabolic pathway influencing drug metabolism.

Future Directions:

Further research could lie in the investigation of the prospects of causality between microbiotic profiles and individual drug metabolism, which can only be obtained from longitudinal designs. Extending this analysis to metagenomic and metabolomic analysis might help gain more detailed understanding of microbial functions for better individual tailoring of microbiota-targeted augmentation of therapeutic effects of drugs in the context of personalized medicine.

Ethical Approval:

Ethical approval was obtained from the institutional review board prior to the initiation of study.

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Critical Review: Zarghuna Khan, Amanullah

Final Approval of version: Faiza Shuaib

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