Extended Abstract | Acute and Chronic Disease Reports | 2019 | Vol.3 No.1

# Infectious Diseases & Endocrinology 2019: Does diabetes mellitus cause CYP2C19 phenoconversion? Evaluation of metformin and cinnamon effects on CYP2C19 activity in type 2 diabetic rats- Hanieh Entezari- Tehran University of Medical Sciences

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**Introduction:** Change in the metabolism of drugs is very likely in diabetes mellitus. This study assessed the changes in enzymatic activity of CYP450 2C19 in liver by using omeprazole as probe in the animal model of type II diabetes, before and after administration of metformin and cinnamon. In these reactions, substrate encounters oxidation, reduction, hydrolysis, hydration, and several other reactions. Although cytochromes P450 (CYPs) are divided into 18 families and 57 subfamilies, the most important CYPs with the largest contribution in xenobiotic metabolisms are CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2, respectively. Meanwhile, CYP2C19 is involved in the metabolism of at least 10% of the medications present in the clinic, including antidepressants, proton pump inhibitors (PPIs), anticoagulants, anticonvulsants, anti-malarias, and anxiolytics.

The changing levels of cytochrome P450 enzymes can considerably affect the pharmacokinetics of medications and clinical response. This would be more important in medications with a narrow therapeutic index or prodrugs requiring metabolizing systems for activation. Genetic polymorphism is one of the most critical features of CYP2C19. This enzyme majorly shows deficient activity in 3-5% of the Caucasian and 15-20% of the Asian population. Furthermore, the expression of most genes in the family of CYP1, CYP2, CYP3, and CYP4 could be induced or inhibited by multiple environmental factors. Some studies have reported that certain, acute or chronic diseases can affect the levels of cytochrome P450 enzymes by altering gene expression through stimulating the inflammatory response. A wide range of diseases, including cancers, microbial infections, rheumatoid arthritis, head trauma, and some cardiovascular diseases can stimulate inflammatory responses in the body. Type 2 diabetic mellitus (T2DM) is a severe metabolic disorder that can decrease the quality of life, if not treated properly.

Considering the nature of diabetes and various vascular (micro vascular and macro vascular) and non-vascular disorders, changes in the absorption, distribution, and metabolism of drugs is highly probable. Several studies have investigated the content of liver microsomal enzymes in diabetic patients in comparison with healthy controls (15, 16). As previously mentioned, most studies have merely focused on protein content and mRNA expression as well as variations in the metabolic ratio of antipyrine as a probe for the CYP450 activity. Considering the high prevalence of diabetes along with the use of various medications besides drugs associated. Additionally, cinnamon is generally used as a traditional medicine in many countries to reduce blood glucose levels in the diabetic patients. Although recent studies have demonstrated its anti-inflammatory and hypoglycaemic effects and its effects on improving metabolic syndrome, its potential effects on other common processes in the body, such as the expression of carriers and enzymes, have rarely been taken into consideration. However, many patients do not disclose the use of herbal supplements to their physician.

This is an expected to be one of the main reasons for the failure of therapeutic responses. Based on the above, an animal model of diabetes was considered in this study to investigate the effect of diabetes and the potential impact of cinnamon on the CYP2C19 activity. Since the streptozotocin (STZ) - induced diabetes was widely used in pharmacokinetic studies, the same approach was chosen in this study. On the other hand, liver perfusion has been extensively used in pharmacological and toxicological studies over the past few years. In this method, the liver is discrete from other organs by preserving the structure, function, and vascular system. Penetration occurs physiologically through the cells as well as the enzymatic pathways so that the mechanisms of metabolism and excretion are all naturally preserved.

**Method:** 28 male Wistar rats randomly divided into 7 groups. 7 days after the induction of diabetes type, test groups received metformin, cinnamon and metformin plus cinnamon daily for 14 days. In day 21, rats were subjected to liver perfusion by Krebs-Henselit buffer containing omeprazole as CYP2C19 probe. Perfusate samples are analysed by HPLC-UV in order to evaluate CYP2C19 activity.

**Result:** The average metabolic ratio of omeprazole was changed from 0.091±0.005 in the control group to 0.054±0.005 in the untreated diabetic group (p-value=0.003). This average was increased inordinately to 0.218±0.036 in the treated group with metformin. Interestingly, administration of cinnamon with metformin in diabetic rats caused the enzyme activity to return (0.085±0.002) to the observed levels (0.091±0.005) in control group (p-value=0.26).

This work is partly presented at Global Experts Meeting on Infectious Diseases, Diabetes and Endocrinology February on 27-28, 2019 Tokyo, Japan

**Conclusion:** The results of the study showed that despite the suppression of CYP2C19 enzyme activity in type 2 diabetic rats, administration of metformin can severely increase the enzyme activity. Surprisingly, simultaneous use of cinnamon and metformin can modulate the function of CYP2C19 to the observed level in control group and make it more predictable to treat diabetes mellitus and fate of other drugs that metabolize by this enzyme.

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