

# Influence of diabetes mellitus on pharmacokinetics of drugs

## Editorial

Diabetes Mellitus (DM) is a prevalent disease caused by the body's inability to produce or make use of insulin. According to International Diabetes Federation, an estimated 382 million people had diabetes in 2014 and by 2035, this number is estimated to almost double. In 2010, diabetes was named the 7<sup>th</sup> leading cause of death in the United States. The disease lends itself in the development of multiple complications and co-morbid conditions such as hypertension, dyslipidemia, kidney disease, blindness and eye problems, hypoglycemia, amputations, cardiovascular disease, heart attacks, and strokes. Therefore, diabetic patients are expected to use more drugs compared to their age-matched non-diabetics.

There is limited number of studies related to the influence of Diabetes Mellitus on the pharmacokinetics of drug. This limitation of information translates to absence of available guidelines that help practitioners adjust dosages where necessary to help patients reach their therapeutic effect. Pathophysiological changes during diabetes have the potential to affect absorption, distribution, metabolism and excretion of various drugs.

### Effects of diabetes mellitus on absorption

Membrane permeability can affect the bioavailability (F) of medications. It has been found that an increase in extracellular glucose can activate the intracellular signaling protein, protein kinase C, which could lead to dose-dependent increase in endothelial cell permeability.<sup>1</sup>

One of the major microvascular complications of DM includes a 60–70% reduction of gastric mucosal blood flow in diabetic patients which ultimately influences the rate of gastric emptying.<sup>2</sup> It has been reported that 28–65% of diabetic patients experience delayed gastric emptying with an inverse relationship between the rate of gastric emptying and the blood–glucose concentration.<sup>2</sup> It is not surprising that delayed gastric emptying causes more than 300% longer gastric transit time in diabetic patients compared to non-diabetic patients.<sup>3</sup> These significant changes in gastric motility and gastric transit time may have the potential to impact rate and extent of absorption of orally-administered medications in diabetic patients.

Poorly controlled Type 1 diabetic's patient's demonstrated significantly lower serum concentration of oral ampicillin when compared to their corresponding healthy controls, despite unaltered elimination kinetics.<sup>4</sup> Similarly, the rate of absorption of tolazamide was significantly (26%) slower in diabetic patients than non-diabetic healthy subjects.<sup>5</sup>

On the other hand, oral bioavailability and area under the concentration–time curve (AUC) of ciprofloxacin were not statistically significant different in diabetic patients with gastro paresis from healthy subjects.<sup>6</sup>

In a similar study to assess the bioavailability of provitamin carotenoids (absorption and conversion into retinol) in type 1 diabetic

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patients compared to non-diabetics, Granado F et al.<sup>7</sup> found no significant difference among the two groups.<sup>7</sup>

### Effects of diabetes mellitus on distribution

Albumin is a major protein in blood with 2 main binding sites. Site 1 tends to bind to larger compounds such as warfarin and salicylates, and site 2 often bind to smaller compounds such as aromatic carboxylic acids and ketoprofen. Albumin, along with hemoglobin, can become glycated in the presence of high glucose concentrations. Non-enzymatic glycation of albumin which occur in diabetic patients can lead to a conformational change in the albumin structure therefore altering the fraction of unbound drugs. Albumin purified from diabetic patients or glycated in vitro had significant impairment in binding affinity with highly-albumin binding drugs.<sup>8</sup> For example, the free fraction of salicylic acid and sulfafurazole was 1.5 and 5 fold higher in diabetic when compared to non-diabetic patients.

Another factor that may decrease drug binding to albumin is increased levels of free fatty acids, as stated by Cabello et al.<sup>9</sup> The team found in the presence of elevated free fatty acid levels as seen in diabetics, free diazepam level was significantly higher in diabetic patients compared to healthy subjects. They also noticed that posttranslational change via glycosylation of albumin did not affect diazepam binding as much as it did for sulfisoxazole, a sulfonamide antibacterial described as a site 1 drug, where an increase in glycosylated albumin yielded higher amounts of unbound sulfisoxazole.

It should be noted that the duration of the disease and presence of complications may affect the impact of diabetes on the extent of protein binding. Therefore, the published reports illustrate inconsistent outcome where volume of distribution of several drugs can be higher, similar, or lower in diabetic patients compared to healthy subjects.

### Effects of diabetes mellitus on metabolism

Patients with diabetes mellitus are often on multiple medications. Many medications are metabolized by liver cytochrome P450 (CYP) enzymes, specifically CYP 3A enzymes. In a study to investigate the effect of diabetes on these liver enzymes, it was found that diabetes is associated with a significant decrease in CYP 3A4, but

not CYP3A5, activity and expression compared to non-diabetic patients.<sup>10</sup> CYP 2E1 has a high capacity to generate free radicals which is thought to be linked to alcoholic and nonalcoholic liver disease. Using chlorzoxazone hydroxylase activity as a marker for CYP2E1 in diabetic patients, Wang et al. revealed that CYP2E1 activity was twice as much in type 2 DM patients than in healthy subjects and type 1 diabetics.<sup>11</sup> Biotransformation of probe substrates for other CYP enzymes such as tolbutamide (CYP2C9), theophylline (CYP1A2), and aryl hydrocarbon (CYP1A1) were not different in diabetic versus non diabetic patients.<sup>12</sup>

## Effects of diabetes mellitus on excretion

According to the American Diabetes Association, 44% of new kidney failure cases in 2011 were primarily caused by diabetes. It is well known that micro- and macro-vascular complications can arise from long-term uncontrolled diabetes. This can lead to an increased glomerular filtration rate (GFR). Some researchers have studied the effect of GFR using antibiotics. One study reported a significant increase in GFR and clearance of penicillin G in diabetic children when compared to age-matched healthy subjects.<sup>13</sup> On the contrary, clearance and serum concentration of renally-excreted drugs such as kanamycin, benkanamicin, and amikacin were similar among diabetic and non-diabetic patients.<sup>14</sup> With varying results, it is difficult to a prediction on the impact of diabetes on renal function and renal clearance of drugs.

## Conclusion

Diabetes has effects on pharmacokinetics and pharmacodynamics that have not been completely understood. Previous studies have provided inconsistent data for multiple drugs, possibly due to variations of patient characteristics or control of patients' diabetes at the time of data collection. Dostalek et al.<sup>15</sup> study on the effects of diabetes on PK of drugs had comparable outcomes to a similar study published in 1991 by Gwilt et al.<sup>16</sup> in which the results are unclear. Further clinical studies are required to understand the impact of diabetes on the PK of drugs and to determine the clinical significance of the pharmacokinetic effects.

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## Conflict of interest

The author declares no conflict of interest.

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