Clinical Toxicology

Vahabzadeh and Mohammadpour, J Clin Toxicol
2015, 5:2
http://dx.doi.org/10.4172/2161-0495.1000233

Review Article Open Access

Effect of Diabetes Mellitus on the Metabolism of Drugs and Toxins

Maryam Vahabzadeh[1]* **and Amir-Houshang Mohammadpour**[2]

[1]*Department of Toxicology, Mashhad University of Medical Sciences, Mashhad, IR-Iran*

[2]*Deapatment of Clinical Pharmacology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, IR-Iran*

***Corresponding author:** Maryam Vahabzadeh, Associate Professor of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, IR-Iran, Tel: +98(51)38823255; E-mail: MohamadpoorAH@mums.ac.ir

Received date: Aug 21, 2014; **Accepted date:** Mar 25, 2015; **Published date:** Mar 28, 2015

Abstract

Diabetes mellitus (DM) is a complicated endocrine disorder that can clinically impair tissues and organs due to hyperglycemia. One of the areas of concern in diabetes would be the higher amount of medications being consumed by diabetes sufferers that is the corollary of its inevitable complications such as micro-and macro-vascular damages to various organs. Different metabolic pathways are involved in the biotransformation of drugs and toxins, thus their pharmacokinetic/toxicokinetic can be affected by DM primarily due to changes in enzymes and drug transporters. On the other hand, different enzymatic pathways are involved in the metabolic processes of substances. While not many human studies are available, several investigations have been carried out in animal models of diabetes, the majority of them being rodents. Given the high prevalence of DM and its important complications, the effect of this disease on the metabolism of some of the toxins and drugs is discussed herein.

Keywords: Diabetes mellitus; Metabolism; Hepatic cytochrome P (CYP); Toxin

Abbreviations

CYP450: Cytochrome P450; DM: Diabetes Mellitus; DZN: Diazinon; FFA: Free Fatty Acids; FMO: Flavin-containing Mono-Oxygenase; IDDM: Insulin-Dependent Diabetes Mellitus; NIDDM: Non-Insulin-Dependent Diabetes Mellitus; STZ: Streptozotocin

Introduction

Being considered as one of the foremost health concerns in the world, diabetes mellitus (DM) is a complicated endocrine disorder which can clinically impair tissues and organs due to hyperglycemia [1]. Two major types of diabetes are known in the population: type, described as "an inability of the body to produce insulin"; and type, which is defined as a deficiency in the secretion of insulin with or without the existence of insulin resistance. Other types of diabetes are ascribed to conditions such as pancreatic disorders, malnutrition, certain drugs or toxins, infections and immunologic states [2]. However, the most significant risk factors for type 2 diabetes, yet preventable, nowadays are attributable to obesity and inadequate physical activity [3-4]. Despite many surveys of the prevalence of diabetes worldwide, few published data from the Middle East and especially Iran exist in this regard. In an article by Esteghamati et al., they documented a considerably high prevalence of diabetes in Iran. Roughly 80,000 native Iranian aged between 25 and 64 were included, among whom 7.7% had diabetes with one-half of them being undiagnosed cases. Thereby they concluded that, with the aging of the fairly young population and the developing urbanized society, the prevalence of diabetes would almost certainly increase [5].

One of the areas of concern in diabetes would be the higher amount of medications being consumed by diabetes sufferers which is the corollary of its inevitable complications such as micro-and macro-vascular damages to various organs [6-7].

On the other hand, different metabolic pathways are involved in the biotransformation of drugs and toxins, thus their pharmacokinetic/toxicokinetic can be affected by DM primarily due to changes in enzymes and drug transporters [2]. Different enzymatic pathways are involved in the metabolic processes of substances. In murine models of diabetes using streptozotocin, microsomal N-demethylase activity was suppressed, while hydroxylase activity and CYP-450 content were increased in diabetic animals. Moreover, it was concluded that the function of hepatic xenobiotic biotransformation enzymes can be altered under chronic uncontrolled diabetes [8-9].

Diabetes can influence the plasma protein-binding of some drugs, possibly via glycosylation or displacement of proteins by plasma free fatty acids, since the amount of FFA is raised in diabetic patients. However, there would be no changes in plasma concentrations of albumin and α1-acid glycoprotein. Contrary to the experimental studies, the metabolic clearance of the majority of drugs in humans appears to remain unchanged or slightly decreased in DM [10].

Based on the available data, it appears that significant changes in pharmacokinetics and pharmacodynamics occur due to diabetes. A limited number of studies have been published discussing the effect of diabetes on pharmacokinetic and pharmacodynamic of drugs [1-2,10,11], but to our knowledge, there are no publications regarding the changes in the metabolism of toxins in this disease thus far. Given the high prevalence of DM and its important complications, the effect of this disease on the metabolism of some of the toxins and drugs is discussed herein.

Effect of DM on Drugs Metabolism

Human studies

Several researchers have studied the effect of DM on different drugs metabolism. Goldstein et al. studied changes in drug metabolism in 14 patients with insulin-dependent diabetes whom their disease was poorly controlled. They used antipyrine as an indicator for drug metabolism by hepatic cytochrome P450 enzymes (CYP450) and afterward, antipyrine kinetics and urinary excretion of its metabolites were evaluated. Nine of the patients underwent appropriate treatments so as changes in the antipyrine kinetic in after-treatment conditions could be studied. Normalization in HbA1 levels was considered as the basis for improved treatment. Results indicated an increase in the half-life of antipyrine from 4.7 ± 0.2 hours at the beginning of the study to 7.8 ± 0.3 hours in the 9 treated patients and it was similar to that of the healthy subjects. The volume of distribution for antipyrine in the treatment group was akin to that of untreated diabetic patients [12]. Based on these results, there were no differences between the two groups regarding kinetic indices of antipyrine.

Salmela et al. prepared liver biopsies from 56 diabetic patients to assess the metabolic activity of the liver by in vivo testing. Hepatic CYP450 was measured in biopsy samples as an in vitro parameter because it directly reflects the enzymatic microsomal activity of the liver for drug metabolism. Among 56 patients, there was a 40-fold difference in CYP450 content and 8-fold in the metabolism of antipyrine; thus, demonstrating that a wide range of inter-individual differences exist in drug metabolism in diabetic patients. Levels of CYP450 were higher and antipyrine metabolism was faster in patients who had a healthy liver than those associated with disorders such as fatty liver, cirrhosis and inflammatory changes in parenchymal tissue. Therefore, Salmela, et al. believed that diabetes alone did not seem to affect the capacity of hepatic drug metabolism, and different treatment regimens did not have a considerable effect on drug metabolism [13]. Such deduction is comparable to the results of the previous study.

In a study by Sotaniemi, diagnostic liver biopsies of 298 patients with diabetes was analyzed with the patients being classified based on the type of diabetes, age, sex, liver involvement and treatment duration. In order to determine the capacity of liver for drug metabolism, plasma clearance rate of antipyrine and CYP450 levels in the liver biopsies were measured. Results indicated that the metabolism of drugs in diabetic patients was affected by factors such as age, sex, effectiveness of treatment, and type of diabetes. On the other hand, in patients with untreated type 1 diabetes the excretion rate was higher when compared with the patients treated with insulin. Among those with type 2 diabetes participated in the study, women had a normal antipyrine metabolism, whereas men over 40, showed a decrease in the metabolism [14]. It can be concluded that antipyrine excretion rate can change depending on the type of diabetes and gender.

The concentrations of cyclosporine metabolites were measured in 17 recipients of kidney transplant, 7 of them with diabetes. All patients were male with nonfunctional CYP3A5*3 genotype, and were on ketoconazole and cyclosporine regimen as a combination therapy. It was concluded that cyclosporine metabolites were significantly affected by diabetes, since cyclosporine has biliary metabolism. Thus, low concentrations of its metabolites during post-absorption phase of drug, probably represents less activity of CYP4503A4 enzyme in the liver; although other mechanisms such as disruption in the expression of transporters can be effective as well [15].

Some researchers have studied the content of the liver microsomal enzymes in diabetic patients. In a study by Dostalek et al., pieces of human liver microsomes from 12 diabetic and 12 non-diabetic donors being demographically matched, were genotyped for polymorphisms of CYP3A4*1B and CYP3A5*3. A comparison of mRNA expression, protein level, and enzymatic activity of CYP3A4, 3A5 and 2E1 was made between the two groups. Results showed significant reduction in P4503A4 protein and mRNA levels in the liver microsomes of diabetic individuals. The authors concluded that their results could be germane to those diabetic patients who receive multiple medications and have additional co-morbidities [16].

In other research by Dostalek et al., 11 nondiabetic and 9 diabetic kidney transplant recipients as well as 10 nondiabetic and 10 diabetic volunteers who did not need transplant were studied for enzyme activity, gene expression, and protein levels of inosine 5'-monophosphatedehydrogenase 1 and 2 (IMPDH1 and IMPDH2). According to their results, significant reduction in gene expression, protein levels and enzymatic activity of IMPDH were observed in diabetic patients in comparison with nondiabetic patients [17].

Similarly, in a study to investigate the activity and expression of UDP-glucuronosyltransferase 2B7 (UGT2B7) in the liver and kidneys of diabetic and non-diabetic subjects, 16 samples from the liver and 8 samples of the kidneys were taken and tested. The results of this study showed a significant reduction in the expression of mRNA, protein levels and enzymatic activity of UGT2B7 in the liver and kidneys of diabetic patients. Therefore, since Mycophenolic acid metabolizes through UGT2B7 producing MPA acyl glucuronide (AcMPAG) metabolite, the reduction of concentrations of this metabolite in the circulation can be justified in diabetic individuals [18].

In a prospective controlled study on 15 patients with DM type, 16 patients with type 2 DM, and 16 healthy volunteers, Matzke et al. evaluated the effect of DM on the metabolism of antipyrine as well as the activity of CYP2D6 and CYP1A2. Simultaneous administrations of antipyrine 10 mg/kg (as a general metabolic probe), caffeine 100 mg (as a probe for CYPP450 1A2 and N-acetyltransferase activity), and dextromethorphan 30 mg (a specific probe for CYP2D6 activity) were performed in all subjects. Urine and saliva samples were then used for pharmacokinetics analyses of antipyrine and its primary metabolites. Their results showed that type 1 diabetes had noticeable effects on the antipyrine metabolism, while none of the three probes was affected by type 2 DM. Therefore, a general conclusion of this study would be that antipyrine metabolism and CYP1A2 activity is increased in DM type 1 [19].

Pirttiaho et al. studied the plasma antipyrine kinetics, hepatic CYP450, the size of the liver and the level of fatty infiltration in 21 obese patients with NIDDM. The capacity of the liver for drug metabolism (antipyrine was calculated based on the total clearance) and the estimated amount of CYP450 was akin to those of non-diabetic patients with normal liver, while the relative clearance of antipyrine and CYP450 concentrations were significantly lower in diabetic patients [20]. This finding clearly shows the diminishing effect of DM on the metabolic capability of the liver. There are also additional studies coming to the same conclusion. Several groups of patients, including 20 patients with IDDM, 8 patients with liver cirrhosis, 5 patients with fatty liver and hepatitis, and 3 alcoholic patients with normal hepatic morphology, were also studied for the

clearance of antipyrine after respective intravenous injections. Results showed that the drug metabolic capacity of the liver is substantially reduced in diabetes, thus dose adjustment strategies should be considered in these patients [21].

In another comparable study by Saenger, the antipyrine kinetics and urinary excretion of its metabolites were determined in 14 poor-controlled IDDM patients with normal renal function, and comparisons were made with their matched age group. An increase was observed in the urinary levels of three metabolites of antipyrine in a specific volume of the sample. Moreover, separate CYP450 isoenzymes involved in the metabolism of antipyrine were stimulated to a similar extent in the individuals with poorly controlled diabetes [22]. As seen, these results represent an increase in the hepatic drug metabolism in patients with uncontrolled IDDM.

One research on 8 well-controlled IDDM and 8 control subjects who were matched for their age and gender, aimed to investigate the CYP2E1 expression in the peripheral blood lymphocytes by Western blot and Phoretix image analyses. Levels of CYP2E1 in the diabetic group were higher (3.1 times) than those of the control group with no association with HbA1c and duration of the disease. However, significant differences existed among the participants regarding CYP2E1 induction rate. The results of this study implied that even in good metabolic control, CYP2E1 expression is higher in IDDM patients than controls [23].

Compared to the above research, Haufroid et al. evaluated CYP2E1 expression in peripheral blood lymphocytes in two different settings: chronic hepatitis C and poorly controlled IDDM. Total RNA was isolated and gene expression for CYP2E1 was determined. The results indicated a significant increase in lymphocyte CYP2E1 expression levels in IDDM patients compared to controls [24].

Similarly in Pucci's study, the expression and activity of CYP2E1 in lymphocytes microsomes of three groups consisted of 12 healthy volunteers, 11 patients with type 1 diabetes and 12 patients with DM type 2 were studied. The results showed no effect of DM on CYP2E1 expression and activity in the lymphocytes [25].

Diagnostic liver biopsies of nearly 300 diabetic individuals have been studied for the capacity of hepatic drug metabolism. Two indices, the plasma clearance rate of antipyrine and CYP450 content, were used as the determinants. Results showed a reduced metabolism due to age, while gender and type of DM affected the clearance rate of antipyrine as untreated-type 1-diabetes resulted in faster elimination of antipyrine. Insulin therapy, however, normalized the clearance rates of antipyrine. Having had an inadequate response to insulin therapy, men under 60 had a higher rate of antipyrine clearance, while women had the elimination rate akin to that in the control group. Conversely, in type 2 diabetes, antipyrine metabolism was normal in women, whilst it was reduced in men above 40. The authors thereby concluded that the type of DM, efficacy of treatment, age, and sex of diabetic patients can influence the drug metabolism. Such finding should be entailed in pharmacokinetics studied of novel drugs in the diabetic population [14].

Despite some discrepancies in the above-mentioned studies, it can be concluded that not only DM itself can negatively affect the metabolic capacity of the liver mostly in poor controlled disease conditions, but also some other factors such as gender and age are involved.

Animal studies

Several studies have been conducted in animal models regarding the effect of DM on the metabolism of different drugs. Study on perfused livers of male rats in which diabetes had been induced with either alloxan or streptozotocin (STZ) showed an increase in the amounts of p-chloro-N-methylaniline in both alloxan and streptozotocin rat perfused livers [26].

Dixon reported the suppressed microsomal metabolism of hexobarbital, chlorpromazine and codeine in the liver of alloxan-induced diabetic male rats. Insulin therapy reversed such phenomenon with no direct action [27].

Furthermore, Alloxan-induced diabetes in rabbits did not alter the expression of CYP2B4 using immunoblot analysis and benzphetamine N-demethylase activity in the animals' kidneys and lungs. The activity level of aniline 4-hydroxylase and p-nitrophenol hydroxylase in the lungs and kidneys were noticeably higher. CYP2B4-and CYP2E1-dependent drug metabolism showed no differences in diabetic rabbits, which was contrary to the results yielded from studies on rats, mice and hamster. The aforementioned results [28], along with another study by the same research group [29] supported the idea of "species-dependent response of CYP-dependent drug metabolizing enzymes to diabetes". In the former study, a considerable increase of NDMA N-demethylase activity associated with CYP2E1 in the liver, kidneys and lungs were observed in diabetic rabbits. Given the outcome of the two studies, it can be concluded that the diabetic subjects have a higher risk of nitrosamine-induced carcinogenesis in their liver, kidneys and lungs [28].

In order to further study the effect of diabetes on drug metabolism, Toda et al. performed aminopyrine injections to normal, alloxan-and STZ-diabetic rats and evaluated the unchanged aminopyrine and its main metabolites concentrations using HPLC. Their results showed slow drug metabolism, increased serum levels of the intact drug, reduced serum clearance, and increased serum half-life of aminopyrine in diabetic rats. The changes in serum levels of aminopyrine metabolites were larger in alloxan-induced than in STZ-induced diabetic animals [30].

Cook, et al. studied a group of guinea pigs that had spontaneously developed diabetes. Both sexes exhibited hyperinsulinemia (4 times above normal). In such condition, inhibition of the hepatic drug metabolism occurred in male diabetic guinea pigs, but no such effect had been caused by diabetes in females [31]. This can demonstrate the effect of gender along with the DM on the metabolism.

Past and Cook measured the catalytic activity of CYP450 in the liver of rats with diabetes and concluded that diabetes induces a group of CYP450 with a specific catalytic activity that causes alterations in drug metabolism in the liver of diabetic rats [32]. In another study by Past, et al. the catalytic activities of major purified diabetic and normal CYP450 enzymes were compared with each other in a reconstituted drug metabolizing system. The maximum rate of aniline hydroxylation was performed by diabetic CYP450 enzymes (molecular weight 52000) that was 7 times higher than that of normal. However, the same diabetic CYP450 had the slowest rate of ethylmorphine N-demethylation than the other enzymes [33].

In one study in which oral triazolam had been administered to mice, the expression of small intestinal cytochrome CYP3A in the obese-diabetic mice were significantly lower than that in non-obese mice. The same assessment was carried out on small intestinal CYP3A

expression of STZ-induced diabetic mice and control mice where insignificant difference was observed. Amongst the control mice and insulin-treated mice, the expression of the small intestinal CYP3A was markedly lower in the latter group. The authors, therefore, proposed that the differences in insulin plasma levels could result in alterations of the expression of the small intestinal CYP3A between the two types of DM. This, in turn, can cause different pharmacokinetics of drugs in IDDM (type 1) and NIDDM (type 2) [34].

The results of a study on diabetic (induced by either STZ or alloxan) and normal rats suggested that the content of enzymes involved in hepatic drug metabolism were lower in diabetic rats. The decreased enzymes included glutathione reductase, glutathione peroxidase, p-nitrophenol glucuronosyltransferase, aryl sulphotransferase I and II. Conversely, activities of aryl sulphotransferase IV, flavin-containing monooxygenase (FMO), and Glutathione S-transferase (GST) were markedly higher in diabetic animals compared with those in the normal group. Insulin therapy in both STZ-and alloxan-induced diabetic rats could normalize the enzymatic activities of FMO, UDP-glucuronosyltransferase, aryl sulphotransferase and glutathione-related enzymes. The authors deduced that the activity of GST can be increased directly by STZ, and not because of the diabetes induced by diabetogenic agent. Nevertheless, it can be concluded that diabetic states is responsible for the instability in the activities of some metabolic enzymes [35].

Sindhu et al. conducted a 4-week research on male Sprague-Dawley rats to evaluate the expression of major isozymes of CYP450 in STZ-induced diabetes with simultaneous treatment with insulin. Results showed a microsomal up-regulation in the activity of CYP1B, CYP1A, heme oxygenase (HO)-2 proteins and CYP1A2-dependent 7-ethoxyresorufin O-deethylase (EROD) in the diabetic rats. The EROD activity as well as the expression of CYP1A, CYP1B1 and HO-2 had been improved by insulin and there was a noticeable induction in CYP2B1 and 2E1 proteins in diabetic animals. Treatment with insulin caused total and partial ameliorations of CYP2E1 and CYP2B1 proteins, respectively. Similarly, insulin could in part improve CYP2C11 protein while diabetic state decreased it by >99%. In sum, Sindhu pointed out that ubiquitous changes in the expression of different isozymes of CYP450 exist in diabetic rats that insulin therapy can ameliorate them [36].

Survey of mitochondrial changes in the reactive oxygen species (ROS) production and antioxidant defense system in four tissues (the pancreas, kidneys, brain, and liver) of diabetic rats has shown that mitochondrial and cytosolic glutathione metabolism can be affected by the increase in ROS and oxidative stress. Among the studied organs, the liver was affected less as much as the pancreas, kidneys, and brain. Mitochondrial levels of CYP2E1 and GST A4-4 were 5-8 times higher in diabetic than in non-diabetic animals' tissues that imply feasible roles in the progression of DM. Furthermore, the increased steady state levels of Hsp70 in mitochondria and cytosol of various tissues of diabetic rats were observed; therefore, indicating the direct role of mitochondrial CYP2E1 in ROS production within mitochondria [37].

In order for studying the effect of DM on pharmacokinetics parameters and changes in hepatic cytochromes, different drugs have been studied. Following oral and intravenous administration of clarithromycin in diabetic rats (induced by both STZ and alloxan), Kim et al. observed a significantly smaller area under the concentration-time curve in diabetic animals than that in the normal group. In addition, the intrinsic in vitro clearance of clarithromycin in both diabetic groups was faster than the control group. According to such findings, they stated that the higher metabolism of clarithromycin was due to an increase in the expression and the level of mRNA of CYP3A1 enzymes in both diabetic rats groups [38].

In another study on two groups of diabetic rats (also induced by STZ and alloxan), Kim, et al. evaluated the pharmacokinetics parameters of theophylline. Theophylline is converted to, 3-dimethyl uric acid by CYP1A2 and CYP2E1 in rats. Based on their results, the expression of CYP1A2 and CYP2E1 in diabetic rats was 3 times higher than in the normal group. Subsequent to intravenous administration of theophylline, a significant increase in the area under the curve of, 3-dimethyl uric acid was reported while the area under the curve for theophylline had been significantly reduced (due to a significant increase in total body clearance to time) in both diabetic groups of rats. Observations from in vitro studies on hepatic microsomes have suggested that the intrinsic clearance of, 3-dimethyl uric acid in both diabetic rats were significantly faster. It should be noted that the findings from oral administration of theophylline in this study were similar to those administered intravenously in previous studies [39].

Li, et al. evaluated the activity of aniline dehydroxylase and other drug metabolizing enzymes as an indirect index of CYP2E1 activity in diabetic rats. The results from diabetic animals showed a 53% increase in aniline dehydroxylase activity, along with 37% and 34% decreases in Cmax and AUC of chlorzoxazone, respectively. The Tpeak for 6-hydroxy-chlorzoxazone was apparently shorter in diabetic rats. In addition, the hydroxylation ability of 6-hydroxy-chlorzoxazone had been enhanced in diabetic rats. Since diabetic state induces CYP2E1 activity, careful consideration is required for administration of drugs metabolized by this isozyme in diabetic patients [40].

A recent publication by Lee et al., in which the changes in non-renal clearance of metoprolol after intravenous administration in diabetic rats had been studied, reported a 40.9% increase in non-renal clearance rate of metoprolol in diabetic animals. Such increase was attributed to a significantly higher hepatic blood flow. Since there were no differences between the plasma concentrations of free drug and hepatic intrinsic clearance of the drug in vitro, in the control and diabetic rats, it can be concluded that CYP2D activity in the liver of diabetic animals had not been altered. Following oral administration of metoprolol in diabetic rats and despite the intestinal absorption of >99%, significant decrease in the area under the curve was reported. The authors concluded that this could be due to greater hepatic metabolism of the intravenously administered drug [41].

According to Shimojo's study on CYP450 isozymes, in which changes in hepatic and renal microsomes of rodents with STZ-induced diabetes was evaluated and compared with the catalytic activities, the amounts of CYP2E1 and CYP4A2 in the liver of diabetic rats were 2.5 and 3 times higher than that in normal rats, respectively. Other CYP450 isozymes had also increased except for CYP2C11. Cytochromes 2E, 4A2 and K-4 were induced in the diabetic rats kidneys. However, all of the above changes were restored to normal levels following insulin therapy. The alterations of CYP450 isozymes in diabetic rodents were compatible with changes in their catalytic activities. Their results lead to the conclusion that metabolic alterations in ketones and fatty acids in diabetes may play a role in such changes [42].

Pharmacokinetics study on glibenclamide and diclofenac, showed a decline in the expression of CYP2C9 in diabetic rats when compared to the control group. Thus, the researchers concluded that the slower rate of glibenclamide and diclofenac clearance could be due to this

reduction in the expression of hepatic CYP2C9. Another finding was an increase in the AUC of glibenclamide for both intravenous and oral routes in the diabetic rats [1].

There are further parallel studies yielding the same results. In one of them, non-obese diabetic rats (Goto-kakizaki) with normal ketone bodies were studied by Oh et al. and the expression and activity of CYP was evaluated. Results demonstrated an increase in the expression and activity of the hepatic CYP-reductase, but decline in the activity of hepatic CYP1A2 and CYP3A1 in the diabetic group. No significant difference was reported in the levels of microsomal proteins, total CYP, and hepatic expression of cytochromes b5, CYP1B, CYP2B, and CYP2C11 between the two groups of normal and diabetic rats. The increased activity and expression of CYP2E1 in DM along with hyperketonemia has been shown earlier. However, the CYP activity and expression showed no significant difference between the diabetic and control groups in the population of rats studied by Oh et al. Thus, it can be posited that ketone bodies are possibly at play in increasing the hepatic CYP2E1 in diabetic animals [43].

Borbás et al. conducted a study in a murine model of diabetes, in which hepatic activity of FMO1 was restored following insulin therapy despite insulin having no effect on FMO1 activities in non-diabetic animals. Moreover, significant increases in the total amount of CYP together with reduction in the specific enzymatic activity of CYP3A in the small intestine of the diabetic rats were reported. Such alterations were diminished by insulin therapy. In addition, they showed that the levels of activity of the hepatic FMO1 and intestinal CYP3A were associated with mean serum glucose concentrations in diabetic rats. In other words, their results suggest a role for insulin in the regulation of intestinal CYP3A and hepatic FMO1 [44].

Tsai et al. studied coronary artery endothelial cells of pigs, whereby enzymatic alterations resulting from high levels of glucose in the animals were evaluated. They proclaimed that the inhibition of CYP activity in these cells is the corollary of increased levels of superoxide [45].

Three groups of diabetic rats (induced by both STZ and alloxan, and those with spontaneous diabetes) were subjected to a research. Results indicated that DM could induce microsomal CYP450ac (a form that is induced by acetone or ethanol) and increase mRNA in all 3 groups [46]. Thus, it is the diabetic state that causes the enzymes to change.

There are reports that ascribe the gender-specific changes in CYP450 proteins to IDDM, albeit such sex differences in a study by Branett et al. did not affect the severity of diabetes being induced by STZ in rats; since the levels of hyperkenoemia and hyperglycemia were similar in both male and female animals. Therefore, various enzyme changes in male and female diabetic rats possibly depend on differences between triglycerides and growth hormone (GH) levels among the two sexes [47].

Another research showed a significant increase in systemic clearance of the hepatic CYP1A2 protein and antipyrine in diabetic rats (induced by STZ), but no differences in the hepatic CYP3A2 protein levels [48].

A study on diabetic male rabbits over a period of two months demonstrated that diabetes does not affect microsomal concentrations (per mg protein) of CYP450. However, when CYP450 concentrations were assessed as per g of the liver weight, the increased concentrations of CYP450 in diabetic rabbits after a month of diabetes were observed. In addition, significantly higher activity of NADPH-cytochrome P450 reductase enzyme was reported in the diabetic group [49].

As can be summed up from the aforementioned studies, diabetes can increase the expression and levels of hepatic CYPs and particularly CYP2E, which in turn affects the metabolic state in the liver. However, insulin therapy may restore such alterations.

Effect of DM on Toxins Metabolism

Human studies

No ample evidence exists for the effects of DM on the metabolism of toxins in humans. Nonetheless, recent data indicate that oxidative damage in Type 1 and 2 DM is increased, and antioxidant enzymes and vitamins have insufficiencies as well. One assumption is that high blood glucose increases oxidative stress and alters the redox potential of glutathione, which results in the production of reactive oxygen species and therefore causes hyperglycemia [50].

On the other hand, it has been shown that damaged antioxidant mechanisms can increase oxidative stress in the individuals suffering from insulin-dependent diabetes mellitus (IDDM). Atalay et al. investigated the activity of major erythrocyte antioxidant enzymes either at rest or in response to continues moderate exercise in a group of diabetic young men. Activity of erythrocyte glutathione reductase was higher in diabetic group at rest which can be a compensatory up-regulation of glutathione homeostasis following increased oxidative stress. Lower activities of Cu, Zn-superoxide dismutase and catalase were observed in the erythrocytes of the IDDM group at rest, which might as well be a result of increase in oxidative stress. Se-glutathione peroxidase and GST activities were similar between the two groups and it can be the consequence of damage in the up-regulation of se-glutathione peroxidase after physical exercise in the individuals with IDDM [51]. Similarly, in a previous report, obviouse high blood glutathione levels and plasma lipid peroxidation were observed in IDDM patients [52].

Animal studies

A 90-day study on diabetic (induced by STZ) adult male Sprague-Dawley rats showed evident ketonemia 6 days after administration of streptozotocin. Markedly higher levels of hepatic aminotransferases (AST, ALT) following exposure to bromobenzene or carbon tetrachloride (CCl_4) was observed in diabetic rats that was indicative of potential hepatotoxicity of these chemicals due to diabetes. When diabetic rats were administered with CCl_4, enzyme activities toward benzphetamine, sulfobromophthalein, 1-chloro-,4-dinitrobenzene, and 1-naphthol declined. Similar changes in the enzymes activities were caused by significantly higher doses of CCl_4 in normal animals. Results demonstrated that the total CYP450 content was decreased due to diabetes and hepatotoxicants [9].

Wang et al. aimed to explore the effect of DM on liver injury and mortality from thioacetamide (300 mg/kg, single dose, i.p.) in STZ-induced diabetic rats. Thioacetamide resulted in 90% mortality in diabetic rats with a normally non-lethal dose. Plasma alanine aminotransferase (ALT), bilirubin, and sorbitol dehydrogenase (SDH) levels determinations, as well as histopathology tests were utilized to assess the hepatic damage and function during 60 hours after thioacetamide injection. Proliferating cell nuclear antigen (PCNA) and [3H] thymidine (3H-T) incorporation assays were used to estimate cell proliferation and tissue repairs. Results from diabetic rats were as

follows: liver necrosis started significantly earlier than that in normal rats, leading to hepatic failure and death; DNA synthesis was reduced by nearly 50% in the liver; a decrease in cell-cycle development was found, suggestive of languid tissue repair reactions that could extend hepatic injury. The authors thereby deduced that increased liver damage due to bio-activation of thioacetamide along with deficient tissue repair result in higher hepatotoxicity of thioacetamide in diabetic animals and thus, making a non-lethal dose of the chemical become peculiarly lethal [53].

Among all toxins, organophosphate pesticides have been undertaken research far more. Study on normal and STZ-induced diabetic rats explored the effect of organophosphate diazinon (DZN) on the activities of plasma cholinesterase and acetylcholinesterase (AChE) in the red blood cells and the brain. Antipyrine clearance and the expression of CYP3A2 and CYP1A, associated with the metabolism of DZN to DZN-oxon, were assessed in order to make an approximation of drug metabolic activity of the liver. Results from this research revealed that although insignificant differences in cholinesterase and AChE activities existed between the two groups, administration of DZN could drastically reduce such activities in diabetic rats more than those in the normal group. When urinary metabolites of DZN (diethylthiophosphate) and DZN-oxon (diethylphosphate) were measured, the recovery of the latter was markedly higher in diabetic animals while diethylthiophosphate was intact. Total clearance of antipyrine and levels of CYP1A2 protein was increased in diabetic rats. In conclusion, it can be stated that diabetes results in the enhanced CYP1A2-related metabolism of DZN and therefore makes its metabolite more toxic [48].

The research group continued their study to investigate the effect of DZN on glucose tolerance in genetical type 2 diabetic rats (Goto-Kakizaki (GK) rats) compared to Wistar rats. The plasma glucose concentrations were noticeably higher in GK rats that sampled 1 and 2 weeks following an intraperitoneal injection of 6.5 mg/kg of DZN. The activity and expression of different types of CYP450 involving in DZN metabolism showed no significant difference between the GK and Wistar rats. There was a drastic reduction in plasma cholinesterase of both groups, with no remarkable difference between the groups. The team suggested that glucose tolerance was degenerated by DZN in GK rats [54].

An experimental study challenged STZ-induced diabetic mice with lethal single doses of acetaminophen (APAP), CCl_4, or bromobenzene, and reported the resistance to the three hepatotoxicants. Aimed to scrutinize the mechanisms of protection against hepatotoxicity with acetaminophen, the authors observed a markedly lower liver damage following acetaminophen administration in diabetic mice when the hepatic aminotransferases and histopathology tests were checked. Pharmacokinetics parameters of acetaminophen in the diabetic mice demonstrated lower plasma $t_{1/2}$, and higher volume of distribution and plasma clearance. Results from cell division assessments indicated that the S-phase occurred earlier in the diabetic animals following acetaminophen administration. Shankar et al. at the end concluded that the increased clearance of acetaminophen along with the compensatory sturdy mechanism of tissue restoration is likely to protect diabetic mice against liver damage and toxic effects of APAP [55].

A similar study, in which type 2 diabetic mice were exposed to the same three hepatotoxicants (acetaminophen, CCl_4, and bromobenzene), showed hepatotoxic resistance to the mentioned chemicals. The authors conjectured that reduced bioactivation of acetaminophen, toxicokinetics alterations, and improved tissue repair can play a role. Plasma and urine acetaminophen levels or its glucuronidation-mediated detoxification, content and activity of hepatic CYP2E, glutathione, and [14C] APAP covalent binding in diabetic mice were akin to those in the healthy mice. Being closely resembled to the previous study, results suggested that improvements in tissue repair inhibit the progression of hepatotoxicity thereby protecting diabetic mice against the APAP toxicity [56].

Conclusion

Numerous pathological or abnormal physiological states can affect the microsomal drug-metabolizing enzymes. Although it has not been adequately investigated in humans thus far, general data show that the metabolism of drugs and toxins is altered in diabetes. Being ethically restricted, clinical studies are not commonly performed and therefore, animal models of diabetes have been used with the aim of addressing such problem. Murine models, specially the rats, are most commonly established in drug metabolism studies. Data from majority of the STZ-induced diabetic animals reveal that the expression of several CYP450 isozymes (2E,2B,3A and 4A) increases in the uncontrolled diabetes state, thus making the drug/toxin to exert stronger adverse effects. However, treatment with insulin can reverse this to a normal state. In sum, the effect of diabetes on drugs and toxins metabolism is yet to be fathomed via further clinical and experimental studies.

References

1. Li Y, Wei Y, Zhang F, Wang D, Wu X (2012) Changes in the pharmacokinetics of glibenclamide in rats with streptozotocin-induced diabetes mellitus. Acta Pharmaceutica Sinica B 2: 198-204.
2. Dostalek M, Akhlaghi F, Puzanovova M (2012) Effect of diabetes mellitus on pharmacokinetic and pharmacodynamic properties of drugs. Clin Pharmacokinet 51: 481-499.
3. LaMonte MJ, Blair SN, Church TS (2005) Physical activity and diabetes prevention. J Appl Physiol (1985) 99: 1205-1213.
4. Wing RR, Goldstein MG, Acton KJ, Birch LL, Jakicic JM, et al. (2001) Behavioral science research in diabetes: lifestyle changes related to obesity, eating behavior, and physical activity. Diabetes Care 24: 117-123.
5. Esteghamati A, Gouya MM, Abbasi M, Delavari A, Alikhani S, et al. (2008) Prevalence of diabetes and impaired fasting glucose in the adult population of Iran: National Survey of Risk Factors for Non-Communicable Diseases of Iran. Diabetes Care 31: 96-98.
6. Engelgau MM, Geiss LS, Saaddine JB, Boyle JP, Benjamin SM, et al. (2004) The evolving diabetes burden in the United States. Ann Intern Med 140: 945-950.
7. Isacson D, Stålhammar J (1987) Prescription drug use among diabetics--a population study. J Chronic Dis 40: 651-660.
8. Reinke LA, Stohs SJ, Rosenberg H (1978) Altered activity of hepatic mixed-function mono-oxygenase enzymes in streptozotocin-induced diabetic rats. Xenobiotica 8: 611-619.
9. Watkins JB 3rd, Sanders RA, Beck LV (1988) The effect of long-term streptozotocin-induced diabetes on the hepatotoxicity of bromobenzene and carbon tetrachloride and hepatic biotransformation in rats. Toxicol Appl Pharmacol 93: 329-338.
10. Gwilt PR, Nahhas RR, Tracewell WG (1991) The effects of diabetes mellitus on pharmacokinetics and pharmacodynamics in humans. Clin Pharmacokinet 20: 477-490.
11. Skett P, Joels LA (1985) Different effects of acute and chronic diabetes mellitus on hepatic drug metabolism in the rat. Biochem Pharmacol 34: 287-289.
12. Goldstein S, Simpson A, Saenger P (1990) Hepatic drug metabolism is increased in poorly controlled insulin-dependent diabetes mellitus. Acta Endocrinol (Copenh) 123: 550-556.

13. Salmela PI, Sotaniemi EA, Pelkonen RO (1980) The evaluation of the drug-metabolizing capacity in patients with diabetes mellitus. Diabetes 29: 788-794.
14. Sotaniemi EA, Pelkonen O, Arranto AJ, Tapanainen P, Rautio A, et al. (2002) Diabetes and elimination of antipyrine in man: an analysis of 298 patients classified by type of diabetes, age, sex, duration of disease and liver involvement. Pharmacol Toxicol 90: 155-160.
15. Akhlaghi F, Dostalek M, Falck P, Mendonza AE, Amundsen R, et al. (2012) The concentration of cyclosporine metabolites is significantly lower in kidney transplant recipients with diabetes mellitus. Ther Drug Monit 34: 38-45.
16. Dostalek M, Court MH, Yan B, Akhlaghi F (2011) Significantly reduced cytochrome P450 3A4 expression and activity in liver from humans with diabetes mellitus. Br J Pharmacol 163: 937-947.
17. Dostalek M, Gohh RY, Akhlaghi F (2013) Inosine Monophosphate Dehydrogenase Expression and Activity Are Significantly Lower in Kidney Transplant Recipients With Diabetes Mellitus. Ther Drug Monit 35: 374-383.
18. Dostalek M, Hazarika S, Akhlaghi F (2011) Diabetes mellitus reduces activity of human UDP-glucuronosyltransferase 2B7 in liver and kidney leading to decreased formation of mycophenolic acid acyl-glucuronide metabolite. Drug Metab Dispos 39: 448-455.
19. Matzke GR, Frye RF, Early JJ, Straka RJ, Carson SW (2000) Evaluation of the influence of diabetes mellitus on antipyrine metabolism and CYP1A2 and CYP2D6 activity. Pharmacotherapy 20: 182-190.
20. Pirttiaho HI, Salmela PI, Sotaniemi EA, Pelkonen RO, Pitkänen U, et al. (1984) Drug metabolism in diabetic subjects with fatty livers. Br J Clin Pharmacol 18: 895-899.
21. Oltmanns D, Dennin DE, Pentz R, Siegers CP (1984) [Antipyrine clearance as a measure of drug metabolism in patients with diabetes mellitus]. Z Gastroenterol 22: 598-601.
22. Saenger P (1987) Hepatic drug metabolism is increased in poorly controlled insulin dependent diabetes mellitus (Iddm). Pediatric Research 21: 346.
23. Hannon-Fletcher MP, O'Kane MJ, Moles KW, Barnett YA, Barnett CR (2001) Lymphocyte cytochrome P450-CYP2E1 expression in human IDDM subjects. Food Chem Toxicol 39: 125-132.
24. Haufroid V, Ligocka D, Buysschaert M, Horsmans Y, Lison D (2003) Cytochrome P4502E1 (CYP2E1) expression in peripheral blood lymphocytes: evaluation in hepatitis C and diabetes. Eur J Clin Pharmacol 59: 29-33.
25. Pucci L, Chirulli V, Marini S, Lucchesi D, Penno G, et al. (2005) Expression and activity of CYP2E1 in circulating lymphocytes are not altered in diabetic individuals. Pharmacol Res 51: 561-565.
26. Cook DE, Past MR (1979) Drug metabolism in diabetic isolated perfused rat liver. Res Commun Chem Pathol Pharmacol 24: 389-392.
27. Dixon RL, Hart LG, Fouts JR (1961) The metabolism of drugs by liver microsomes from alloxan-diabetic rats. Journal of Pharmacology and Experimental Therapeutics 133: 7-11.
28. Arinç E, Arslan S, Bozcaarmutlu A, Adali O (2007) Effects of diabetes on rabbit kidney and lung CYP2E1 and CYP2B4 expression and drug metabolism and potentiation of carcinogenic activity of N-nitrosodimethylamine in kidney and lung. Food Chem Toxicol 45: 107-118.
29. Arinç E, Arslan S, Adali O (2005) Differential effects of diabetes on CYP2E1 and CYP2B4 proteins and associated drug metabolizing enzyme activities in rabbit liver. Archives of toxicology 79: 427-433.
30. Toda A, Shimeno H, Nagamatsu A, Shigematsu H (1987) Effects of experimental diabetes on aminopyrine metabolism in rats. Xenobiotica 17: 1075-1083.
31. Cook DE, Jackson JD, Past MR, Lang CM, Bullock LP (1984) Drug metabolism in spontaneously diabetic guinea pigs. Experientia 40: 840-841.
32. Past MR, Cook DE (1983) Catalytic activities of cytochrome P-450 from female rat liver: correlation with sex differences in drug metabolism in diabetic liver. Res Commun Chem Pathol Pharmacol 40: 379-390.
33. Past MR, Cook DE (1982) Drug metabolism in a reconstituted system by diabetes-dependent hepatic cytochrome P-450. Res Commun Chem Pathol Pharmacol 37: 81-90.
34. Kudo T, Toda T, Ushiki T, Ohi K, Ikarashi N, et al. (2010) Differences in the pharmacokinetics of Cyp3a substrates in TSOD and streptozotocin-induced diabetic mice. Xenobiotica 40: 282-290.
35. Toda A, Eyanagi R, Saito H, Soeda S, Shimeno H, et al. (2004) Effects of experimental diabetes on hepatic drug metabolism in rats: the activities of flavin-containing monooxygenase, the phase II conjugation reactions and glutathione related enzymes. Research communications in molecular pathology and pharmacology 117: 13-27.
36. Sindhu RK, Koo JR, Sindhu KK, Ehdaie A, Farmand F, et al. (2006) Differential regulation of hepatic cytochrome P450 monooxygenases in streptozotocin-induced diabetic rats. Free Radic Res 40: 921-928.
37. Raza H, Prabu SK, Robin M-A, Avadhani NG (2004) Elevated mitochondrial cytochrome P450 2E1 and glutathione S-transferase A4-4 in streptozotocin-induced diabetic rats tissue-specific variations and roles in oxidative stress. Diabetes 53: 185-194.
38. Kim YC, Lee JH, Kim SH, Lee MG (2005) Effect of CYP3A1(23) induction on clarithromycin pharmacokinetics in rats with diabetes mellitus. Antimicrob Agents Chemother 49: 2528-2532.
39. Kim YC, Lee AK, Lee JH, Lee I, Lee DC, et al. (2005) Pharmacokinetics of theophylline in diabetes mellitus rats: induction of CYP1A2 and CYP2E1 on, 3-dimethyluric acid formation. Eur J Pharm Sci 26: 114-123.
40. Li L, Zhang Y (1998) [Changes of CYP2E1 activity in diabetic rat model]. Yao Xue Xue Bao 33: 891-895.
41. Lee U, Lee I, Lee BK, Kang HE (2013) Faster non-renal clearance of metoprolol in streptozotocin-induced diabetes mellitus rats. Eur J Pharm Sci 50: 447-453.
42. Shimojo N, Ishizaki T, Imaoka S, Funae Y, Fuji S, et al. (1993) Changes in amounts of cytochrome P450 isozymes and levels of catalytic activities in hepatic and renal microsomes of rats with streptozocin-induced diabetes. Biochemical pharmacology 46: 621-627.
43. Oh SJ, Choi JM, Yun KU, Oh JM, Kwak HC, et al. (2012) Hepatic expression of cytochrome P450 in type 2 diabetic Goto-Kakizaki rats. Chem Biol Interact 195: 173-179.
44. Borbás T, Benko B, Dalmadi B, Szabó I, Tihanyi K. (2006) Insulin in flavin-containing monooxygenase regulation: flavin-containing monooxygenase and cytochrome P450 activities in experimental diabetes. European Journal of Pharmaceutical Sciences 28: 51-8.
45. Tsai SH, Hein TW, Kuo L, Yang VC (2011) High glucose impairs EDHF-mediated dilation of coronary arterioles via reduced cytochrome P450 activity. Microvasc Res 82: 356-363.
46. Dong ZG, Hong JY, Ma QA, Li DC, Bullock J, et al. (1988) Mechanism of induction of cytochrome P-450ac (P-450j) in chemically induced and spontaneously diabetic rats. Arch Biochem Biophys 263: 29-35.
47. Barnett CR, Rudd S, Flatt PR, Ioannides C (1993) Sex differences in the diabetes-induced modulation of rat hepatic cytochrome P450 proteins. Biochem Pharmacol 45: 313-319.
48. Ueyama J, Wang D, Kondo T, Saito I, Takagi K, et al. (2007) Toxicity of diazinon and its metabolites increases in diabetic rats. Toxicol Lett 170: 229-237.
49. Longhurst PA, LaCagnin LB, Staats DA, Colby HD (1986) Changes in hepatic drug metabolism in alloxan-diabetic male rabbits. Biochem Pharmacol 35: 1768-1771.
50. West IC (2000) Radicals and oxidative stress in diabetes. Diabet Med 17: 171-180.
51. Atalay M, Laaksonen D, Niskanen L, Uusitupa M, Hänninen O, et al. (1997) Altered antioxidant enzyme defences in insulin-dependent diabetic men with increased resting and exercise-induced oxidative stress. Acta physiologica scandinavica 161: 195-201.

52. Laaksonen DE, Atalay M, Niskanen L, Uusitupa M, Hänninen O, et al. (1996) Increased resting and exercise-induced oxidative stress in young IDDM men. Diabetes Care 19: 569-574.

53. Wang T, Fontenot RD, Soni MG, Bucci TJ, Mehendale HM (2000) Enhanced hepatotoxicity and toxic outcome of thioacetamide in streptozotocin-induced diabetic rats. Toxicol Appl Pharmacol 166: 92-100.

54. Ueyama J, Kamijima M, Asai K, Mochizuki A, Wang D, et al. (2008) Effect of the organophosphorus pesticide diazinon on glucose tolerance in type 2 diabetic rats. Toxicol Lett 182: 42-47.

55. Shankar K, Vaidya VS, Apte UM, Manautou JE, Ronis MJ, et al. (2003) Type 1 diabetic mice are protected from acetaminophen hepatotoxicity. Toxicol Sci 73: 220-234.

56. Sawant SP, Dnyanmote AV, Mitra MS, Chilakapati J, Warbritton A, et al. (2006) Protective effect of type 2 diabetes on acetaminophen-induced hepatotoxicity in male Swiss-Webster mice. J Pharmacol Exp Ther 316: 507-519.