

# **Alterations in the Gene Expression of Drug Metabolizing Enzymes in Diabetic Animal Models**

**By**

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## **ABSTRACT**

**Background:** Diabetic patients have lower capacity to metabolize drugs in comparison to normal people.

**Aims:** The present study aimed to investigate the alterations in gene expression of drug and arachidonic acid metabolizing cytochrome p450s (*cyp450s*) in the livers of controlled (CDM) and uncontrolled (UDM) insulin-dependent diabetic mice.

**Methods:** This study was done on twenty eight Balb/c mice, divided into four groups. Each group had seven mice as following: the first group which was control group and was treated with the vehicle citric buffer (pH=4.5) by intraperitoneal route (IP). The second group was uncontrolled diabetes mellitus (UDM) insulin dependent group, which was treated with single dose of streptozocin (STZ) (240 mg/kg IP); to induce diabetes mellitus type I (DM I). After 3 days, the blood glucose level was measured to confirm the induction of diabetes. The third group was controlled diabetes mellitus

(CDM) insulin dependent and it was treated with STZ and after 3 days, normalization the blood glucose level in diabetic mice was normalized by 0.1ml/kg Mixtard® insulin therapy twice daily for 5 days. The fourth group was insulin treated hypoglycemic group which was exposed only to Mixtard® insulin twice daily. Then, the mice livers were isolated to extract RNA and convert it to cDNA. The gene expression of 14 genes, which play a major role in drug and arachidonic acid metabolism, were measured using quantitative real-time polymerase chain reaction (RT-PCR) technique.

**Results:** It is found that the gene expression of drug and arachidonic acid metabolizing enzymes was down-regulated (*t*-test, *p* value <0.05) in the livers of UDM mice. The most down-regulated genes were *cyp4a12*, *cyp1a2* and *slc22a1* with more than 10 folds reduction. The livers of CDM mice showed significant (*t*-test, *p* value <0.05) higher levels of gene expression than UDM mice, but still lower than the controlled non-diabetic mice.

**Conclusion:** This study concluded that hepatic gene expression of drug metabolizing and arachidonic acid-*cyp450* enzymes is reduced in insulin-dependent diabetic mice, which can explain, at least in part, the variation in drug and fatty acid metabolism between controlled and uncontrolled diabetic mice.

**Keywords:** Drug metabolism, gene expression, diabetes, insulin, arachidonic acid.