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Opinion

# Drug-Drug Interactions with Relevance to Drug Induced Mitochondrial Toxicity and Accelerated Global Chronic Diseases

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Prevalent chronic diseases such as cardiovascular disease, non alcoholic fatty liver disease (NAFLD) and neurodegenerative diseases [1-5] have raised major concern with relevance to diabetes and the global problem for chronic diseases [6] extending to various parts of the developing world. The role of various factors such as diet, environment, stress and lifestyle as important factors that regulate chronic disease progression have been explored with various studies that indicate major changes in unhealthy diets (Figure 1) may assist with a delay in the acceleration of these chronic diseases. Drug therapy to stabilize insulin resistance and various chronic diseases that reverse cell senescence and apoptosis has been implemented in various global populations. The need to optimize drug therapy and improve therapeutic outcomes has become of major concern with relevance to alarming reports of drug-drug interactions or drug-disease interactions [7] with relevance to the global chronic disease epidemic. In diseases of the heart, brain and liver cell senescence is now connected to mitochondrial apoptosis with nutrition of major importance in the maintenance of mitochondrial biogenesis and the prevention of NAFLD and obesity [8]. The search for specific genes that maintain mitochondria biogenesis has identified the anti-aging gene Sirtuin 1 (Sirt 1) as the gene involved in mitochondrial biogenesis [8]. Sirt 1 is a NAD+ dependent class III histone deacetylase activity involved in the regulation of metabolic activity, insulin resistance and inflammatory processes and is now important to drug therapy and metabolism with relevance to prevention of drug-drug interactions [9]. Sirt 1is involved in the deacetylation of the pregnane X receptor that is critical to drug metabolism [9] and regulation of other transcription factors (deacetylation) are also linked to hepatic glucose, fatty acid and caffeine metabolism [9-11]. Nutritional interventions that regulate Sirt 1 have become critical to prevent NAFLD, cardiovascular disease and neurodegeneration [5] with consumption activators of Sirt 1 (magnesium, leucine, alpha-lipoic acid, pyruvic acid, resveratrol) important to maintain drug therapy and metabolism (Figure 1). Downregulation of Sirt 1 by unhealthy diets (high calorie, palmitic acid rich diets, arginine rich diets) [12] and drugs such as sirtinol and suramin that inhibit the Sirt 1 have become of concern to maintenance of hepatic drug metabolism and prevention of insulin resistance with connections to various organ diseases.

The delivery of specific therapeutic drugs to the mitochondria [13] to prevent mitochondrial metabolic over activity has recently proven to be an effective therapeutic strategy to assist insulin resistance and the metabolic syndrome in individuals with cardiovascular disease, NAFLD and neurodegeneration. Healthy diets that accelerate hepatic drug metabolism prevent the accumulation of drugs in various cells of the heart, liver and brain that may induce mitochondrial cell apoptosis. Healthy diets in individuals with NAFLD is essential to prevent drug-drug interactions versus drug-disease interactions involved in drug induced mitochondrial apoptosis [14-16] that is of major concern to the global chronic disease epidemic. The liver is the organ that is of critical importance to caffeine metabolism and the dose of caffeine consumed by individuals is now under review to prevent caffeine induced insulin resistance and mitochondrial apoptosis [10]. Caffeine overload may delay drug metabolism [17] and promote the drug-drug interactions with mitochondrial induced apoptosis. In the developing world plasma xenobiotic [9] and bacterial lipopolysaccharide levels (LPS) [18] have increased markedly with relevance

to drug-drug interactions and drug-disease induced mitochondrial apoptosis. LPS induces NAFLD with inactivation of drug therapy that are essential for the treatment of cardiovascular disease and neurodegenerative diseases [5]. Withdrawal of drugs with relevance to toxicity [19] and adverse effects on various organs have been reported and in the developing world plasma LPS and xenobiotic levels may be mechanisms involved in the drug-induced toxicity [7,17,19]. In individuals with Type 3/Type 2 diabetes [20] or geriatric individuals [21] consumption of caffeine and various therapeutic drugs should be carefully controlled with relevance to increased risk of NAFLD with poor drug transport and metabolism that may induce pancreas toxicity [5] in these individuals.

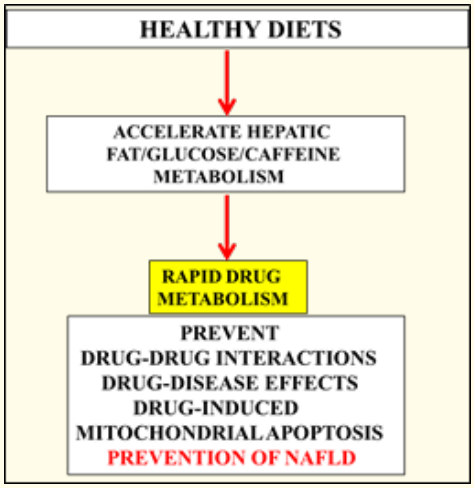


***Figure 1:*** *Healthy diets that activate liver Sirt 1 are critical to the maintenance of hepatic drug metabolism with the prevention of drug induced mitochondrial apoptosis in various tissues. Low calorie diets (glucose, fatty acids) allow rapid metabolism of caffeine that may be connected to rapid drug metabolism. Diets that are unhealthy prevent rapid glucose, fatty acids and caffeine metabolism and delay drug metabolism with toxicity to the heart, pancreas, liver and brain.*

## Conclusion

Drug therapy to stabilize insulin resistance and various chronic diseases has become a major concern in various global populations. Nutritional interventions are required to optimize drug therapy and improve therapeutic outcomes to reverse drug-drug interactions or drug-disease interactions in the current global chronic disease epidemic. Low calorie diets that activate Sirt 1 have become critical to prevent NAFLD, cardiovascular disease and neurodegeneration with consumption Sirt 1 activators important to maintain drug therapy and metabolism. Unhealthy diets that reduce drug metabolism increases the risk for chronic diseases with relevance to drug induced mitochondrial apoptosis in the liver, pancreas, heart and brain. In the developing world caffeine consumption should be assessed with relevance to the elevated levels of xenobiotic and LPS that may inactivate drug metabolism and accelerate drug induced mitochondrial apoptosis in these populations.

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