

## Review Article

# Nutrition Therapy Regulates Caffeine Metabolism with Relevance to NAFLD and Induction of Type 3 Diabetes

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## Abstract

In the developed and developing world nutritional interventions have become essential to prevent global Non Alcoholic Fatty Liver Disease (NAFLD) and to maintain the metabolism of glucose, fatty acids, cholesterol, amyloid beta, bile acids and xenobiotics. The World Health Organization (WHO) has reported that cardiovascular disease is the most prevalent global chronic disease that may be connected to NAFLD and the alarming death rate in various communities. Caffeine (appetite suppressant) may improve the adipose tissue-liver cross talk with the prevention of NAFLD in obese and Type 2 diabetic populations. Overeating may accelerate chronic diseases with repression of anti-aging genes linked to NAFLD and delayed caffeine clearance linked to the induction of Type 3 diabetes in global populations. Nutritional interventions to reverse NAFLD in the developing world are associated with accelerated caffeine clearance rates with prevention of caffeine induced mitochondrial apoptosis that is linked to early neuron loss and the development of Type 3 diabetes in these populations.

**Keywords:** Anti-aging genes; Appetite; Caffeine; Diabetes; Diet; Gall bladder; Mitochondria; Myocardial infarction; NAFLD; Neurodegeneration

## Abbreviations

Sirt 1: Sirtuin 1; T3D: Type 3 Diabetes; NAFLD: Non Alcoholic Fatty Liver Disease; SCN: Supra Chiasmatic Nucleus; FOXO: Forkhead Box Protein; Cytochrome A1, CYP 1A1; BDNF: Brain Derived Neurotrophic Factor; NO: Nitric Oxide; LPS: Bacterial Lipopolysaccharides

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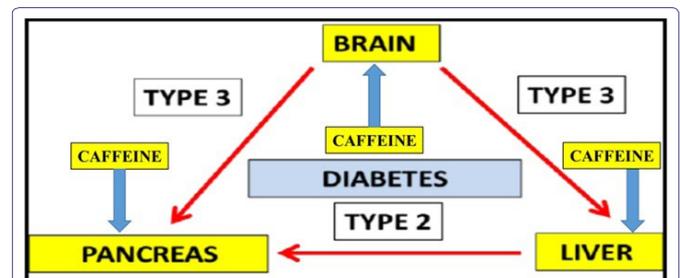
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## Background

In the developing and developed world Non Alcoholic Fatty Liver Disease (NAFLD) and diabetes [1-7] has escalated in various communities with the essential need for nutritional interventions [8] to improve and control overeating and to accelerate the clearance of hepatic of glucose, fatty acids, bile acids, xenobiotics, amyloid beta and cholesterol that are associated with various chronic diseases. Appetite dysregulation is connected to NAFLD and the defective metabolism of various plasma components [4-6] that may accelerate chronic diseases that include obesity, diabetes, cardiovascular disease and neurodegenerative diseases. Nutrition therapy is essential to maintain appetite control [4] and determines the hepatic degradation of glucose, fatty acids and cholesterol that is connected to the toxic amyloid beta oligomers [8,9] and xenobiotics with relevance to programmed cell death in various chronic diseases.

Caffeine is an appetite suppressant [10-12] and with the aging process its delayed clearance can be related to the induction of NAFLD and Type 3 Diabetes (T3D) [6,7]. The beneficial effects of caffeine may be corrupted with toxic caffeine doses transported to the brain relevant to neurodegeneration and induction of T3D diabetes. In previous studies Alzheimer's disease represents a form of T3D and related to extensive disturbances in brain insulin and insulin-like growth factor signalling pathways with relevance to critical abnormalities in AD [13].

T3D is associated with Supra Chiasmatic Nucleus (SCN) dysfunction with the abnormal maintenance of brain and whole body glucose in various species and man [14-16]. Nutritional interventions have become important to increase caffeine metabolism and prevent the induction of T3D [17-19] in global populations (Figure 1). Delayed caffeine metabolism may further induce myocardial infarction, pancreas and thyroid disorders relevant to Type 1 (T1D), Type 2 (T2D) and T3D [20] and various other chronic diseases [21-30] (Figure 1).



**Figure 1:** In the global epidemic for chronic diseases T3D and T2D are now connected to Non Alcoholic Fatty Liver Disease (NAFLD). Hepatic caffeine metabolism in T3D/T2D is corrupted with the induction of caffeine induced pancreatic disease and various chronic diseases.

Appetite control in diabetic populations is essential to prevent mitochondrial apoptosis that induce diseases such as NAFLD, myocardial infarction and neurodegenerative disease [21-30]. T3D diabetes and appetite dysregulation is a major concern with brain disorders and autonomic dysregulation [6] related to a defect in the cross talk between the adipose tissue and the liver [31,32]. Interests in the adipose tissue has escalated with relevance to the global obesity epidemic [5] with

NAFLD as the major disease progression. Caffeine and prevention of adipogenesis [33-35] has been reported but in T3D caffeine toxicity [36,37] may be relevant to caffeine intake (dose) and the nature of food composition (fat/glucose) important to the induction of mitochondrial apoptosis and NAFLD in T3D.

### Anti-aging Genes and Caffeine Metabolism with relevance to NAFLD, diabetes and chronic diseases

Interests in nutrition therapy to prevent NAFLD and diabetes now involve low calorie diets that identify a single anti-aging gene defect in the development of diabetes [38-40]. The gene defect involves the anti-aging gene Sirtuin 1 (Sirt 1) that regulates appetite, nuclear-mitochondria interaction, adipose tissue-liver crosstalk, synaptic plasticity and neuron proliferation in various populations in the developing and developed world [6,31,32,41-46]. Sirt 1 is important to SCN function that maintains synchrony between neurons that is critical to circadian rhythm and glucose clearance in the brain and periphery [14-16]. Metabolic disturbances in neurons may be linked to other anti-aging genes associated glucose dyshomeostasis and dyslipidemia. Interests in calorie restriction, appetite regulation and neurodegeneration that involve Sirt 1 mediated regulation of other anti-aging genes has accelerated [47-49] and involve p53 and FOXO deacetylation in relation to autonomous disease of the brain and liver. Over nutrition is associated with the repression of Sirt 1 and control the other anti-aging genes such as Klotho, p66shc (longevity protein) and FOXO1/FOXO3a that are connected to brain and liver with SCN disturbances. Nutritional interventions that maintain Sirt 1 activity are important to T3D, T2D and T1D with Sirt 1 down regulation in NAFLD relevant to the defective metabolism of caffeine, glucose, fatty acids, cholesterol, amyloid beta, bile acids, and xenobiotics.

Regulation of food intake involves Sirt 1 and is the gene that is linked to life span, obesity and cardiovascular disease with effects on NAFLD, inflammation, energy, cognition, mitochondrial biogenesis, neurogenesis, glucose/cholesterol levels and amyloidosis. Sirt 1 is a Nicotinamide Adenine Dinucleotide (NAD<sup>+</sup>) dependent class III Histone Deacetylase (HDAC) that targets transcription factors to adapt gene expression to metabolic activity and the deacetylation of the nuclear receptors with its critical involvement in insulin resistance. Sirt 1 is important to telomerase reverse transcriptase and genomic DNA repair with its involvement in telomere maintenance that maintains chromosome stability and cell proliferation [7]. Tissue nuclear receptors undergo deacetylation of histone and non-histone targets by Sirt 1 (NAD<sup>+</sup> dependent class III histone deacetylase) that target transcription factors peroxisome Proliferator-Activated Receptor-Gamma Coactivator (PGC-1 alpha), p53, Pregnane X Receptor (PXR) to adapt gene expression to metabolic activity, insulin resistance and inflammation. Sirt 1 is linked to glucose regulation with the involvement of Forkhead box protein O1 (FOXO1) deacetylation (apoptosis) that involve p53 transcriptional dysregulation and Peroxisome Proliferator Activated Receptor (PPAR) gamma nuclear receptor. Furthermore Sirt 1/p53 interactions may regulate adipocytokines and immune responses that may be important to NAFLD, obesity and neurodegeneration [31]. Sirt 1 is critical to caffeine metabolism with Sirt 1 regulation of Cytochrome A1 (CYP 1A1) and Cytochrome A1 (CYP 1A2) essential for caffeine [50] and xenobiotic clearance [51]. Sirt 1 regulation of Brain Derived Neurotrophic Factor (BDNF) has been shown [47] with caffeine linked to Sirt 1/BDNF regulation and synaptic plasticity [52,53]. Caffeine induces FOXO1 transport to the nucleus [54,55] with relevance to neuron apoptosis and neurodegeneration in

diabetes. Nutrition therapy that involves coffee (composition) versus caffeine intake (dose) is critical to the regulation of Sirt 1 with the primary hepatic caffeine metabolism (Figure 2) that determines the secondary clearance of hepatic glucose, fatty acids, bile acids, xenobiotics and amyloid beta that are closely connected to various chronic diseases such as NAFLD, cardiovascular disease, diabetes, stroke and neurodegeneration [56-63]. Caffeine is essential for the prevention of blood brain barrier disruption [64-68] but with NAFLD excess caffeine transport to the brain is associated with neurodegeneration. Coffee may contain ochratoxin A that is a potent neurotoxin relevant to mitochondrial apoptosis and overrides Sirt's regulation of mitochondrial biogenesis with relevance to neurodegeneration [69].

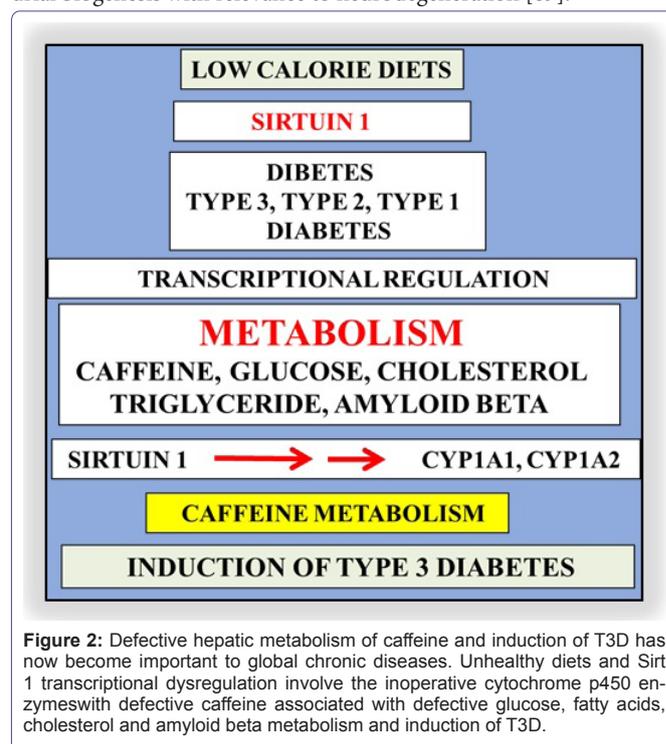
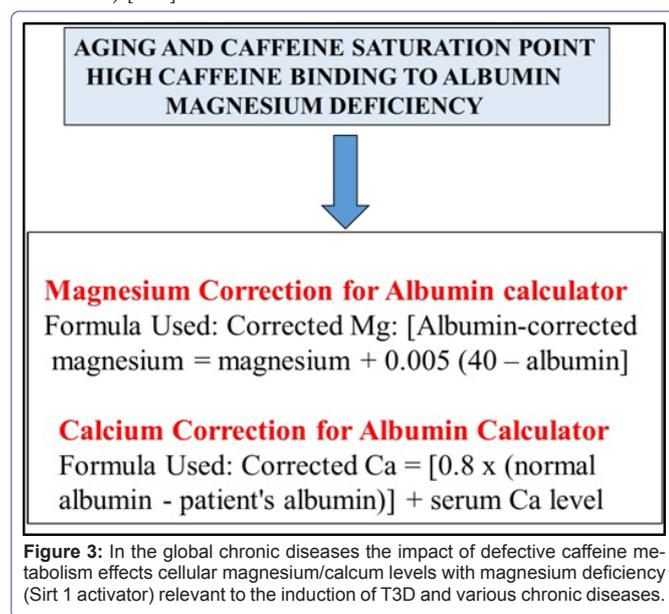


Figure 2: Defective hepatic metabolism of caffeine and induction of T3D has now become important to global chronic diseases. Unhealthy diets and Sirt 1 transcriptional dysregulation involve the inoperative cytochrome p450 enzymes with defective caffeine associated with defective glucose, fatty acids, cholesterol and amyloid beta metabolism and induction of T3D.

The global death rate by the WHO has reported cardiovascular disease to be the most prevalent chronic disease and connected to appetite dysregulation with Sirt 1 defects relevant to myocardial infarction in various studies. Defective Sirt 1 [38-40,47-49] is associated with glucose dysregulation with inhibition of insulin signalling and acute mitochondrial apoptosis that may be relevant to myocardial infarction. Over nutrition that down regulates Sirt 1 interferes with hepatic caffeine and cellular Nitric Oxide (NO) homeostasis with implications to cardiovascular disease [70-76] and various global organ diseases [6]. Over nutrition that involves excessive NO consumption prevents mitochondrial biogenesis [4] with effects on mitochondria size, number and shape [77-80].

Mitochondrial function has been reported to be important to chronic disease with Sirt 1/p53 defects critical to mitophagy with relevance to NAFLD, cardiovascular disease, obesity and neurodegenerative diseases [7,20,31]. In the current obesity/diabetes epidemic caffeine metabolism is possibly defective [18] and effects of caffeine is via Sirt 1/p53 regulated mitochondria biogenesis with caffeine doses related to p53 mediated mitophagy relevant to cellular programmed cell death [17]. Sirt 1 is relevant to mitophagy [17-20] in myocardial infarction [81-86] and hepatic caffeine metabolism now important to endothelial death and interference of the endothelial NO synthase

pathway with promotion of neurodegeneration and T3D [6]. Caffeine and its defective clearance in NAFLD may indicate that caffeine may reach a saturation point by binding to albumin [18,87] with primary saturation of albumin (Figure 3) in the plasma and secondary caffeine saturation of cell membranes. Caffeine can be converted to theophylline in cells but beneficial theophylline effects may be sensitive to toxic elevated caffeine levels in cells. Furthermore delayed caffeine clearance and increased theophylline levels [88-94] may interfere with magnesium and calcium binding to albumin (Figure 3). Saturation of albumin by caffeine or theophylline interferes with plasma magnesium and calcium corrections [95,96] that are related to plasma albumin contents (Figure 3). Caffeine excess with aging is relevant to magnesium deficiency [97-99] and relevant to neuron calcium dyshomeostasis [17,100] that is connected to SCN dysynchrony critical to the maintenance of circadian rhythms [7]. Disturbances in neurons by caffeine involve neuron calcium disturbances that involve the adenosine receptors, synapses and neuron networks [101,102] with detrimental effects on the central nervous system with irreversible T3D [36,37]. Sirt 1 regulation of SCN synchrony and neuron synapse plasticity is completely corrupted by caffeine as caffeine overload in the CNS occurs with aging process. Magnesium deficiency is connected to endothelial dysfunction [103-105], myocardial infarction [106-110], NAFLD [111,112] and the induction of T3D (magnesium/Sirt 1 activator) [113].



The expression of four G-protein-coupled receptors referred to as adenosine receptors (AR) A1, A2A, A2B, A3 can be induced to regulate various mechanisms involved in the onset and progression of T1DM and T2DM [114,115]. Adenosine (signalling metabolite) and AR receptors are involved in cell growth and proliferation, apoptosis, immune response, and angiogenesis in various other diseases such as cardiovascular disease, asthma, Parkinson's disease and Alzheimer's disease. Under diet, stress or cell damage AR receptor genes may be induced [116] with adenosine released from tissues such as the liver, pancreas, muscle and adipose tissue. Connections between the stress sensitive Sirt 1 [6,7] and AR receptors [117] to hepatic glucose, fatty acids and cholesterol metabolism are relevant to hyperlipidemia and cardiovascular disease. High dietary fat that down regulates Sirt 1 and effects adenosine cell levels with relevance to glucose and lipid metabolism related to the induction of NAFLD [118]. Ethanol

(Sirt 1 inhibitor) is involved with adenosine generation and with A1 and A2B receptors accelerate NAFLD [119]. Sirt 1 regulation of cell cholesterol may be related specifically to membrane cholesterol interactions that involve the A2A receptor [120,121] with critical relevance to reverse cholesterol transport [8,9].

The neuromodulatory role of adenosine is important to the control of brain disorders and modulation of AR receptors has become critical to the long-term burden of brain disorders in different neurodegenerative conditions [122-126] such as ischemia, epilepsy, Parkinson's or Alzheimer's disease. Adenosine acts as a neuromodulator [127] by activation of inhibitory A1 Receptors (A1R) and facilitatory A2A Receptors (A2AR) and controls the excitatory glutamatergic synapses that are engaged to promote synaptic plasticity. Sirt 1 dysfunction and connections to defective amyloid beta metabolism and synaptic plasticity [7,41,42] is now relevant to diabetes and various neurological diseases. The A1 receptor has long been known to mediate neuroprotection with amyloid beta regulation and by blockade of Ca<sup>2+</sup> influx which results in inhibition of glutamate release and reduction of its excitatory effects at a postsynaptic level [128,129]. Astrocytic adenosine A2A receptors control the amyloid- $\beta$  peptide metabolism and toxicity to neurons [130].

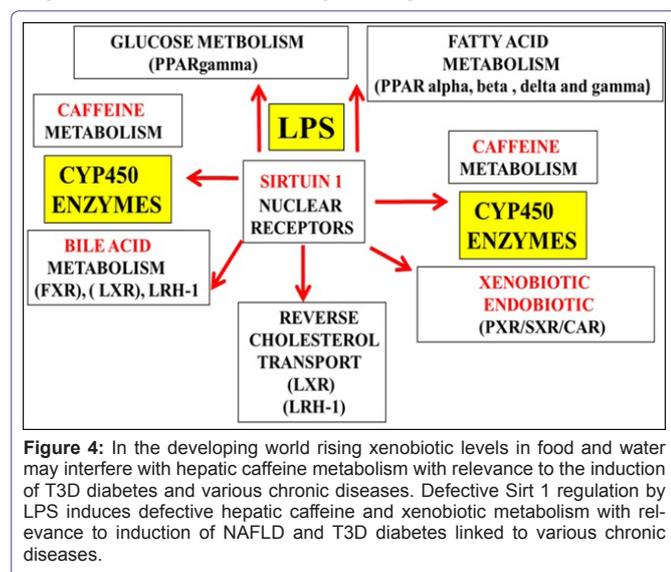
Caffeine neuroprotection involves blockade of adenosine A2A receptor to prevent amyloid beta induced neurotoxicity [131]. Caffeine via adenosine and AR receptors affects brain functions such as sleep, cognition, learning, and memory, and modify brain dysfunctions and diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, epilepsy, pain/migraine, depression and schizophrenia [101,102,132-136]. Sirt 1 is critical to the regulation of the SCN circadian rhythm and NAFLD [7] that determine hepatic caffeine metabolism with excessive transport of caffeine to the brain. Caffeine has been shown to have major effects on the circadian rhythm *in vitro* and *in vivo* with sleep disrupting effects associated with delayed human circadian timekeeping [137-139]. Pharmacological modulation of the A2A and A3 receptors via selective ligands now represents a novel strategy for acute or chronic neurodegenerative events. Sirt 1 and AR receptors are connected to NO modulation [6,140] indicating their important role in cellular processes. Sirt 1 dysregulation with relevance to NO metabolism [6] may override effects of NO modulation by adenosine with relevance to adenosine A2A and A1 receptors in neurons and adenosine and NO mediated vasodilation effects in arterial and endothelial cells [141-144].

## Bacterial LPS and Caffeine Metabolism with Relevance to NAFLD and Chronic Diseases in the Developing World

In the developing world the sensitivity to accelerated aging and induction of diabetes is now related to repression of the anti-aging gene Sirt 1 [145]. In the developing world alarm has been raised with the increase in plasma bacterial Lipopolysaccharides (LPS) levels with LPS [8,9,19,20,31,49] of relevance to Sirt 1 repression and associated with the development of insulin resistance and NAFLD. LPS may induce zinc [9] and magnesium [113] deficiency with LPS effects on zinc, magnesium and albumin levels relevant to increased free caffeine levels and linked to increased mitochondrial apoptosis in cells. The role of zinc/magnesium (Sirt 1 activators) deficiency in the developing world [146] may indicate Sirt 1 to be non-functional in the central nervous system and relevant to the induction of T3D. LPS dysregulation of nuclear Sirt 1 involve circadian rhythm abnormalities

[7,147] with LPS associated with defective rhythmic release of various proteins such as albumin from cells [148,149]. The role of nutritional interventions to maintain zinc and albumin levels in developing world may be important with relevance to caffeine consumption. Caffeine, zinc and albumin levels determine the induction of various chronic diseases with albumin sensitivity to myocardial infarction [108,109].

In the developed world the aging process may allow caffeine to be metabolized faster when compared with individuals from the developing world with the slow caffeine clearance related to the hydrophobic caffeine deposition in cell membranes with relevance to cell membrane fluidity alterations [150]. The membrane interactions of caffeine may be completely abnormal with relevance to LPS induced membrane alterations. LPS and caffeine may interfere with hepatic cholesterol levels (Figure 4) with relevance to bile acid metabolism [151-155] and induction of NAFLD [156-158] in the developing world. Repression of Sirt 1 in cells is responsible for major intracellular defects and caffeine induced mitochondrial apoptosis relevant to adipogenesis defects [31,32] related to NAFLD with NAFLD to reach 30% of the developing world [159-162]. Defective hepatic caffeine clearance rates in the developing world may be connected to pancreatic [163-170] and thyroid disease [171-173] but xenobiotics may also be the inducing factor in these chronic diseases. LPS induced Sirt 1 repression may involve both caffeine and xenobiotic toxic effects with the induction of NAFLD, NAFLD linked to gall bladder disease [174-177] and cardiovascular disease [107-109].

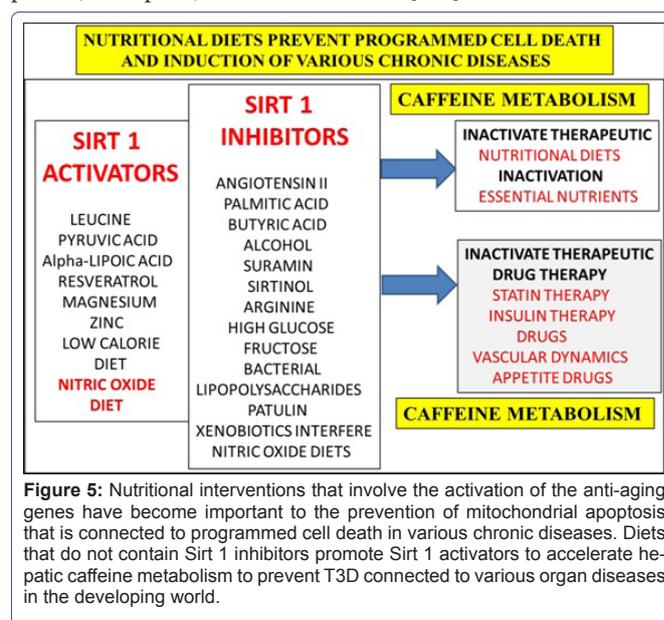


**Figure 4:** In the developing world rising xenobiotic levels in food and water may interfere with hepatic caffeine metabolism with relevance to the induction of T3D diabetes and various chronic diseases. Defective Sirt 1 regulation by LPS induces defective hepatic caffeine and xenobiotic metabolism with relevance to induction of NAFLD and T3D diabetes linked to various chronic diseases.

In the developing world xenobiotic levels have increased in food and water [51] with relevance to caffeine and the induction of T3D [17,18]. Caffeine consumption should be assessed with regard to common metabolic pathways that involves Sirt 1/CYP450 enzymes (Figure 4) involved in both caffeine and xenobiotic clearance [17,51]. Caffeine as a Sirt 1 modulator [17,178] can interfere with the clearance of bile/cholesterol/xenobiotic with relevance to primary clearance of caffeine versus secondary clearance of xenobiotic and thirdly bile acid metabolism in these populations (Figure 4).

Nutritional diets that contain Sirt 1 activators (Figure 5) may reverse NAFLD with relevance to the metabolism of caffeine, glucose, fatty acids, cholesterol, amyloid beta, bile acids and xenobiotics. Consumption of Sirt 1 inhibitors (Figure 5) should be avoided that induce NAFLD that inactivate consumption of essential nutrients with

relevance to the prevention of NAFLD. Delayed caffeine metabolism may induce mitophagy and impair various therapeutic drugs/insulin therapy [179] (Figure 5) that are essential for treatment of various chronic diseases. Diets that contain patulin [69] in the developing world should be avoided with relevance to Sirt 1 inactivation to NAFLD and induction of various chronic diseases. Vegetarian diets should be carefully checked with relevance to caffeine containing plants (coffee plant), tea leaves and herbs [180].



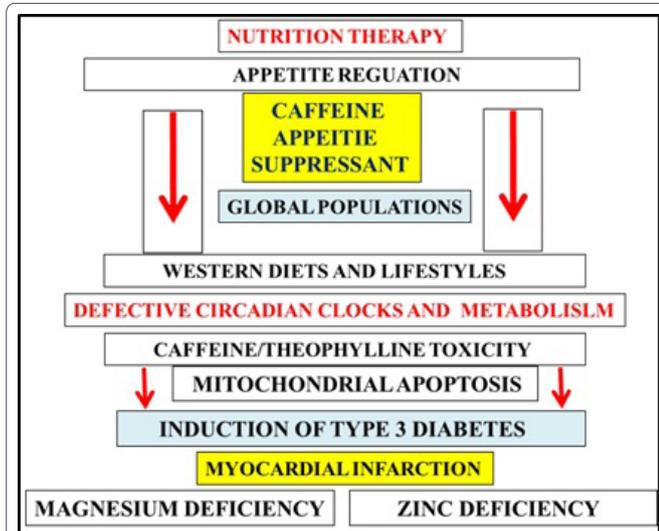
**Figure 5:** Nutritional interventions that involve the activation of the anti-aging genes have become important to the prevention of mitochondrial apoptosis that is connected to programmed cell death in various chronic diseases. Diets that do not contain Sirt 1 inhibitors promote Sirt 1 activators to accelerate hepatic caffeine metabolism to prevent T3D connected to various organ diseases in the developing world.

Caffeine over consumption (Figure 5) in the developing world are critical to the induction of caffeine induced magnesium deficiency in myocardial infarction [107,113] and pancreatitis [181-184]. Caffeine can interfere with thyroid replacement therapy with effects on cardiovascular disease, hypothyroidism and gall bladder disease [185-186]. Other caffeine containing foods such as coffee, coca cola, energy drinks, caffeine tablets, dark chocolate, chocolate chips and energy mints should be assessed for caffeine content (mg) with NAFLD, gall bladder disease and various chronic diseases. Over nutrition with glucose and fatty acids such as palmitic acid [150] involved in Sirt 1 inhibition (Figure 5) should be avoided that are involved in the delay of hepatic caffeine metabolism. Controlled exercise regimes should be supervised to prevent magnesium deficiency [113] and the over ingestion of caffeine containing drinks that promote endurance and performance [187-190]. Nitric oxide foods [6] (Figure 5) should be restricted to prevent caffeine related endothelial death with caffeine interference of the Sirt 1 eNOS pathway [75,76] related to myocardial infarction [70-74].

## Conclusion

Unhealthy western diets and lifestyles lead to circadian rhythm disorders with defective nutrient and caffeine metabolism associated with NAFLD, cardiovascular disease and T3D diabetes in the developed world (Figure 6). Nutritional interventions are required to prevent mitophagy that is linked to the induction of chronic disease. Caffeine doses in various global populations should be reassessed with relevance to NAFLD and induction of T3D diabetes and neurodegeneration (Figure 6). In the developing world LPS may induce NAFLD and associated with defective anti-aging genes and accelerated mitochondrial apoptosis. Delayed caffeine and xenobiotic metabolism with

zinc/magnesium deficiency may be associated to other organ diseases such as gall bladder disease, cardiovascular disease and pancreatic disease in the developing world (Figure 6).



**Figure 6:** Nutrition therapy and circadian clock function has now become essential to prevent mitochondrial apoptosis that is relevant to the induction of Type 3 diabetes and cardiovascular diseases. Caffeine consumption should be reduced markedly in the developed and developing world with relevance to NAFLD and various global chronic diseases. Plasma magnesium/zinc/caffeine are important appetite control with overeating critical to the induction of diabetes, myocardial infarction and various organ diseases.

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