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Caffeine with Links to NAFLD and Accelerated Brain Aging

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Abstract

Nutritional diets are essential to prevent nonalcoholic fatty liver disease (NAFLD) in the global obesity and diabetes epidemic. The ingestion of palmitic acid-rich diets induces NAFLD in animal and human studies. The beneficial properties of olive oil (oleic acid) may be superseded by ingestion of palmitic acid-rich diets. Hepatic caffeine metabolism is regulated by palmitic and oleic acid with effects of these fats on amyloid beta metabolism. Healthy fats such as olive oil may facilitate rapid amyloid beta clearance in the periphery to maintain drug therapy in diabetes and various neurological diseases. Repression of the anti-aging gene sirtuin 1 (Sirt 1) prevents the beneficial properties of olive oil. Brain disorders induce NAFLD and supersede caffeine's therapeutic effects in the prevention of NAFLD. Delayed hepatic caffeine metabolism in NAFLD and increased caffeine transport to the brain with aging-induced mitophagy in neurons with induction of type 3 diabetes and neurodegenerative disease.

Keywords: caffeine, nonalcoholic fatty liver disease, brain aging, palmitic acid, mitochondria

1. Introduction

The global increase in nonalcoholic fatty liver disease (NAFLD) is linked to various induction factors such as excessive caloric intake, genetic, environmental inducing factors and psychosocial factors that override the liver's ability to metabolize lipids and determine excess body fat (adipose tissue size) with the risk of dyslipidemia, obesity, cardiovascular disease, hypertension, and insulin resistance that lead to population mortality in developed countries. In developed countries, the Western diet is known to be high in fat and glucose and closely involved in early liver disease associated with excess transfer of fat to the adipose tissue (visceral fat) and the induction of the metabolic syndrome and obesity. Increased susceptibility

to obesity in man compared with other species now indicates NAFLD to be the clinical condition involved in the induction of obesity in man [1–3]. In North America, the rate of childhood obesity has doubled in the last 20 years and similar statistics are reported in countries like Thailand, China, Brazil, and South Africa. The prevalence of childhood and adolescent obesity has increased since 1980 with concerns for NAFLD to exceed 50% of the childhood population [4–6]. Early dietary intervention in genetic and obese/diabetic mice models has indicated reversal and stabilization of NAFLD with relevance to the global NAFLD and neurodegeneration. Education programs such as food restriction programs (**Figure 1**) have been performed but induction of global NAFLD has not decreased in the world [7, 8]. The projected health care costs by the year 2018 in relation to obesity/diabetes-related medical expenses in the United States have been reported to be 344 billion dollars accounting for 21% of total health care costs. Excessive caloric intake, genetic, environmental inducing agents, and psychosocial factors all contribute to the cause of NAFLD (**Figure 1**) with the reduced metabolism of lipids involved in the development of obesity in middle adult life. In the global population, the prevalence of NAFLD has increased from 15% in 1980 to 25% in 2010 with NAFLD to increase to 40% of the global population by the year 2050. In the developing world, the increased obesity/diabetes epidemic is now associated with diet and the presence of specific chemicals such as xenobiotics [9]. The interactions between the brain, liver, and adipose tissue are defective [10] with reduced adipose tissue-liver crosstalk [10–12] responsible for the defective hepatic metabolism of dietary fat, xenobiotics, and drugs and related to the induction of global NAFLD epidemic. Major interests in caffeine intake have accelerated with relevance to global mitophagy, amyloid beta aggregation, NAFLD, and neurodegenerative

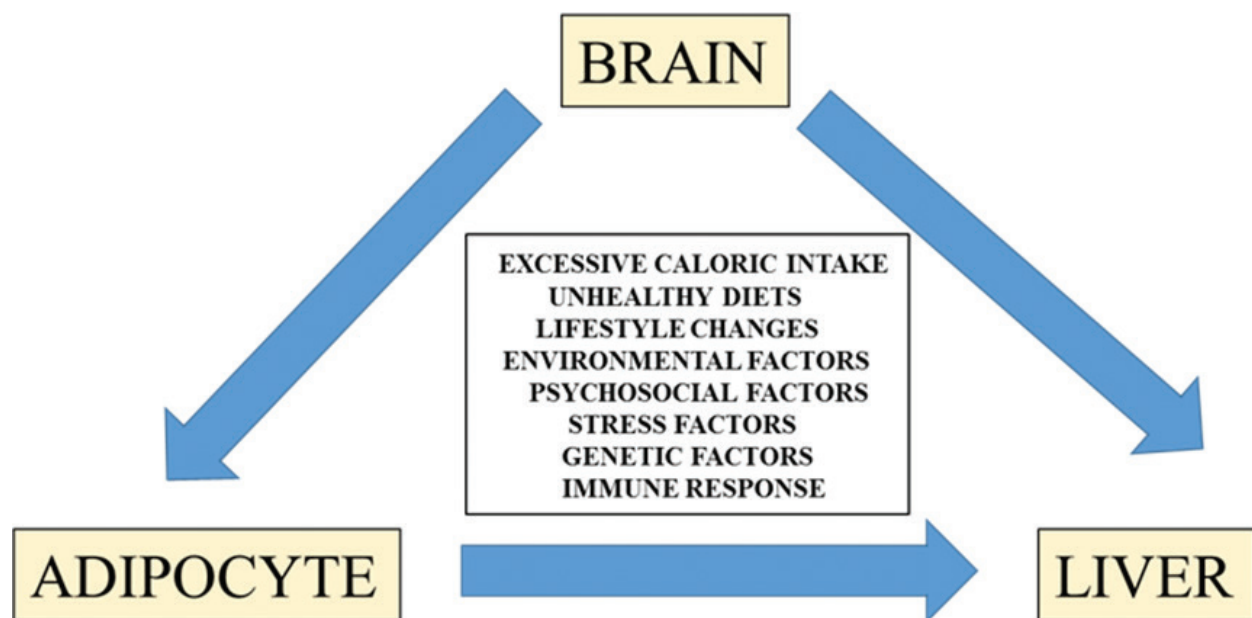


Figure 1. Inducing factors for NAFLD override the brain regulation of the adipose tissue-liver crosstalk. The dose of caffeine used in healthy diets has become important with relevance to the brain control of liver function. Palmitic acid-rich diets induce NAFLD and delay caffeine metabolism with increased caffeine transport to the brain. Other factors such as stress and psychosocial factors disturb brain function with altered cellular lipid metabolism which is now linked to obesity and the NAFLD epidemic.

disease [13]. Caffeine is an appetite suppressant with effects on improving liver fat metabolism and adipogenesis [14] and important to the adipose tissue-liver crosstalk. Brain regulation of the adipose tissue-liver crosstalk is impaired by various inducing factors with excess transport of caffeine to the brain that interferes with the circadian rhythm with relevance to accelerated aging [14–17]. Inducing factors for NAFLD (**Figure 1**) override the beneficial effects of caffeine on adipocyte/liver fat metabolism [18, 19] and the dose of caffeine used in diets has become important with relevance to the NAFLD epidemic since the pharmacokinetics of caffeine may be completely impaired in the liver (NAFLD) in overweight/obese individuals [2, 20–27].

Unhealthy diets (**Figure 1**) that contain palmitic acid (cream, butter, and cheese) increase cholesterol levels and induce NAFLD [28–32] and neurodegeneration with complete impairment of caffeine actions with relevance to its role as a modulator of receptors relevant to the adipose tissue and liver fat metabolism. Palmitic acid diets alter cell cholesterol and phospholipid dynamics with increased contents of phospholipids such as dipalmitoylphosphatidylcholine (DPPC) that are relevant to increased membrane cholesterol content [33, 34] with relevance to delayed hepatic caffeine and amyloid beta transport and metabolism. Palmitic acid and DPPC have major effects on membrane cholesterol formation that stimulate amyloid beta formation [35, 36]. Amyloid beta is a 4-kDa hydrophobic peptide (**Figure 2**) released from neurons in the brain for metabolism by the liver [37] with recent research that caffeine (hydrophobic

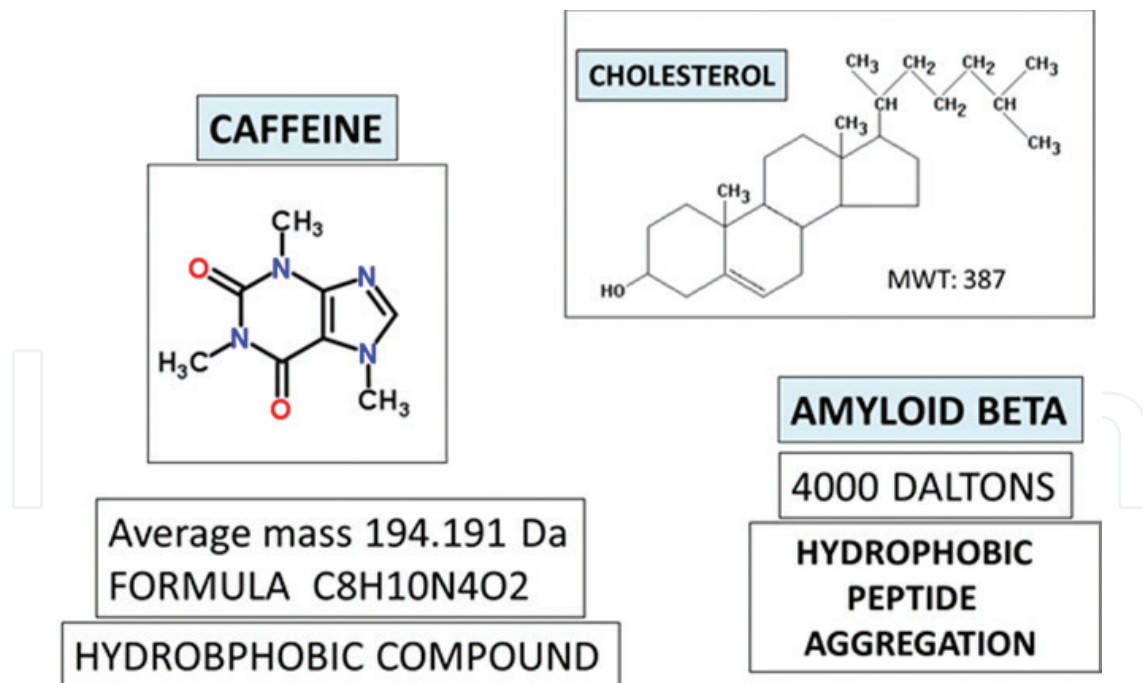


Figure 2. Increased cholesterol levels have been associated with toxic amyloid beta formation. Diets with increased palmitic acid increase cell cholesterol and the phospholipid dipalmitoylphosphatidylcholine (DPPC) with relevance to delayed cell amyloid beta transport and caffeine metabolism. Caffeine is a hydrophobic compound and its increased insertion into the cell membrane with aging is related to abnormal cholesterol and amyloid beta metabolism with the induction of mitophagy. The consumption of olive oil (oleic acid) is associated with the phospholipid 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) and is related to rapid amyloid beta and caffeine metabolism.

compound, **Figure 2**) improves brain-liver amyloid beta transport and metabolism with the prevention of neurodegeneration [38, 39]. DPPC/cholesterol interactions accumulate cellular caffeine with corruption of the brain-liver amyloid beta metabolism with accelerated brain aging associated with toxic amyloid beta aggregation (**Figure 2**). Increased cell phospholipid dynamics with consumption of olive oil (oleic acid) are associated with phospholipids such as 1-palmitoyl-2-oleoylphosphatidylcholine (POPC) that is a common pattern of naturally occurring phospholipids in cells and relevant to cell phospholipid dynamics [40] and rapid caffeine metabolism. Palmitic acid and DPPC are sensitive to cholesterol with toxic effects involved in the interference with brain-liver amyloid beta and caffeine metabolism with relevance to caffeine-induced mitophagy [41, 42] and the induction of NAFLD and neurodegeneration in global communities.

2. Defective adipose tissue-liver crosstalk in the induction of the global NAFLD epidemic

New quantitative genetic methods such as the use of DNA and RNA microarrays have been used to examine novel genetic pathways and now identify a single gene to be involved in the NAFLD and obesity epidemic. The anti-aging gene sirtuin 1 (Sirt 1) has now been implicated as a NAD(+)-dependent class III histone deacetylase (HDAC) protein that targets transcription factors to adapt gene expression to metabolic activity, insulin resistance, and inflammation in chronic diseases [43–46]. Sirt 1 is involved in food intake regulation [47, 48], gluconeogenesis in the liver [49], fat mobilization from white adipose tissue, cholesterol metabolism, and energy metabolism [50, 51]. In adipose tissue, Sirt 1 activates fat mobilization by inhibiting peroxisome proliferator-activated receptor gamma (PPAR-gamma) [52, 53] and in the pancreas Sirt 1 repression decreases insulin secretion with effects on beta cell uncoupling protein 2 levels [54]. Sirt 1 influences mitochondrial biogenesis in the adipose tissue and liver with relevance to NAFLD [10]. Furthermore, diet and nutrigenomics are involved in Sirt 1 regulation of DNA repair with transcription factors regulated by Sirt 1 connected to the nuclear receptors such as peroxisome proliferator-activated receptor (PPARalpha, PPARgamma), liver X receptor, pregnane X receptor, and farnesoid X receptor involved in liver metabolic homeostasis with roles in lipid metabolism in adipose tissue [9].

The effects of dysregulated Sirt 1 on adipocyte differentiation [55–59] and regulation of gene expression involves the secretion of adiponectin [60–62] with adipocyte size negatively correlated with adiponectin levels, adipose tissue ceramide metabolism, and HDL levels [63–67]. Adiponectin is mainly secreted from the adipose tissue into the bloodstream and inversely correlated with body fat in adults. Adiponectin self-associates into larger structures from trimers to form hexamers or dodecamers with the high-molecular weight form, biologically more active with regard to glucose homeostasis. High fat intake is associated with decreased adiponectin levels [68] and downregulation of Sirt 1 [10] with low adiponectin levels associated with the metabolic syndrome, NAFLD [69–71] with effects on hypercholesterolemia (low high-density lipoproteins, apolipoprotein AI levels and high low-density lipoprotein, apolipoprotein B levels) associated with insulin resistance and NAFLD (**Figure 3**). Adiponectin

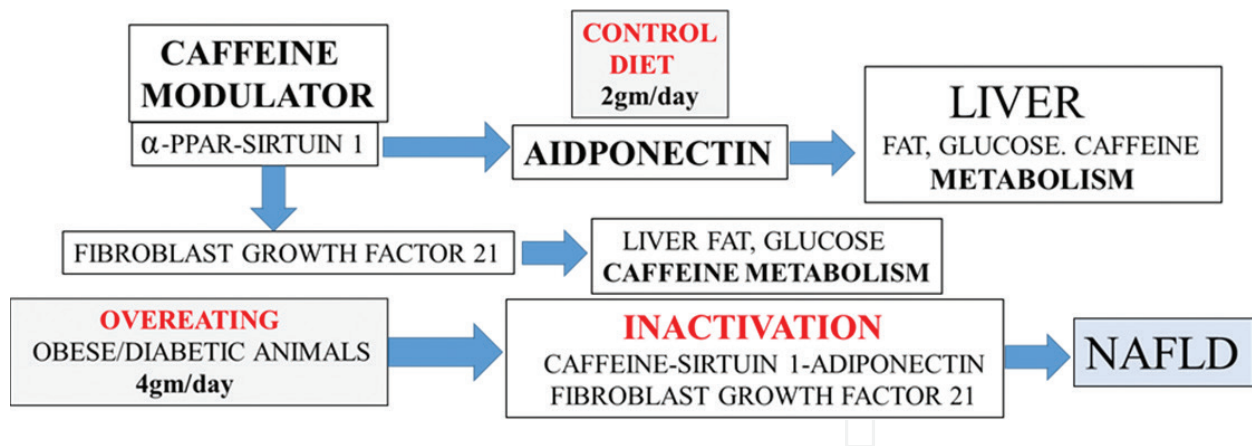


Figure 3. Dietary fat consumption in man needs to be carefully controlled to allow caffeine to modulate cell Sirtuin 1 activity that is involved in mitochondrial biogenesis and the metabolism of cellular fatty acids. Diets that are low in calories activate Sirtuin 1 and allow caffeine-induced modulation of adiponectin levels essential for the adipose tissue-liver crosstalk and the hepatic metabolism of glucose and fatty acids. In rodents, feeding mice 2 g/day instead of 4 g/day increases hepatic fatty acid metabolism and activates hepatic Sirtuin 1 involved in glucose and fatty acid metabolism. Sirtuin 1 is involved in adipose tissue-liver FGF21 production essential for mitochondrial function in the brain and the metabolism of fatty acids, glucose, and caffeine in the liver. The calculated fat content by (Martins IJ, author) in man is related to between 20 and 30 g/day and fat intake at this consumption rate is essential for the prevention of NAFLD.

deficiency has been shown to reduce hepatic ATP-binding cassette transporter ABCA1 (ABCA1) and apo AI synthesis with relevance to the reverse cholesterol transport [72]. FGF21 is now associated with NAFLD [73–76] with hepatic FGF21 shown to regulate lipolysis (fatty acid release) with FGF21 critical in the reduction of adipose tissue ceramides. In insulin resistance and AD, FGF21 and adiponectin levels are implicated in increased cellular ceramide levels and NAFLD [77–81] associated with cholesterol displacement in membranes [82–84] with relevance to amyloid beta aggregation [85]. Sirt 1/adiponectin/FGF21 dysregulation determine hepatic cholesterol metabolism with effects on plasma apo B levels mediated via Sirt 1 and transcription factor C/EBPalpha, which regulates the transcription of the apo B gene [85]. Adipocytes from obese and diabetic individuals are associated with increased adipocyte APP gene expression and plasma amyloid beta levels that implicate adiponectin and Sirt 1 dysregulation with cholesterol and amyloid beta metabolism [86–90]. High-calorie diets downregulate Sirt 1 with reduced adiponectin expression in obesity and diabetes [91] associated with adipose tissue transformation and liver development [60, 86]. Fasting and feeding regulate PPAR alpha-Sirt 1 expression related to hepatic FGF21 production and have become important to NAFLD and the metabolic syndrome [85]. FGF21 is an important activator of Sirt 1-mediated release of adiponectin [85]. FGF21 binds to FGF receptor and beta klotho receptor complex [85] and activates adipose tissue Sirt 1 by increase in NAD⁺ and activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-alpha) and AMP-activated protein kinase (AMPK). Unhealthy diets and Sirt 1 repression effect the release of adipose tissue adipokines (adiponectin and leptin) and cytokines (tumor necrosis factor alpha, interleukin-6 and C-reactive protein levels, and Ang II) [92] with FGF21 [73–76] implicated in NAFLD and other chronic diseases associated with accelerated brain aging. In man, caffeine has been associated with increased adiponectin levels with relevance to beneficial effects on liver function [93, 94]. Caffeine and its effects on the adipose tissue-liver

crosstalk involve caffeine related to adipose tissue adiponectin release essential for liver function. Caffeine is a modulator of histone deacetylase and its effects as a histone deacetylase modulator [27, 95] in the adipose tissue-liver crosstalk involve the dose of caffeine that is of critical importance to Sirt 1/adiponectin release [85, 96, 97] essential to maintain hepatic metabolism of fatty acids and glucose [18, 98]. Caffeine is important to reduce inflammatory processes [99, 100] with adipose tissue transformation and release of inflammatory cytokines that induce NAFLD [100]. Sirt 1 is involved in autoimmunity [101, 102] with relevance to regulation of various immune cell events in the adipose tissue and liver.

Assessment of hepatic lipid metabolism has been extensively conducted in obese and diabetic rodents with relevance to NAFLD in man [103–107]. In rodents with diets (5% fat), the intake of food per day was approximately 2 g/day and the hepatic metabolism of injected labeled lipoproteins was rapid and cleared and metabolized from the blood plasma within 30 min. In obese and diabetic rodents that had appetite dysregulation consumed approximately 4 g/day (**Figure 3**), the hepatic clearance and metabolism of fats were defective. The excess and ingested fat in obese/diabetic rodents completely downregulated hepatic Sirt 1 with relevance to the NAFLD that develops in these mice with the aging process. In Sirt 1 knockout mice [108, 109], NAFLD develops with relevance to the importance of Sirt 1 in liver fat and cholesterol metabolism [110]. The primary role of fat intake was assessed in obese/diabetic mice that were only allowed to consume 2 g/day (**Figure 3**) instead of 4 g/day and hepatic lipid metabolism was improved in these obese/diabetic rodent experiments with relevance to calorie-sensitive regulation of hepatic Sirt 1 (**Figure 3**). Dietary fat consumption in man needs to be carefully controlled to allow caffeine/adiponectin effects to prevent the induction of NAFLD. The calculated fat content in man has now been determined by author's calculations to be approximately 20–30 g/day [13] and differs from other international researchers [111]. In several laboratories, cellular cholesterol levels are associated with increased amyloid beta formation in the brain and periphery [37], and Sirt 1 downregulation is associated with defective caffeine and cholesterol metabolism (**Figure 4**) with relevance to hepatic amyloid beta clearance and induction of NAFLD [112]. Increased plasma caffeine levels displace amyloid beta and fatty acids from albumin by competition for albumin binding sites [113] with relevance to amyloid beta aggregation [114]. Increased caffeine membrane levels in the liver and brain may affect cholesterol efflux with toxic amyloid beta aggregation (**Figure 4**) relevant to cell apoptosis. Sirt 1 is essential for neuron proliferation with effects of excess cell caffeine that interferes with cell magnesium levels (**Figure 4**) and supersedes the anti-amyloid beta aggregation properties of caffeine [115]. Magnesium deficiency has been associated with hypercholesterolemia and induction of NAFLD [116]. Magnesium is now relevant to maintenance of peripheral hepatic amyloid beta metabolism with magnesium levels critical to the prevention of high-cell cholesterol-induced amyloid beta formation. In NAFLD (**Figure 4**), caffeine consumption should be carefully controlled to prevent magnesium deficiency [117] and to assist with the reduction in hepatic fibrosis in NAFLD [118].

Palmitic acid-rich diets (20–30 g fat/day) should carefully calculate palmitic acid consumption per day to prevent interference of the adipose tissue-crosstalk and induction of NAFLD [13]. Palmitic acid is an Sirt 1 inhibitor [119, 120] with induction of cell cholesterol efflux disturbances

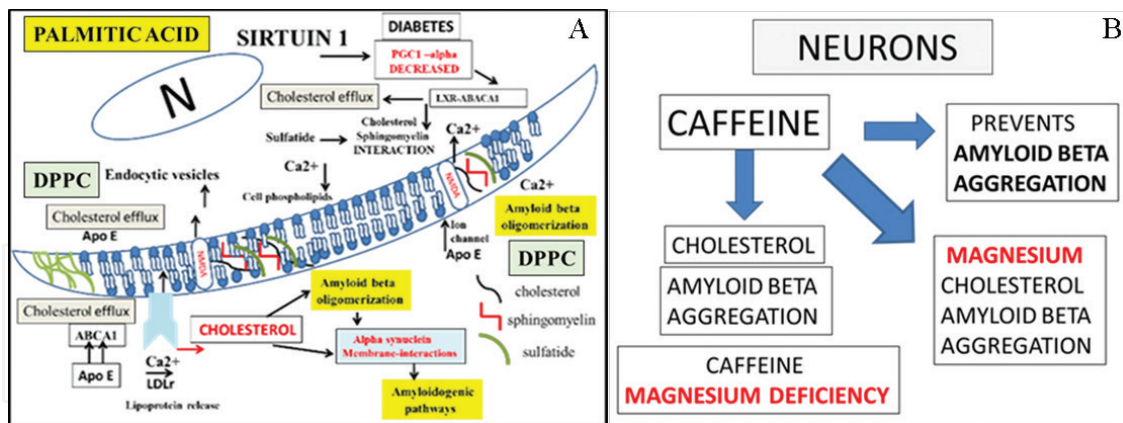


Figure 4. In panel A, palmitic acid as an inhibitor of Sirt 1 is associated with defective caffeine and cholesterol metabolism with relevance to hepatic amyloid beta clearance and induction of NAFLD. Cell caffeine levels are associated with calcium-induced amyloid beta oligomer formation with mitophagy in the liver and brain. In panel B, irreversible effects with aging of palmitic acid induce cell DPPC/cholesterol formation and interfere with caffeine's anti-amyloid beta oligomer properties with increased cell caffeine levels related to magnesium deficiency (NAFLD) and increased cholesterol associated amyloid beta aggregation.

relevant to cell amyloid beta-induced mitophagy [121] with liver inflammation. Palmitic acid induces DPPC phospholipid/cholesterol membrane changes that delay caffeine metabolism with increased cell caffeine levels associated with calcium-induced amyloid beta oligomer formation in the liver and brain [27]. Palmitic acid converts to glucose in cells and with increased palmitic acid levels that are not controlled with aging may inactivate cell Sirt 1 glucose regulation (gluconeogenesis) and nullify the brain to liver amyloid beta clearance pathway with defective adipose tissue-liver crosstalk [10] relevant to induction of chronic diseases.

The gene-environment interaction identifies Sirt 1 in many global populations as the defective gene involved in the defective nuclear-mitochondria interactions in the adipose tissue and the liver relevant to the mitochondrial theory of aging [10]. Sirt 1 targets transcription factors such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-alpha) and p53 to adapt gene expression to mitochondrial function by deacetylation of PGC1-alpha and p53 transcription factors [10], which are important to mitochondrial DNA homeostasis and mitochondrial biogenesis [122–126]. Inhibitors and activators of Sirt 1 [112] have been identified that may override caffeine and its role as a Sirt 1 modulator [27, 95, 112]. Inhibitors include alcohol, sirtinol, suramin and activators include leucine, pyruvic acid, and alpha-lipoic acid. These inhibitors may induce mitochondrial apoptosis and may override the adipose tissue-liver interaction with the induction of NAFLD. Sirt 1 is now referred to as the heat-shock gene with its critical role in heat-shock protein (HSP) metabolism [127, 128]. HSP is a chaperone for amyloid beta and with Sirt 1 repression is important to HSP-amyloid beta-induced endoplasmic reticulum stress relevant to mitophagy and induction of NAFLD [129, 130]. *Caenorhabditis elegans* sirtuins have similar homology to human Sirt 1 with relevance to effects of caffeine on Sirt 1 circadian dysregulation [129]. Induction of HSP from cells in the nematode *C. elegans* has been used for toxicological studies and indicates caffeine doses that induce HSP release with relevance to programmed cell death [129].

3. Accelerated brain aging and type 3 diabetes-induced NAFLD and chronic diseases

In the developed and developing world, the induction of NAFLD has become one of the major interests with its primary or secondary role in the induction of various chronic diseases. Accelerated brain aging with appetite dysregulation indicates that NAFLD may play a secondary role in the induction of various chronic diseases (**Figure 5**). Mitophagy and the induction of neurodegeneration with type 3 diabetes are now the primary defects with accelerated NAFLD connected to various chronic diseases (**Figure 5**). Major concerns for suprachiasmatic nucleus (SCN) defects in the hypothalamus may involve appetite dysregulation [11], core-body temperature defects [131], and whole-body glucose disorders (type 3 diabetes) may induce toxicity to the liver and various other organs. Factors such as stress, psychosocial, environmental factors [9], and sleep disorders [132] disturb SCN regulation of the circadian rhythm with toxic effects of glucose, cholesterol, caffeine, and amyloid beta levels to the brain and various tissues (**Figure 5**). Higher brain dysregulation corrupts the hypothalamus-pituitary axis, sympathetic and nonsympathetic pathways that have direct neural innervation to organs such as the liver. Defective hepatic caffeine metabolism may induce magnesium deficiency, adrenergic system imbalances [133, 134], interference with sympathetic pathways [26] connected to mitophagy, and various chronic diseases.

The ingestion of the amount of fat is critical to the adipose tissue-liver cross with immune reactivity [10, 135] connected to mitophagy and induction of NAFLD. Multiple theories of aging have been proposed and the immune theory of aging may involve adipose tissue transformation with activation of immune responses that involve macrophages and immune cells that lead to liver inflammation [10, 99] and the induction of NAFLD. The defect in the neural loop (autonomic nervous system) between the brain and adipose tissue [136] now may be

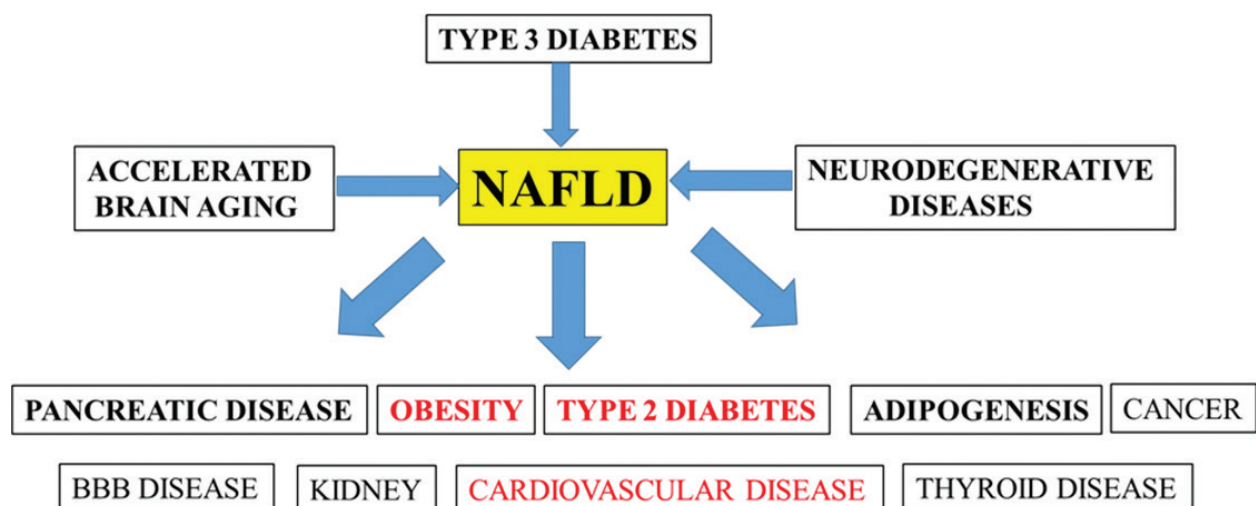


Figure 5. Defects in the suprachiasmatic nucleus (SCN) that involve appetite dysregulation, core-body temperature defects, and whole-body glucose disorders (type 3 diabetes) may induce NAFLD and various other chronic diseases. The primary role in the induction of NAFLD may be related to mitophagy-induced neurodegeneration with relevance to circadian rhythm disorders and complete nullification of hepatic caffeine metabolism by interference with the adipose tissue-liver crosstalk.

related to immunometabolism disorders with adipose tissue transformation. The nature of dietary fat with relevance to adipose tissue as the organ most susceptible to programmed cell death pathways involves transformation that is now important to determine the release of adipocyte inflammatory cytokines, hormones, and heat-shock proteins (HSP) that trigger liver inflammation and NAFLD in global communities [135]. Immunometabolism and accelerated aging are now connected to the adipose tissue and liver crosstalk with the mitochondria theory of aging important to both immune function [10] and metabolism of fats in the adipose tissue and liver. The transcription factor p53 is involved in immune responses, metabolism, and mitochondrial apoptosis [10, 123, 125] with diet, drugs, and environment [9] critical to the regulation of Sirt 1/p53 immunometabolism and induction of NAFLD in the developed world.

Rapid urbanization from 20 to 60% has occurred in Africa, India, China, and Asia and possibly involved with the large global diabetic population in these developing countries. The number of people with diabetes is projected to be double in Africa, Asia, and India. In Asia, the diabetic epidemic has escalated and accounts for 60% of the world diabetic population [137]. The diabetic epidemic has been associated with NAFLD in developing countries of Latin America, Asia [138], India, and Africa with prevalence (20–40%) [9] similar to developed countries [138–141]. Evidence from various studies [9] indicates that environmental factors (xenobiotics) are the major determinants of the increasing rate of diabetes (**Figure 6**). Major threats of xenobiotics such as environmental pollutants may increase with age in individuals

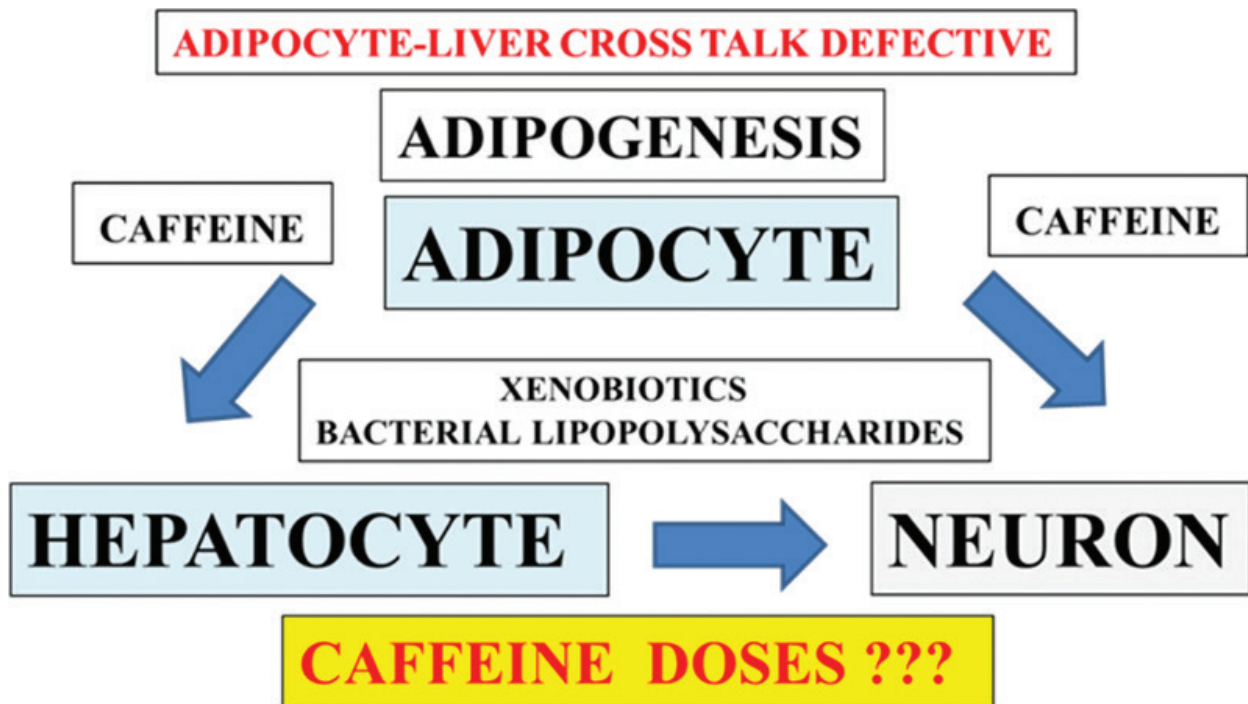


Figure 6. Caffeine is essential for the release of adiponectin from adipose tissue in obesity but the therapeutic effects of caffeine may be superseded with relevance to adipogenesis disorders. In the developing world, xenobiotics induce mitophagy in the adipose tissue and liver and supersede caffeine’s protective effects on the mitochondria. In the developing world, plasma LPS levels have increased with effects on the induction of NAFLD and interference with neuron function. Caffeine doses should be carefully controlled with relevance to LPS cell membrane transformations that override caffeine and cell membrane interactions and promote caffeine effects on albumin involved in amyloid beta and fatty acid transport between the brain and the liver.

from developing countries. The NAFLD epidemic is connected to unhealthy diets and reduced hepatic xenobiotic metabolism with blood-brain barrier disorders [9] involved with interference of brain Sirt 1's role in DNA repair [10] with the induction of neuronal apoptosis and type 3 diabetes. The association between xenobiotics in food and the beneficial effects of caffeine (Sirt 1 modulation) on insulin resistance [142, 143] may be superseded with caffeine consumption in these individuals to be revised with relevance to toxic xenobiotic effects associated with delayed caffeine metabolism relevant to NAFLD and neurodegenerative diseases.

The interests in bacterial lipopolysaccharides (LPS) and their influence on cell membrane fluidity in the brain has accelerated with the increase in plasma LPS levels in individuals (30%) of the developing world [144, 145]. LPS is a critical repressor of Sirt 1 actions with the induction of dyslipidemia, mitophagy, and NAFLD [145]. LPS from Gram-negative bacteria is an amphiphile (covalently linked segments, surface carbohydrate polymer O-specific chain, core oligosaccharide, Lipid A) that can rapidly insert into cell membranes and transform mammalian cells. LPS may supersede POPC properties of the cell membrane and induce amyloid beta oligomerization [144].

4. Nutritional diets maintain brain and adipose tissue-liver crosstalk with prevention of NAFLD

In developed world, the consumption of fat consumed in man is between 44 and 78 g/day [111, 146]. The amount of fat consumed (20–30 g/day) is critical to maintain the brain regulation of the adipose tissue-liver crosstalk and connected to the maintenance of the circadian rhythm (12 h light/12 h dark cycle) that is critical to hepatic amyloid beta and glucose metabolism [147, 148]. The SCN is controlled by Sirt 1 with its dysfunction connected to brain circuitry disorders (**Figure 7**) and disconnections between the autonomic nervous system and the liver [148]. The amount of fat consumed with the aging process inactivates the effects of caffeine by interfering with hepatic caffeine metabolism with increased transport to the brain (**Figure 7**). In the brain, SCN neurons are sensitive to caffeine [149] with complete inactivation of the brain to adipose tissue-liver crosstalk and interfere with caffeine's beneficial effects on the sympathetic nervous system and reversal of NAFLD. Caffeine and its role in thermogenesis by modulation of mitochondrial function versus mitochondrial apoptosis are relevant to the consumption of various fats and diets in the developed and developing world. Sirt 1 is now referred as the gene involved in mitochondrial biogenesis that is critical to maintain cell function with the prevention of cell apoptosis [9–12, 122–125]. Sirt 1 is critical to SCN function and the maintenance of core-body temperature with essential control of the adipose tissue-liver crosstalk [131, 150]. The consumption of coconut oil (saturated fat) and palm oil (palmitic acid) should be carefully evaluated in individuals with core-body temperature disorders. These fats are solid at temperatures between 20 and 24°C and with abnormal body temperature dysregulation may be involved in the induction of NAFLD when compared with the consumption of olive oil (monounsaturated) that is liquid at a temperature (4°C) [130, 150]. Fish contains high levels of omega-3 fatty acids, docosahexaenoic acid (DHA 22:6n-3), and eicosapentaenoic acid (EPA 20:5n-3). These fatty acids are essential for liver fat metabolism

with prevention of NAFLD [151, 152] and brain function but with changes in core body temperature (**Figure 7**), therapeutic lipids essential for the prevention of NAFLD may be completely inactivated [130, 131, 150]. Palmitic acid content in milk should be carefully controlled to allow the therapeutic effects of caffeine with relevance to mitochondrial thermogenesis and SCN regulation (**Figure 7**). Nutritional diets with timed meals are important for the prevention of NAFLD and with consumption of essential foods which include protein, eggs, cottage cheese, dairy, red meat, poultry, legumes, nuts, and seeds. These foods may contain minerals such as magnesium and zinc that are needed by many enzymes involved with DNA replication and repair with total magnesium intake that should be between 400 mg and 800 mg/day. Zinc deficiency has been reported in global communities with both minerals important to prevent liver and brain diseases and to allow effective vitamin and caffeine therapy. Vitamins such as vitamin B12, folic acid, vitamin B6, vitamins C, D, and E are essential to maintain liver and brain function. The consumption of phosphatidylinositol (PI) (g/day) is essential and lack of PI may not allow the maintenance of SCN function and whole body glucose homeostasis. In individuals with strenuous exercise, the PI half-life is rapid and may require PI ingestion of (g/day) to prevent amyloid beta aggregation and induction of NAFLD [153, 154]. Strenuous exercise may induce magnesium deficiency [116] and magnesium consumption needs revision to prevent SCN disturbances with type 3 diabetes and NAFLD.

The major defects with relevance to the global NAFLD epidemic involve the defective brain circadian circuitry and the adipose tissue-liver crosstalk [136, 155]. The SCN control of the

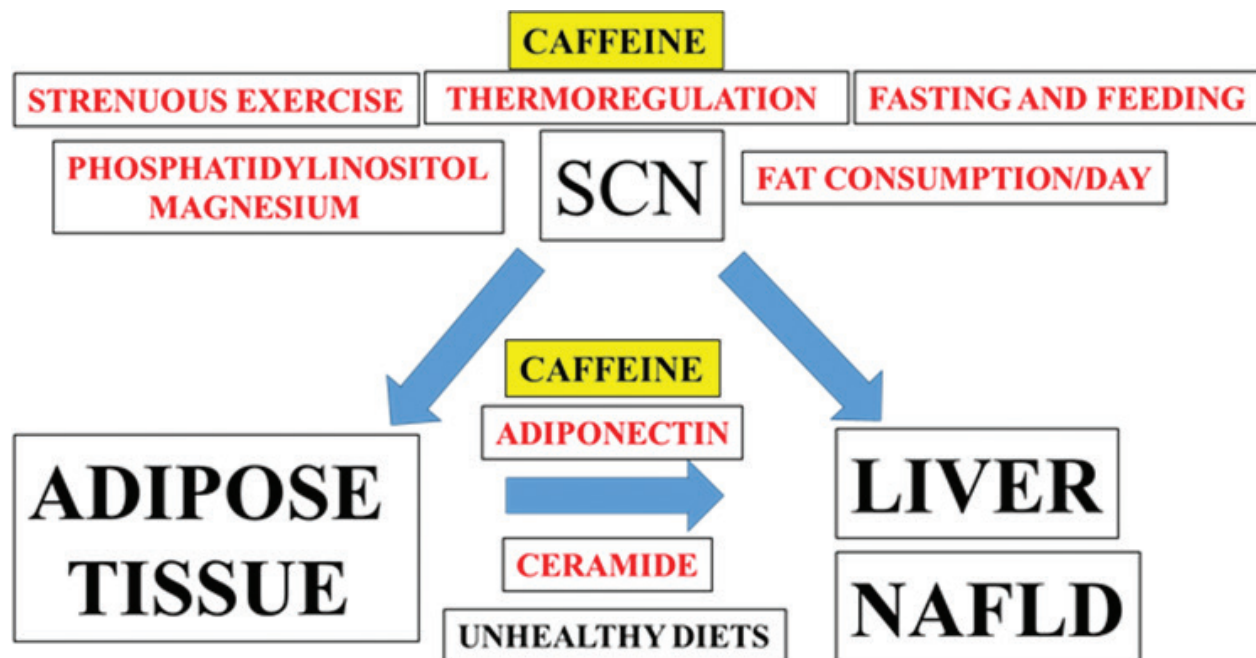


Figure 7. In the current global NAFLD epidemic, plasma ceramides indicate that the adipose tissue-liver crosstalk is completely defective with the release of toxic ceramides into the blood plasma. Sirt 1 downregulation is possibly connected to cell ceramide formation with adipose tissue disorders, liver steatosis development, and complete inactivation of caffeine's involvement in the prevention of NAFLD [94]. Integration of factors such as stress, sleep disorders, and environmental factors (strenuous exercise) inactivate the SCN regulation of the circadian rhythm with toxic effects of glucose, cholesterol, caffeine, and amyloid beta levels to mitochondria in various peripheral tissues.

adipose tissue metabolism allows adipocyte adiponectin release with essential effects on liver glucose and lipid homeostasis [155]. Sirt 1 and its modulation by caffeine have become important with caffeine involved in increased adiponectin levels in man. Apart from caffeine, other foods have been assessed to increase adiponectin levels such as omega-3 supplementation, fruit intake, green tea, magnesium, and hypolipidemic drugs are all involved in the modification of adiponectin levels [156–159]. In individuals with NAFLD, long-term dietary salt restriction is essential to increase adiponectin levels. Fasting and feeding is essential to maintain SCN circadian regulation of liver function that involves peripheral glucose homeostasis with adiponectin release critical to maintain insulin sensitivity and prevent NAFLD [85]. Gamma PPAR-Sirt 1 function in adipocytes is critical to adiponectin release with low adiponectin levels unsuitable to the maintenance of liver ceramide levels that are toxic to the liver and involved in insulin resistance. Ceramide levels and NAFLD [81–84] are now closely linked with programmed cell death. Alcohol consumption should be carefully controlled (Sirt 1 inhibition) with relevance to adiponectin levels in man [160]. Pyruvic acid, leucine, quercetin, green tea catechins, grape seed extract, curcumin, alpha lipoic acid, and resveratrol are Sirt 1 activators essential for SCN maintenance and the adipose tissue-liver cross talk. High-protein diets should be avoided to reduce amyloid beta formation by cells and to reduce the arginine content of the diet that switches leucine (Sirt 1 activator) for arginine in cells and tissues [132].

High-fiber diets [37] in various foods have become important with the consumption of phytosterols [37] involved in reducing intestinal cholesterol absorption and increased hepatic cholesterol metabolism relevant to the prevention of NAFLD in man. Phytosterols should be consumed (1–2 g/day) and excessive intake of phytosterols leads to neurotoxicity with neurodegeneration [37]. Phytosterols cross the blood–brain barrier in neurons to maintain neuron amyloid beta homeostasis [161]. Consumption of plant-based foods essential for phytosterol ingestion should be assessed for caffeine content since approximately 40 caffeine containing plants have been reported. Other caffeine containing foods such as coca cola, energy drinks, caffeine tablets, dark chocolate, chocolate chips, and energy mints should be assessed for caffeine content (mg). Vegetarians should carefully regulate phytosterol consumption over their lifespan to prevent interference with the beneficial effects of caffeine on cholesterol metabolism with relevance to NAFLD [37]. Excessive fructose consumption (fruit, fruit juices) should be avoided with fructose reported as a Sirt 1 inhibitor [162, 163] with the induction of NAFLD. In the developing world, very low carbohydrate diets should be consumed to prevent the absorption of LPS into the blood stream with beneficial effects on magnesium deficiency and the induction of NAFLD [164]. Diets with low-fat contents and without alcohol are essential to prevent the transport of LPS into lipoproteins and proteins in the blood plasma. LPS interferes with the SCN and adipose tissue-liver crosstalk [10, 85, 135, 136] and delays hepatic drug metabolism [165, 166] with premature brain aging and chronic disease progression (**Figure 6**). LPS induces changes in plasma albumin contents [112] in individuals in the developing world with relevance to interference with caffeine and its therapeutic properties with relevance to SCN regulation of adipose tissue-liver crosstalk. In recent studies, caffeine intake and glucose dyshomeostasis that supersede insulin therapy [142, 143] has raised concerns with relevance

to glucose/amyloid beta-induced mitochondrial apoptosis and the induction of NAFLD. In the global chronic disease, adiponectin levels are low and to prevent mitochondrial apoptosis, a number of agents are required to maintain mitochondrial function and to prevent cell apoptosis. Diets that contain magnesium, pyrroloquinoline, quinone, resveratrol, and rutin stimulate mitochondrial biogenesis essential to stimulate SCN neuron mitochondrial function [167] with relevance to the global NAFLD epidemic and chronic diseases.

5. Conclusion

In global world, diabetes and mitochondrial disease are expected to cost the developing world US \$400 million in the next 30 years. The quality of food consumed has raised major concerns with mitochondrial apoptosis linked to programmed cell death and nonalcoholic fatty liver disease (NAFLD). The amount, nature, and time of day of fat consumption are essential to maintain mitochondrial biogenesis. In the developed and developing world, nutritional interventions are essential to prevent NAFLD and ingestion of caffeine (appetite suppressant) that is associated with the prevention of adipocyte dysfunction and linked to liver function may be completely inactivated by unhealthy diets. In the developing world, bacterial lipopolysaccharides (LPS) may override healthy fat consumption and induce NAFLD. In the developing world, diets that contain LPS, mycotoxins, and xenobiotics interfere with caffeine metabolism with relevance to mitophagy and induction of NAFLD relevant to the survival of various species and man.

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References

- [1] de la Monte SM, Longato L, Tong M, Wands JR. Insulin resistance and neurodegeneration: Roles of obesity, type 2 diabetes mellitus and non-alcoholic steatohepatitis. *Current Opinion in Investigational Drugs*. 2009;10:1049-1060
- [2] Fabbrini E, Sullivan S, Klein S. Obesity and non-alcoholic fatty liver disease: Biochemical, metabolic, and clinical implications. *Hepatology*. 2010;51:679-689
- [3] Bleich SN, Cutler D, Murray C, Adams A. Why is the developed world obese? *Annual Review of Public Health*. 2008;29:273-295
- [4] Brody J. The global epidemic of childhood obesity: Poverty, urbanization, and the nutrition transition. *Nutrition Bytes*. 2002;8:1-7
- [5] Roberts EA. Non-alcoholic fatty liver disease (NAFLD) in children. *Frontiers in Bioscience*. 2005;10:2306-2318
- [6] Vos MB, McClain CJ. Nutrition and non-alcoholic fatty liver disease in children. *Current Diabetes Reports*. 2008;8:399-406
- [7] Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Digestive Diseases*. 2010;28:155-161
- [8] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of non-alcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73-84
- [9] Martins IJ. Increased risk for obesity and diabetes with neurodegeneration in developing countries. *Journal of Molecular and Genetic Medicine*. 2013;S1:001
- [10] Martins IJ. Unhealthy nutrigenomic diets accelerate NAFLD and adiposity in global communities. *Journal of Molecular and Genetic Medicine*. 2015;9:1-11
- [11] Martins IJ. Appetite control with relevance to mitochondrial biogenesis and activation of post-prandial lipid metabolism in obesity linked diabetes. *Annals of Obesity and Disorders*. 2016;1:1-3
- [12] Martins IJ. Diet and nutrition reverse type 3 diabetes and accelerated aging linked to global chronic diseases. *Journal of Diabetes Research and Therapy*. 2016;2:1-6
- [13] Martins IJ. Food intake and caffeine determine amyloid beta metabolism with relevance to mitophagy in brain aging and chronic disease. *European. Journal of Food Science and Technology*. 2016;4:11-17
- [14] Martins IJ. Caffeine consumption and induction of obesity in the developed world. *Annals of Obesity Disorders*. 2017;2:1-3
- [15] Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. *Comprehensive Physiology*. 2013;3:655-665

- [16] Gimble JM, Sutton GM, Ptitsyn AA, Floyd ZE, Bunnell BA. Circadian rhythms in adipose tissue: An update. *Current Opinion and Clinical Nutrition and Metabolic Care*. 2011;**14**:554-561
- [17] Buijs RM, Escobar C, Swaab DF. The circadian system and the balance of the autonomic nervous system. *Handbook of Clinical Neurology*. 2013;**117**:173-191
- [18] Kennedy OJ, Roderick P, Poole R, Parkes J. Coffee, caffeine and non-alcoholic fatty liver disease? *Therapeutic Advances in Gastroenterology*. 2016;**9**:417-418
- [19] Chen S, Teoh NC, Chitturi S, Farrell GC. Coffee and non-alcoholic fatty liver disease: Brewing evidence for hepatoprotection? *Journal of Gastroenterology and Hepatology*. 2014;**29**:435-441
- [20] Patell R, Dosi R, Joshi H, Sheth S, Shah P, Sarfaraz S. Non-alcoholic fatty liver disease (NAFLD) in obesity. *Journal of Clinical and Diagnostic Research*. 2014;**8**:62-66
- [21] Wong RJ, Ahmed A. Obesity and non-alcoholic fatty liver disease: Disparate associations among Asian populations. *World Journal of Hepatology*. 2014;**6**:263-273
- [22] Targher G, Byrne CD. Obesity: Metabolically healthy obesity and NAFLD. *Nature Reviews Gastroenterology and Hepatology*. 2016;**13**:442-444
- [23] Ezzat WM, Ragab S, Ismail NA, Elhosary AY, AM NEAEB, et al. Frequency of non-alcoholic fatty liver disease in overweight/obese children and adults: Clinical, sonographic picture and biochemical assessment. *Journal of Genetic Engineering and Biotechnology*. 2012;**10**:221-227
- [24] Suano de Souza FI, Silverio Amancio OM, Saccardo Sarni RO, Sacchi Pitta T, Fernandes AP, Affonso Fonseca FL, et al. Non-alcoholic fatty liver disease in overweight children and its relationship with retinol serum levels. *International Journal of Vitamin Nutrition Research*. 2008;**78**:27-32
- [25] Kim NH, Kim JH, Kim YJ, Yoo HJ, Kim HY, Seo JA, et al. Clinical and metabolic factors associated with development and regression of non-alcoholic fatty liver disease in non-obese subjects. *Liver International*. 2014;**34**:604-611
- [26] Acheson KJ, Gremaud G, Meirim I, Montigon F, Krebs Y, Fay LB, et al. Metabolic effects of caffeine in humans: Lipid oxidation or futile cycling? *American Journal of Clinical Nutrition*. 2004;**79**:40-46
- [27] Martins IJ. Caffeine consumption with relevance to type 3 diabetes and accelerated brain aging. *Research and Reviews: Neuroscience*. 2016;**1**:1-5
- [28] Ricchi M, Odoardi MR, Carulli L, Anzivino C, Ballestri S, Pinetti A, et al. Differential effect of oleic and palmitic acid on lipid accumulation and apoptosis in cultured hepatocytes. *Journal of Gastroenterology and Hepatology*. 2009;**24**:830-840

- [29] Gambino R, Bugianesi E, Rosso C, Mezzabotta L, Pinach S, Alemanno N, et al. Different serum free fatty acid profiles in NAFLD subjects and healthy controls after oral fat load. *International Journal of Molecular Science*. 2016;**17**:479
- [30] Puri P, Wiest MM, Cheung O, Mirshahi F, Sargeant C, Min HK, et al. The plasma lipidomic signature of non-alcoholic steatohepatitis. *Hepatology*. 2009;**50**:1827-1838
- [31] French MA, Sundram K, Clandinin MT. Cholesterolaeamic effect of palmitic acid in relation to other dietary fatty acids. *Asia Pacific Journal of Clinical Nutrition*. 2002;**11**(Suppl. 7):S401-S407
- [32] Clandinin MT, Cook SL, Konard SD, French MA. The effect of palmitic acid on lipoprotein cholesterol levels. *International Journal of Food Science Nutrition*. 2000;**51**(Suppl):S61-S71
- [33] Miyoshi T, Lönnfors M, Peter Slotte J, Kato S. A detailed analysis of partial molecular volumes in DPPC/cholesterol binary bilayers. *Biochimica et Biophysica Acta*. 2014;**1838**:3069-3077
- [34] Kheyfets BB, Mukhin SI. Simple model of local ordering of DPPC lipids in contact with cholesterol. *Biochemistry (Moscow) Supplement Series A*. 2015;**9**:77-83
- [35] Davis CH, Berkowitz ML. Interaction between amyloid-beta (1-42) peptide and phospholipid bilayers: A molecular dynamics study. *Biophysical Journal*. 2009;**96**:785-797
- [36] Ege C, Lee KY. Insertion of Alzheimer's A beta 40 peptide into lipid monolayers. *Biophysical Journal*. 2004;**87**:1732-1740
- [37] Martins IJ, Fernando WMADB. High fibre diets and Alzheimer's disease. *Food and Nutrition Sciences*. 2014;**5**:410-424
- [38] Cao C, Cirrito JR, Lin X, Wang L, Verges DK, Dickson A, et al. Caffeine suppresses amyloid-beta levels in plasma and brain of Alzheimer's disease transgenic mice. *Journal of Alzheimer's Disease*. 2009;**17**:681-697
- [39] Arendash GW, Mori T, Cao C, Mamcarz M, Runfeldt M, Dickson A, et al. Caffeine reverses cognitive impairment and decreases brain amyloid-beta levels in aged Alzheimer's disease mice. *Journal of Alzheimer's Disease*. 2009;**17**:661-680
- [40] Martins IJ, Lenzo NP, Redgrave TG. Phosphatidylcholine metabolism after transfer from lipid emulsions injected intravenously into rats. Implications for high density lipoprotein metabolism. *Biochimica et Biophysica Acta*. 1989;**1005**:217-224
- [41] Dubrez L, Coll JL, Hurbin A, Solary E, Favrot MC. Caffeine sensitizes human H358 cell line to p53-mediated apoptosis by inducing mitochondrial translocation and conformational change of BAX protein. *Journal of Biological Chemistry*. 2001;**276**:38980-39807
- [42] He Z, Ma WY, Hashimoto T, Bode AM, Yang CS, Dong Z. Induction of apoptosis by caffeine is mediated by the p53, Bax, and caspase 3 pathways. *Cancer Research*. 2003;**63**:4396-4401

- [43] Hansen MK, Connolly TM. Nuclear receptors as drug targets in obesity, dyslipidaemia and atherosclerosis. *Current Opinion in Investigational Drugs*. 2008;**9**:247-255
- [44] Harrison C. Neurodegenerative disorders: A neuroprotective role for sirtuin 1. *Nature Reviews Drug Discovery*. 2012;**11**:108
- [45] Kawada T, Goto T, Hirai S, Kang MS, Uemura T, Yu R. Dietary regulation of nuclear receptors in obesity-related metabolic syndrome. *Asia Pacific Journal of Clinical Nutrition*. 2008;**17**:126-130
- [46] Swanson HI, Wada T, Xie W, Renga B, Zampella A, Distrutti E. Role of nuclear receptors in lipid dysfunction and obesity-related diseases. *Drug Metabolism & Disposition*. 2013;**41**:1-11
- [47] Cakir I, Perello M, Lansari O, Messier NJ, Vaslet CA, Nilni EA. Hypothalamic sirt1 regulates food intake in a rodent model system. *PloS One*. 2009;**4**:e8322
- [48] Kitamura T, Sasaki T. Hypothalamic sirt1 and regulation of food intake. *Diabetology International*. 2012;**3**:109-112
- [49] Wei D, Tao R, Zhang Y, White MF, Dong XC. Feedback regulation of hepatic gluconeogenesis through modulation of SHP/Nr0b2 gene expression by Sirt1 and FoxO1. *American Journal of Physiology Endocrinology and Metabolism*. 2011;**300**:E312-E320
- [50] Li X. SIRT1 and energy metabolism. *Acta Biochimica et Biophysica Sinica (Shanghai)*. 2013;**45**:51-60
- [51] Chang HC, Guarente L. SIRT1 and other sirtuins in metabolism. *Trends in Endocrinology and Metabolism*. 2014;**25**:138-145
- [52] Mayoral R, Osborn O, McNelis J, Johnson AM, DY O, Izquierdo CL, Chung H, et al. Adipocyte SIRT1 knockout promotes PPAR γ activity, adipogenesis and insulin sensitivity in chronic-HFD and obesity. *Molecular Metabolism*. 2015;**4**:378-391
- [53] Picard F, Kurtev M, Chung N, Topark-Ngarm A, Senawong T, Machado De Oliveira R, et al. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. *Nature*. 2004;**429**:771-776
- [54] Bordone L, Motta MC, Picard F, Robinson A, Jhala US, Apfeld J, et al. Sirt1 regulates insulin secretion by repressing UCP2 in pancreatic beta cells. *PLoS Biology*. 2006;**4**:e31
- [55] Xu C, Bai B, Fan P, Cai Y, Huang B, Law IK, et al. Selective overexpression of human SIRT1 in adipose tissue enhances energy homeostasis and prevents the deterioration of insulin sensitivity with ageing in mice. *American Journal of Translational Research*. 2013;**5**:412-426
- [56] Choi Y, Um SJ, Park T. Indole-3-carbinol directly targets SIRT1 to inhibit adipocyte differentiation. *International Journal of Obesity (London)*. 2013;**37**:881-884

- [57] Siersbaek R, Nielsen R, Mandrup SPPAR. Gamma in adipocyte differentiation and metabolism—Novel insights from genome-wide studies. *FEBS Letters*. 2010;**584**:3242-3249
- [58] Körner A, Wabitsch M, Seidel B, Fischer-Posovszky P, Berthold A, Stumvoll M, et al. Adiponectin expression in humans is dependent on differentiation of adipocytes and down-regulated by humoral serum components of high molecular weight. *Biochemical and Biophysical Research Communications*. 2005;**337**:540-550
- [59] Lee MJ, Wu Y, Fried SK. Adipose tissue re-modeling in pathophysiology of obesity. *Current Opinion and Clinical Nutrition and Metabolic Care*. 2010;**13**:371-376
- [60] Qiao L, Shao J. SIRT1 regulates adiponectin gene expression through Foxo1-C/enhancer-binding protein alpha transcriptional complex. *Journal of Biological Chemistry*. 2006;**281**:39915-39924
- [61] Qiang L, Wang H, Farmer SR. Adiponectin secretion is regulated by SIRT1 and the endoplasmic reticulum oxidoreductase Ero1-L alpha. *Molecular and Cellular Biology*. 2007;**27**:4698-4707
- [62] Shen Z, Liang X, Rogers CQ, Rideout D, You M. Involvement of adiponectin-SIRT1-AMPK signaling in the protective action of rosiglitazone against alcoholic fatty liver in mice. *American Journal of Physiology. Gastrointestinal and Liver Physiology*. 2010;**298**:G364-G374
- [63] Lancaster GI, Febbraio MA. Adiponectin sphings into action. *Nature Medicine*. 2011;**17**:37-38
- [64] Samad F, Badeanlou L, Shah C, Yang G. Adipose tissue and ceramide biosynthesis in the pathogenesis of obesity. *Advances in Experimental Medicine and Biology*. 2011;**721**:67-86
- [65] Błachnio-Zabielska AU, Pułka M, Baranowski M, Nikołajuk A, Zabielski P, Górska M, et al. Ceramide metabolism is affected by obesity and diabetes in human adipose tissue. *Journal of Cellular Physiology*. 2012;**227**:550-557
- [66] Matsuura F, Oku H, Koseki M, Sandoval JC, Yuasa-Kawase M, Tsubakio-Yamamoto K, et al. Adiponectin accelerates reverse cholesterol transport by increasing high density lipoprotein assembly in the liver. *Biochemical and Biophysical Research Communications*. 2007;**358**:1091-1095
- [67] Toth PP. Adiponectin and high-density lipoprotein: A metabolic association through thick and thin. *European Heart Journal*. 2005;**26**:1579-1581
- [68] Bullen JW, Bluher S, Kelesidis T, Mantzoros CS. Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice. *American Journal of Physiology: Endocrinology and Metabolism*. 2007;**292**:E1079-E1086
- [69] Polyzos SA, Kountouras J, Zavos C, Tsiaousi E. The role of adiponectin in the pathogenesis and treatment of non-alcoholic fatty liver disease. *Diabetes Obesity and Metabolism*. 2010;**12**:365-383

- [70] Finelli C, Tarantino G. What is the role of adiponectin in obesity related non-alcoholic fatty liver disease? *World Journal of Gastroenterology*. 2013;**19**:802-812
- [71] Pagano C, Soardo G, Esposito W, Fallo F, Basan L, Donnini D, et al. Plasma adiponectin is decreased in non-alcoholic fatty liver disease. *European Journal of Endocrinology*. 2005;**152**:113-118
- [72] Oku H, Matsuura F, Koseki M, Sandoval JC, Yuasa-Kawase M, Tsubakio-Yamamoto K, et al. Adiponectin deficiency suppresses ABCA1 expression and ApoA-I synthesis in the liver. *FEBS Letters*. 2007;**581**:5029-5033
- [73] Badman MK, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPAR α and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metabolism*. 2007;**5**:426-437
- [74] Zhu S, Wu Y, Ye X, Ma L, Qi J, Yu D, et al. FGF21 ameliorates non-alcoholic fatty liver disease by inducing autophagy. *Molecular and Cellular Biochemistry*. 2016;**420**:107-119
- [75] Dushay J, Chui PC, Gopalakrishnan GS, Varela-Rey M, Crawley M, Fisher FM, et al. Increased fibroblast growth factor 21 in obesity and non-alcoholic fatty liver disease. *Gastroenterology*. 2010;**139**:456-463
- [76] Liu J, Xu Y, Hu Y, Wang G. The role of fibroblast growth factor 21 in the pathogenesis of non-alcoholic fatty liver disease and implications for therapy. *Metabolism*. 2015;**64**:380-390
- [77] Tao C, Sifuentes A, Holland WL. Regulation of glucose and lipid homeostasis by adiponectin: Effects on hepatocytes, pancreatic β cells and adipocytes. *Best Practice & Research: Clinical Endocrinology and Metabolism*. 2014;**28**:43-58
- [78] Pagadala M, Kasumov T, McCullough AJ, Zein NN, Kirwan JP. Role of ceramides in non-alcoholic fatty liver disease. *Trends in Endocrinology and Metabolism*. 2012;**23**:365-371
- [79] Kasumov T, Li L, Li M, Gulshan K, Kirwan JP, Liu X, et al. Ceramide as a mediator of non-alcoholic fatty liver disease and associated atherosclerosis. *PloS One* 2015;**10**:e0126910
- [80] Luukkonen PK, Zhou Y, Sädevirta S, Leivonen M, Arola J, Orešič M, et al. Hepatic ceramides dissociate steatosis and insulin resistance in patients with non-alcoholic fatty liver disease. *Journal of Hepatology*. 2016;**64**:1167-1175
- [81] Yu C, Alterman M, Dobrowsky RT. Ceramide displaces cholesterol from lipid rafts and decreases the association of the cholesterol binding protein caveolin-1. *Journal of Lipid Research*. 2005;**46**:1678-1691
- [82] Ali MR, Cheng KH, Huang J. Ceramide drives cholesterol out of the ordered lipid bilayer phase into the crystal phase in 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine/cholesterol/ceramide ternary mixtures. *Biochemistry*. 2006;**45**:12629-12638

- [83] Castro BM, Silva LC, Fedorov A, de Almeida RF, Prieto M. Cholesterol-rich fluid membranes solubilize ceramide domains: Implications for the structure and dynamics of mammalian intracellular and plasma membranes. *Journal of Biological Chemistry*. 2009;**284**:22978-22987
- [84] Martins IJ, Creegan R. Links between insulin resistance, lipoprotein metabolism and amyloidosis in Alzheimer's disease. *Health*. 2014;**6**:1549-1579
- [85] Martins IJ. The role of clinical proteomics, lipidomics, and genomics in the diagnosis of Alzheimer's disease. *Proteomes*. 2016;**4**:1-19
- [86] Puig KL, Floden AM, Adhikari R, Golovko MY, Combs CK. Amyloid precursor protein and proinflammatory changes are regulated in brain and adipose tissue in a murine model of high fat diet-induced obesity. *PloS One*. 2012;**7**:e30378
- [87] Lee YH, Martin JM, Maple RL, Tharp WG, Pratley RE. Plasma amyloid-beta peptide levels correlate with adipocyte amyloid precursor protein gene expression in obese individuals. *Neuroendocrinology*. 2009;**90**:383-390
- [88] Vanitha S, Martin JM, Dixon AE, Ades PA, Savage PD, Spaulding L, et al. Overexpression of amyloid precursor protein in adipose tissue of obese diabetic vs. obese non-diabetic individuals. *Diabetes*. 2007;**56**:363
- [89] Lee YH, Tharp WG, Maple RL, Nair S, Permana PA, Pratley RE. Amyloid precursor protein expression is up-regulated in adipocytes in obesity. *Obesity (Silver Spring)*. 2008;**16**:1493-1500
- [90] Freeman LR, Zhang L, Dasuri K, Fernandez-Kim SO, Bruce-Keller AJ, Keller JN. Mutant amyloid precursor protein differentially alters adipose biology under obesogenic and non-obesogenic conditions. *PloS One*. 2012;**7**:e43193
- [91] Puig KL, Floden AM, Adhikari R, Golovko. The role of adiponectin in the pathogenesis and treatment of non-alcoholic fatty liver disease. *Diabetes Obesity and Metabolism*. 2010;**12**:365-383
- [92] Bahceci M, Gokalp D, Bahceci S, Tuzcu A, Atmaca S, Arikan S. The correlation between adiposity and adiponectin, tumor necrosis factor alpha, interleukin-6 and high sensitivity C-reactive protein levels. Is adipocyte size associated with inflammation in adults? *Journal of Endocrinological Investigation*. 2007;**30**:210-214
- [93] Bhaktha G, Nayak BS, Mayya S, Shantaram M. Relationship of caffeine with adiponectin and blood sugar levels in subjects with and without diabetes. *Journal of Clinical and Diagnostic Research*. 2015;**9**:BC01-BC03
- [94] Yamashita K, Yatsuya H, Muramatsu T, Toyoshina H, Murohara T, Tamakoshi K. Association of coffee consumption with serum adiponectin, leptin, inflammation and metabolic markers in Japanese workers: A cross-sectional study. *Nutrition and Diabetes*. 2012;**2**:e33

- [95] Seidel C, Schneckeburger M, Dicato M, Diederich M. Histone deacetylase modulators provided by mother nature. *Genes and Nutrition*. 2012;**7**:357-367
- [96] SH S, Shyu HW, Yeh YT, Chen KM, Yeh H, Su SJ. Caffeine inhibits adipogenic differentiation of primary adipose-derived stem cells and bone marrow stromal cells. *Toxicology In Vitro*. 2013;**27**:1830-1837
- [97] Kim AR, Yoon BK, Park H, Seok JW, Choi H, JH Y, et al. Caffeine inhibits adipogenesis through modulation of mitotic clonal expansion and the AKT/GSK3 pathway in 3T3-L1 adipocytes. *BMB Reports*. 2016;**49**:111-115
- [98] Sinha RA, Farah BL, Singh BK, Siddique MM, Li Y, Wu Y, et al. Caffeine stimulates hepatic lipid metabolism by the autophagy-lysosomal pathway in mice. *Hepatology*. 2014;**59**:1366-1380
- [99] Horrigan LA, Kelly JP, Connor TJ. Immunomodulatory effects of caffeine: Friend or foe? *Pharmacology and Therapeutics*. 2006;**111**:877-892
- [100] Meli R, Mattace Raso G, Calignano A. Role of innate immune response in non-alcoholic fatty liver disease: Metabolic complications and therapeutic tools. *Frontiers in Immunology*. 2014;**5**:177
- [101] Kong S, McBurney MW, Fang D. Sirtuin 1 in immune regulation and autoimmunity. *Immunology and Cell Biology*. 2012;**90**:6-13
- [102] Chen X, Lu Y, Zhang Z, Wang J, Yang H, et al. Intercellular interplay between Sirt1 signalling and cell metabolism in immune cell biology. *Immunology*. 2015;**145**:455-467
- [103] Martins IJ, Tran JML, Redgrave TG. Food restriction normalizes chylomicron remnant metabolism in murine models of obesity as assessed by a novel stable isotope breath test. *Journal of Nutrition*. 2002;**132**:176-181
- [104] Martins IJ, Redgrave TG. A $^{13}\text{CO}_2$ breath test for the assessment of remnant metabolism in mice. *Journal of Lipid Research*. 1998;**39**:693-699
- [105] Martins IJ, Sainsbury AJ, Mamo JCL, Redgrave TG. Lipid and apolipoprotein B48 transport in mesenteric lymph and the effect of hyperphagia on chylomicron clearance in insulin-deficient rats. *Diabetologia*. 1994;**37**:238-246
- [106] Dane-Stewart CA, Watts GF, Barrett PH, Stuckey BG, Mamo JC, Martins IJ, et al. Chylomicron remnant metabolism studied with a new breath test in postmenopausal women with and without type 2 diabetes mellitus. *Clinical Endocrinology*. 2003;**58**:15-20
- [107] Martins IJ, Redgrave TG. Obesity and post-prandial lipid metabolism. Feast or famine? *The Journal of Nutritional Biochemistry*. 2004;**15**:130-141
- [108] Xu F, Gao ZG, Zhang J, Rivera CA, Yin J, Weng JP, et al. Lack of SIRT1 (mammalian Sirtuin 1) activity leads to liver steatosis in the SIRT1 $^{+/-}$ mice: A role of lipid mobilization and inflammation. *Endocrinology*. 2010;**151**:2504-2514

- [109] Purushotham A, Xu Q, Li XL. Systemic SIRT1 insufficiency results in disruption of energy homeostasis and steroid hormone metabolism upon high-fat-diet feeding. *FASEB Journal*. 2012;**26**:656-667
- [110] Bordone L, Cohen D, Robinson A, Motta MC, Van Veen E, Czopik A, et al. SIRT1 transgenic mice show phenotypes resembling calorie restriction. *Aging Cell*. 2007;**6**:759-767
- [111] Ideally how many grams of fat should you consume daily. Available from: <http://healthyeating.sfgate.com/ideally-many-grams-fat-should-consume-daily-5501.html>
- [112] Martins IJ. Nutrition therapy regulates caffeine metabolism with relevance to NAFLD and induction of type 3 diabetes. *Journal of Diabetes and Metabolic Disorders*. 2017;**4**:19
- [113] Blanchard J. Protein binding of caffeine in young and elderly males. *Journal of Pharmaceutical Sciences*. 1982;**71**:1415-1418
- [114] Martins IJ. Unhealthy diets determine benign or toxic amyloid beta states and promote brain amyloid beta aggregation. *Austin Journal of Clinical Neurology*. 2015;**2**:1060-1066
- [115] Sharma B, Paul S. Action of caffeine as an amyloid inhibitor in the aggregation of A β 16-22 peptides. *Journal of Physical Chemistry B*. 2016;**120**:9019-9033
- [116] Martins IJ. Magnesium therapy prevents senescence with the reversal of diabetes and Alzheimer's disease. *Health*. 2016;**8**:694-710
- [117] Kynast-Gales SA, Massey LK. Effect of caffeine on circadian excretion of urinary calcium and magnesium. *Journal of the American College of Nutrition*. 1994;**13**:467-472
- [118] Shen H, Rodriguez AC, Shiani A, Lipka S, Shahzad G, Kumar A, et al. Association between caffeine consumption and non-alcoholic fatty liver disease: A systemic review and meta-analysis. *Therapeutic Advances in Gastroenterology*. 2016;**9**:113-120
- [119] Shen C, Dou X, Ma Y, Ma W, Li S, Song Z. Nicotinamide protects hepatocytes against palmitate-induced lipotoxicity via SIRT1-dependent autophagy induction. *Nutrition Research*. 2017;**40**:40-47
- [120] Tong X, Zhang D, Arthurs B, Li P, Durudogan L, Gupta N, et al. Palmitate inhibits SIRT1-dependent BMAL1/CLOCK interaction and disrupts circadian gene oscillations in hepatocytes. *PloS One*. 2015;**10**:e0130047
- [121] Chen JX, Yan SS. Role of mitochondrial amyloid-beta in Alzheimer's disease. *Journal of Alzheimer's Disease*. 2010;**20**(Suppl. 2):S569-S578
- [122] Koczor CA, White RC, Zhao P, Zhu L, Fields E, Lewis W. p53 and mitochondrial DNA, their role in mitochondrial homeostasis and toxicity of anti-retrovirals. *American Journal of Pathology*. 2012;**180**:2276-2283
- [123] Park J-H, Zhuang J, Li J, Hwang PM. p53 as guardian of the mitochondrial genome. *FEBS Letters*. 2016;**590**:924-934
- [124] Safdar A, Little JP, Stokl AJ, Hettinga BP, Akhtar M, Tarnopolsky MA. Exercise increases mitochondrial PGC-1 α content and promotes nuclear-mitochondrial

- cross-talk to coordinate mitochondrial biogenesis. *Journal of Biology Chemistry*. 2011;**286**:10605-10617
- [125] Sen N, Satija YK, Das S. PGC-1 α , a key modulator of p53, promotes cell survival upon metabolic stress. *Molecular Cell*. 2011;**44**:621-634
- [126] Aquilano K, Baldelli S, Pagliei B, Cannata SM, Rotilio G, Ciriolo MR. p53 orchestrates the PGC-1 α -mediated antioxidant response upon mild redox and metabolic imbalance. *Antioxidants and Redox Signalling*. 2013;**18**:386-399
- [127] Martins IJ. Type 3 diabetes with links to NAFLD and other chronic diseases in the Western World. *International Journal of Diabetes*. 2016;**1**:1-5
- [128] Martins IJ. Heat shock gene Sirtuin 1 regulates post-prandial lipid metabolism with relevance to nutrition and appetite regulation in diabetes. *International Journal of Diabetes and Clinical Diagnosis*. 2016;**3**:20
- [129] Martins IJ. Calorie sensitive anti-aging gene regulates hepatic amyloid beta clearance in diabetes and neurodegenerative diseases. *EC Nutrition*. 2017;**ECO**. **01**:30-32
- [130] Martins IJ. Heat shock gene dysregulation and inactivation of drug therapy. *EC Pharmacology and Toxicology*. 2017;**ECO**.**01**:13-15
- [131] Martins IJ. Regulation of core body temperature and the immune system determines species longevity. *Current Updates in Gerontology*. 2017;**1**:1-6
- [132] Martins IJ. Induction of NAFLD with increased risk of obesity and chronic diseases in developed countries. *Open Journal of Endocrine and Metabolic Diseases*. 2014;**4**:90-110
- [133] Martins IJ. Nutritional diets accelerate amyloid beta metabolism and prevent the induction of chronic diseases and Alzheimer's disease. In: *The Journal for Endocrinology and Metabolism*, Imprint: Photon, Peer Reviewed Indexed International Journal. Photon ebooks; 2017. p. 1-48
- [134] Martins IJ. Apelinergic system defects with relevance to mental disorders in diabetes. *World Journal of Psychiatry and Mental Health Research*. 2017;**1**:1001
- [135] Martins IJ. Defective interplay between adipose tissue and immune system induces non-alcoholic fatty liver disease. *Updates in Nutritional Disorders and Therapy*. 2017;**1**:3.1
- [136] Pénicaud L. Relationships between adipose tissues and brain: What do we learn from animal studies? *Diabetes and Metabolism*. 2010;**36**(Suppl. 3):S39-S44
- [137] Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World Journal of Diabetes*. 2012;**3**:110-117
- [138] Farrell GC, Wong VW, Chitturi S. NAFLD in Asia—As common and important as in the west. *Nature Reviews Gastroenterology and Hepatology*. 2013;**10**:307-318
- [139] Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: Population based study. *Annals of Hepatology*. 2007;**6**:161-163

- [140] LaBrecque DR, Abbas Z, Anania F, Ferenci P, Khan AG, Goh KL, et al. World gastroenterology organisation global guidelines: Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Journal of Clinical Gastroenterology*. 2014;**48**:467-473
- [141] Hu FB. Globalization of diabetes: The role of diet, lifestyle, and genes. *Diabetes Care*. 2011;**34**:1249-1257
- [142] Shi X, Xue W, Liang S, Zhao J, Zhang X. Acute caffeine ingestion reduces insulin sensitivity in healthy subjects: A systematic review and meta-analysis. *Nutrition Journal*. 2016;**15**:103
- [143] Dewar L, Heuberger R. The effect of acute caffeine intake on insulin sensitivity and glycemic control in people with diabetes. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*. 2017; Available online 23 April 2017. In Press, Accepted Manuscript. <https://doi.org/10.1016/j.dsx.2017.04.017>
- [144] Martins IJ. Bacterial lipopolysaccharides change membrane fluidity with relevance to phospholipid and amyloid beta dynamics in Alzheimer's disease. *Journal of Microbiology and Biochemical Technology*. 2016;**8**:322-324
- [145] Martins IJ. The future of genomic medicine involves the maintenance of sirtuin 1 in global populations. *International Journal of Molecular Biology*. 2017;**2**:00013
- [146] How Much Fat Per Day—How Many Grams of Fat Should You Eat? <http://www.acaloriecounter.com/diet/how-much-fat-per-day>, Accessed 06/07/2017, Copyright © 2007 - 2017 A Calorie Counter. All Rights Reserved. Terms Of Use
- [147] Martins IJ. In: Atta-ur-Rahman, editor *Nutritional and Genotoxic Stress Contributes to Diabetes and Neurodegenerative Diseases such as Parkinson's and Alzheimer's Diseases*. *Frontiers in Clinical Drug Research-CNS and Neurological Disorders* 2015 3. pp. 158-192
- [148] Tahara Y, Shibata S. Circadian rhythms of liver physiology and disease: Experimental and clinical evidence. *Nature Reviews. Gastroenterology & Hepatology*. 2016;**13**:217-226
- [149] Burke TM, Markwald RR, McHill AW, Chinoy ED, Snider JA, Bessman SC, et al. Effects of caffeine on the human circadian clock in vivo and in vitro. *Science Translational Medicine*. 2015;**7**:305ra146
- [150] Martins IJ. Geriatric medicine and heat shock gene therapy in global populations. *Current Updates in Gerontology*. 2016;**1**:1-5
- [151] Scorletti E, Bhatia L, McCormick KG, Clough GF, Nash K, Hodson L, et al. WELCOME Study. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: Results from the Welcome* study. *Hepatology*. 2014;**60**:1211-1221
- [152] Alkhoury N, Dixon LJ, Feldstein AE. Lipotoxicity in non-alcoholic fatty liver disease: Not all lipids are created equal. *Expert Review in Gastroenterology and Hepatology*. 2009;**3**:445-451
- [153] Martins IJ, Gupta V, Wilson AC, Fuller SJ, Martins RN. Interactions between Apo E and amyloid beta and their relationship to nutriproteomics and neurodegeneration. *Current Proteomics*. 2014;**11**:173-183

- [154] Martins IJ. Over-nutrition determines LPS regulation of mycotoxin induced neurotoxicity in neurodegenerative diseases. *International Journal of Molecular Science*. 2015;**16**:29554-29573
- [155] Tong X, Yin L. Circadian rhythms in liver physiology and liver diseases. *Comparative Physiology*. 2013;**3**:917-940
- [156] Gnanou JV, Caszo BA, Khalil KM, Abdullah SL, Knight VF, Bidin MZ. Effects of Ramadan fasting on glucose homeostasis and adiponectin levels in healthy adult males. *Journal of Diabetes and Metabolic Disorders*. 2015;**14**:55
- [157] Martins IJ. The global obesity epidemic is related to stroke, dementia and Alzheimer's disease. *JSM Alzheimer's Disease and Related Dementia*. 2014;**1**:1010
- [158] Cassidy A, Skidmore P, Rimm EB, Welch A, Fairweather-Tait S, Skinner J, et al. Plasma adiponectin concentrations are associated with body composition and plant-based dietary factors in female twins. *Journal of Nutrition*. 2009;**139**:353-358
- [159] Markaki A, Kyriazis J, Stylianou K, Fragkiadakis GA, Perakis K, Margioris AN, et al. The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. *PloS One*. 2012;**7**:e52350
- [160] Sierksma A, Patel H, Ouchi N, Kihara S, Funahashi T, Heine RJ, et al. Effect of moderate alcohol consumption on adiponectin, tumor necrosis factor-alpha, and insulin sensitivity. *Diabetes Care*. 2004;**27**:184-189
- [161] Burg VK, Grimm HS, Rothhaar TL, Grösgen S, Hundsdörfer B, Haupenthal VJ, et al. Plant sterols the better cholesterol in Alzheimer's disease? A mechanistical study. *Journal of Neuroscience*. 2013;**33**:16072-16087
- [162] Sodhi K, Puri N, Favero G, Stevens S, Meadows C, Abraham NG, et al. Fructose mediated non-alcoholic fatty liver is attenuated by HO-1-SIRT1 module in murine hepatocytes and mice fed a high fructose diet. *PloS One*. 2015;**10**:e0128648
- [163] Rebollo A, Roglans N, Baena M, Sánchez RM, Merlos M, Alegret M, et al. Liquid fructose down-regulates Sirt1 expression and activity and impairs the oxidation of fatty acids in rat and human liver cells. *Biochimica et Biophysica Acta*. 2014;**1841**:514-524
- [164] Martins IJ. Magnesium deficiency and induction of NAFLD and Type 3 diabetes in Australasia. *Australasian Medical Journal*. 2017;**10**:235-237
- [165] Martins IJ. Drug therapy for obesity with anti-aging genes modification. *Annals of Obesity and Disorders*. 2016;**1**:1001
- [166] Martins IJ. Inactivation of anti-aging genes is related to defective drug metabolism in diabetes. *International Journal of Drug Discovery*. 2017;**1**:3
- [167] Martins IJ. Early diagnosis of neuron mitochondrial dysfunction may reverse global metabolic and neurodegenerative disease. *Global Journal of Medical Research*. 2016;**2**:1-8

