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Mitochondrial dysfunction in our aging veterans; obesity, fatty liver, and NASH with obstructive sleep apnea treated with CPAP, medication, nutrition and MOVE program

Abstract

Until recently, the medical literature has ignored the contribution of sleep apnea to the etiology of obesity and fatty liver (NAFLD) and its potential to cause Non Alcoholic Steato Hepatitis (NASH), cirrhosis and then possibly, liver cancer. This paper discusses the Medical Hypothesis of a weight loss solutions to the mitochondrial dysfunction associated with aging and co–morbid diseases caused by obstructive sleep apnea leading to diabetes 2, obesity, fatty liver and (NASH). NASH is now the second leading liver disease among those waiting for liver transplantation. The most rapidly growing cause of cirrhosis and liver cancer is fatty liver disease. The observation that obstructive sleep apnea decreases the mitochondrial efficacy with diminished ATP and disordered sleep leading to weight gain, increased abdominal girth, diabetes, fatty liver, NASH, eventual liver fibrosis progressing to cirrhosis and even HCC may be monumental. The free radical theory of aging with reactive oxygen species, the unwanted toxic byproducts of aerobic metabolism, damage the respiratory chain (RC) located in the inner mitochondrial membrane is discussed. Together, these reactive oxygen species (ROS) contribute widely to aging, obesity, fatty liver, NASH and liver fibrosis and cirrhosis. The observation that sleep medicine with CPAP combined with Topramax, Orlistat causing fat malabsorption, the MOVE program with diet and exercise enabled patients at a Veterans Hospital to lose weight, and improve AST and ALT. This solution to this mitochondrial decline and oxidative distress in patients was antioxidant supplementation of Vitamin E and occasionally Silymarin to protect hepatocytes cells from oxidative damage and ultimately up–regulate the RC. Finally, another dramatically different approach is to the up–regulation of mitochondrial function by NIR light and DC EMF with polygenic regulation of antioxidant genes in the future.

Keywords: fatty liver, zucker rats, obstructive sleep apnea, liver fibrosis, nutrition

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Abbrevations: MFRTA, Mitochondrial free radical theory of aging; ROS, reactive oxygen species; ETC, electron transport chain; mtDNA, mitochondrial DNA mutations; FOXO1A, Fork head box O1A; NASH, nonalcoholic steatohepatitis; CoQ10, coenzyme Q; SMF, static magnetic fields; DC EMF, direct current electromagnetic field; NIR, near infra–red

Introduction

Sleep apnea and liver injury

Long ignored, the medical literature has missed the contribution of sleep apnea to the etiology of obesity and fatty liver and its potential to cause Non Alcoholic Steato Hepatitis (NASH) and then liver cancer. Trzepizur and associates in November 2016published the "Association between severity of obstructive sleep apnea and blood markers of liver injury." This was a clinical study of patients in seven sleep centers with a wide variety of Obstructive Sleep Apnea (OSA) severity and blood markers of liver injury. They found that severe OSA conferred a 2.5fold increase in the risk for significant liver fibrosis compared to controls with OSA.[1] However nasal continuous positive airway pressure alone in moderate–to–severe OSA had no impact on visceral adiposity and did not improve blood markers of liver injury in another recent study.[2]

Brain ATP increase with sleep

Another recent manuscript by Dworal and his coworkers found a surge in ATP levels in the initial hours of spontaneous sleep in several brain levels. This surge was prevented or delayed by sleep deprivation and sleep apnea. The authors hypothesized in their conclusion that sleep is for energy surge permitting energy–consuming anabolic process of protein and fatty acids.[3]

History of sleep apnea

At the level of the cell, the management of obesity may well reside in the powerhouse of the cell, the mitochondria. Mitochondrial bioenergetics in obesity was reviewed by Bharadwaj et al.[4] with the fact that mitochondrial function declines with age. The increasing prevalence of obesity among older adults has led to growing concerns among numerous chronic health conditions in this population. Data suggests that electron transport complex (ETC) dysfunction evident with mild insulin resistance, may be related to multiple mitochondrial changes others have reported in diabetic obese patients.[4] Obesity and increased abdominal girth has long been associated with sleep apnea dating to the 19th Century with Pickwick Papers by Dickens described an obese character Joe who often fell asleep who had all the classic symptoms of the condition which lead to the diagnosis of "Pickwickian

Syndrome."[5] In 1965 Sleep Apnea "hyponic and respiratory episodal manifestations of Pickwick syndrome" was published.[6]

Oxidative stress and mitochondrial defects

Denham Harman had already in 1956 introduced the free radical theory of aging based on free radicals and radiation chemistry.[7] The mitochondrial free radical theory of aging (MFRTA) subsequently followed in 1972 when Harman suggested that mitochondria had characteristics that enabled them to be both the sources and the direct victims of toxic free radicals.[8] Wei in 1998 summarized mitochondrial DNA (mtDNA), which unlike chromosomal DNA is not protected by histones or DNA–binding proteins, is continually exposed to a high steady–state level of reactive oxygen species (ROS). The subsequent oxidative modification and mutation of mtDNA occurs with great ease, and the extent of such alterations of mtDNA increases exponentially with age.[9] These conclusions were consistent with the reduced number of ROS scavenging enzymes associated with aging as well as the appearance of rounded organelles structure. Furthermore, a decrease in the absolute number of mitochondria occurs with age in the liver of mice, rats and humans.[10]

Yamauchi et al.[11] investigated the relationship between severity of OSA and oxidative stress in 2005 using urinary excretion of 8–hydroxy–2–deoxyguanosine (8–OHdG) as an in–vivo parameter of oxidative stress. Urinary 8–OHdG excretion was significantly correlated with parameters of sleep–disordered breathing.[11]

Mitochondria are damaged by OSA

Mitochondrial DNA (MtDNA) alterations in obstructive sleep apnea were announced in 2015 by Lacedonia. Using real–time qPCR to measure mitochondrial to nuclear genome ratio (Mt/N), they concluded that in OSA there is a mitochondrial DNA damage induced by increase of oxidative stress. Intermittent hypoxia seems to be the main mechanism which leads to this problem.[12]

Mitochondrial metabolism has been found to be important in mediating longevity through nutrient–sensing pathways and dietary restriction. Insulin/IGF–1 signaling (IIS) and target of rapamycin (TOR) that is a serine/threonine kinase signaling pathways are two main nutrient–sensing pathways in mice and have been linked to the regulation of their life span.[13] In fruit flies, caloric restriction has also been shown via dFOXO modifying expression of its target genes and maybe therefore mediates normal response to dietary restriction.[14]

Mitochondria are defective in DM, fatty liver and NASH

Until the last decade, the mitochondria defects seen in metabolic syndrome and diabetes mellitus 2 and fatty liver has not been emphasized. Defects in oxidative phosphorylation, glucose and fatty acids disposal in various states of insulin resistance suggest that a common pathway of impairment in mitochondrial function contributes to the development of insulin resistance.[15]

Hideyuki Kojima[16] and associates demonstrated that in non–alcoholic steatohepatitis (NASH), the enhanced oxidative stress is associated with hepatic inflammation and the degree of fat infiltration in the liver. Zucker rats and their lean normal littermate rats were fed a choline–deficient diet and when exposed to oxidative stress, both developed NASH. Zucker rats which naturally develop leptin receptor mutations, alone were associated with a mitochondrial abnormality. These findings indicate that a mitochondrial abnormality plays a role in the onset and progression of NASH in correlation with oxidative stress.[16] Kitade and Kojima found that Leptin, a neurohormone essential to energy homeostasis, mediated neovascularization as a prerequisite for progression of NASH in the littermate rats, almost in parallel with fibrosis and cancer development as an expression of (VEGF) vascular permeability and endothelial growth factor.[17]

Mitochondria, double membrane energy exchangers

The powerhouse of the cell, mitochondria is double–membrane organelles that strip electrons from fatty acids, sugars and amino–acids and accumulate them on the soluble electron carrier NADH and on proton–bound FADH2. NADH: ubiquinone reductase or (Complex I) is an enzyme that is located in the inner mitochondrial membrane that catalyzes the transfer of electrons from NADH to coenzyme Q (CoQ) (Figure 1). The electrons are passed down the mitochondrial respiratory chain to drive ATP synthesis by oxidative phosphorylation or coupled respiration. As the electron move down energy gradient from NADH/FADH to oxygen, redox energy is conserved by pumping protons across the inner membrane to build up an electrochemical gradient. Other essential metabolic functions include generation by the tricarboxylic acid cycle (Krebs) of numerous metabolites that function in cytosolic pathways, oxidative catabolism of amino acids, ketogenesis, urea cycle and the generation of reactive oxygen species (ROS) which have important signaling functions. Additionally, the mitochondrial control of calcium and protein cofactors is essential for cellular function and DNA repair.[18]

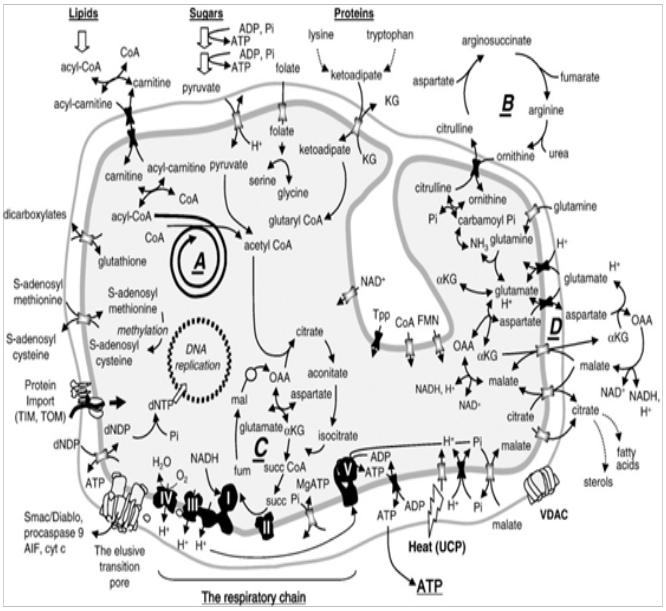

Figure 1 Mitochondrial energy transfer.

Mitochondria's double–edged sword; the balance between oxidants and antioxidants

It has been long time recognized that breathing oxygen which is essential to life in humans also has a dark side. Seviddio demonstrated that oxidative phosphorylation and mitochondrial ATP generation is a double edged sword. Considerable oxidative stress is generated through free radicals ROS (unpaired electrons) and unless antioxidants such as manganese superoxide dismutase (MnSOD), catalase and peroxidase are present in adequate amounts, lipid peroxidation and cell death

occurs in nonalcoholic steatohepatitis, obesity, and diabetes.[19]

Mitochondrial defects as more than just the powerhouse of the cell. Ritu Saxena PhD in a paper demonstrated that although all mitochondrial diseases have the same characteristic of inadequate energy production as compared to the demand, they seem to show diverse manifestations in the form of organs being affected, age of onset and the rate of progression. The reason lies in the unique genetic makeup of mitochondria and the mitochondrial DNA. MtDNA mutates at rate that is six–seven times higher than the rate of mutation of nuclear DNA. One reason is the absence of histones on mtDNA and a second is the exposure of mtDNA to free radicals due to their close proximity to electron transport chain. The lack of DNA repair enzymes results in mutant tRNA, rRNA and protein transcripts is the third reason. Additionally, the percentage of mtDNA carrying defects varies when the ovum divides and one daughter cells receiving more defective mtDNA and the other receiving less. Successive divisions may lead to accumulation of defects in one of the developing organs or tissues.[20]

Obesity and leanness are on a delicate balance of caloric intake, metabolism, energy expenditure and genes

Metabolomic studies in rodents suggest that enhanced fat metabolism seen with high fat feeding overloads muscle mitochondria with oxidation products in a way that restricts their ability to completely metabolize these products to CO_2. High–fat feeding increased acylcarnitines representing products of incomplete β–oxidation of fatty acids was shown by Koves. This was associated with decreased TCA intermediates and an inability of mitochondria to switch from using fat–derived substrates to the glucose–derived metabolite, pyruvate.[21]

One solution: sleep medicine, MOVE program, diet and antioxidants

Therefore, in an attempt to change metabolism, gene expression and up–regulate mitochondria, down–regulate oxidative stress and inflammation in over weight patients with fatty liver in at a Veterans Hospital was used.

A pilot clinical study in 28obese patients with fatty liver or NASH confirmed with US of CT was sent for sleep studies. This study started as a means for US Veterans to lose weight and reduce liver adiposity. All patients who were diagnosed with sleep apnea were prescribed continuous positive airway pressure (CPAP). Topramax, a medication used for weight loss, and for sleep apnea was prescribed at bedtime starting at 25mg for 2weeks, increasing to 50mg. Patients were referred to the dietician for a weight reduction diet[1] and instructed to enroll in the MOVE program which has the veteran keep tract of his exercise (with a small wearable monitor) They were also started on 200units BID vitamin E, an antioxidant for those with elevated AST/ALT. Patients were seen about every 2months and weighed and AST/ALT were measured. If the patient didn't have any weight loss, Orlistat 120mg BID which causes fat malabsorption was added with meals and a multivitamin to ward off vitamin deficiency. All patients lost some weight and the majority felt they had more energy and less depression. All patients continued on their CPAP and medication but unfortunately the study was stopped after 6 months and the physician author's contract was not renewed due to a budgetary deficiency. This prevented any statistical analysis of liver test and repeat imaging.[2]

Discussion

Zaher Fanari[22] reported on the impact of CPAP, weight loss or both on the metabolic syndrome profile in patients with OSA. 181patients with obesity and C–reactive protein (CRP) greater than 1.0mg/liter were randomized to CPAP, a weight–loss intervention, or CPAP plus weight loss intervention for 24weeks. Follow–up data was performed in 146participants with a reduction in CRP levels, insulin resistance and serum triglyceride levels in those assigned to weight loss only and to the combined interventions, but not in the CPAP alone group.[22]

Kanimozhi[23] and associates in 2015 studied twenty adult males and postmenopausal females with metabolic syndrome and symptoms suggestive of OSA with CPAP. In their previously published study they demonstrated an increased lipid peroxidation and decreased total reduced glutathione levels indicating an imbalance between (ROS) and antioxidant capacity. Chronic nocturnal intermittent hypoxia occurring in OSA leads to low grade systemic inflammation. Thus the oxidative stress, metabolic abnormalities and low grade inflammation seem to be the key factors initiating the various cardiovascular morbidity and mortality occurring in these patients. The key findings of their present study are that when patients of obstructive sleep apnea with metabolic syndrome are treated with CPAP therapy at prescribed pressures for duration of 6–8hrs it produced significant improvements in blood pressure and oxidant–antioxidant status.[23]

Fatty liver (NAFLD) and NASH

The range of liver disease in the United States is changing with our increasing rate of obesity and diabetes. Non

Alcoholic Steato–Hepatitis (NASH) is currently the second cause for liver transplantation and is projected to be the leading cause in 2016–2020. The spectrum of fatty liver ranges from NAFLD with normal enzymes to NASH as the leading cause of transaminasemia to NASH. NAFLD is now present in 17% to 33% of Americans.[24]

Important regulators for NAFLD/NASH link over nutrition and under activity, insulin resistance, and genetic factors. Oxidative stress, cytokines, lipotoxicity, and other proinflammatory mediators also play a role in transition of steatosis to NASH. The gold standard management of NASH is modest weight reduction, particularly correction of central obesity achieved by combining dietary measures with increased physical activity. Lifestyle adjustments and anti–obesity surgery, improves insulin resistance and reverses steatosis, hepatocellular injury, inflammation, and fibrosis. The same potential for unwinding fibrotic NASH is indicated by studies of the peroxisome proliferation activator receptor (PPAR) –agonist glitazones, but these agents may improve liver disease at the expense of worsening obesity.[25]

Antifibrotic therapy using farnesoid X receptor lignands (OCA) obeticholic acid clinic trials are ongoing and have received FDA break though status. OCA has significantly reduced serum alkaline phosphatase an important marker in Primary Biliary Cirrhosis.[26]

"NASH is a disease in search of a therapy that works. None

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[2]No informed consent was required as CPAP for sleep apnea, Vitamin E, Move Program, Topramax and Orlistat are all approved VAH medications and therapies.

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have been convincingly shown to be effective." Most of the current regimens have been tested in open label, uncontrolled trials that have been carried out over a relatively short period of time and most of these studies did not adhere to a strict histologic end point.[27]

NIR light activates ATP in the mitochondria; future therapy for NASH

Near infrared light (NIR) in form of LED belt (630–1000nm) and aerobic exercise was demonstrated to be effective in reducing excessive abdominal fat in twenty–six overweight healthy male students over 4weeks as compared to controls.[28] NIR light has been shown to activate ATP in the mitochondria with increased cytochrome C oxidase activity.[29] This activated ATP increases production of ROS and reactive nitrogen species (RNS) and possibly NO.[30]

A previous publication in Medical Hypotheses using DC EMF 0.5Tesla in "Mice and Men", was published by this author in obesity, fatty liver and NASH.[31] However in 2012, there was no home therapy for directed energy available. With the advent of NIR LED light therapy, this problem has now been alleviated.

The availability of NIR light belt has hampered its use in the USA and the VAH although a NIR Light helmet has been used in a clinical trial for Gulf War Syndrome and TBI at the Jamaica Plains VA by Margaret Naesar.[32]

Quietmind Foundation just published a research clinical trial using NIR light helmet in Alzheimer's dementia which is another area where the mitochondria are injured and respond to this therapy with improvement in cognition and executive functioning. Alzheimers dementia also involves decreased insulin sensitivity, obesity and sleep apnea.[33]

Conclusion

The evidence for mitochondrial dysfunction in aging, obesity, NASH/fatty liver has been discussed. The contribution of mitochondrial dysfunction and sleep apnea in obesity, metabolic syndrome, and NASH and neurodegenerative disorders is considerable. The one gene, one protein and one drug therapeutic approach is therefore doomed to failure in these complex diseases. Understanding the biophysical approaches of sleep medicine and the effects of light, especially NIR, temperature, along with diet, exercise, nutrition as well as photonics will be the solutions now for this obesity aging and liver fibrosis epidemic! Mitochondrial and metabolic bioenergetics as well as gene up and down regulation with these modalities has been demonstrated and the wide spread adoption should begin.

Photonic therapy which easily penetrates the entire human body was only limited to initially laser and now safer with home therapy using NIR LED light has opened a door to a whole new therapeutic paradigm!

Although the pilot clinical trial using sleep medicine along with exercise and diet (MOVE program) and antioxidants was small in numbers, the need for larger further clinical trials in obesity, and fatty liver/NASH is sorely needed!

As Andy Bassett MD, a pioneer in directed energy at Columbia University, made this prophetic statement in a 1992 article: "In the decade to come, it is safe to predict *directed energy* will assume a therapeutic importance equal to, or greater than, that of pharmacology and surgery today. With proper interdisciplinary effort, significant inroads can be made in controlling the ravages of cancer, some forms of heart disease, arthritis, hormonal disorders, obesity and neurological scourges such as Alzheimer's disease, spinal cord injury, and multiple sclerosis. This prediction is not pie in–the–sky." Andy Bassett may have envisioned a medical utopia decade's too soon using directed energy but the future demands of this world wide obesity, aging and neurodegeneration epidemic will outstrip medical resources if prompt action is not taken![34]

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None.

Conflicts of interest

The authors declared that there are no conflicts of interest.

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