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Diabetes and Organ Dysfunction in the Developing and Developed World

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Abstract- Induction of global organ disease has become important with the events related to diabetes in both the developed and developing world. Type 2 diabetes and peripheral organ disease are connected to Type 3 diabetes that involves the brain early in life associated with brain diseases (stroke, dementia, Alzheimer's disease).The incidence of diabetes has been predicted to increase to 21% by 2050. In various continents the rise in the global diabetes epidemic has been associated with diseases of various organ diseases related to obesity, diabetes and neurodegenerative diseases (Parkinson's disease and Alzheimer's disease). Nutritional therapy has become of central importance as early nutritional therapy may delay organ disease and aging.

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Diabetes and Organ Dysfunction in the Developing and Developed World

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Abstract- Induction of global organ disease has become important with the events related to diabetes in both the developed and developing world. Type 2 diabetes and peripheral organ disease are connected to Type 3 diabetes that involves the brain early in life associated with brain diseases (stroke, dementia, Alzheimer's disease).The incidence of diabetes has been predicted to increase to 21% by 2050. In various continents the rise in the global diabetes epidemic has been associated with diseases of various organ diseases related to obesity, diabetes and neurodegenerative diseases (Parkinson's disease and Alzheimer's disease). Nutritional therapy has become of central importance as early nutritional therapy may delay organ disease and aging. Environmental factors such as stress, diet and lifestyle are important to consider with the global increase in chronic diseases that alter neuroendocrine responses that cause appetite dysregulation that are closely linked to reduced lifespan relevant to pancreatic disease, NAFLD and neurodegeneration.

Keywords: global, diabetes, appetite, nafld, neurodege - neration, nutrition, obesity, metabolic syndrome, pancreatic disease.

I. Introduction

The projected health care costs by the year 2018 in the United States has been reported to be 344 billion dollars and account for 21% of total health care costs. Age stands as the major risk factor for organ disease and with the global aging population the increase in individuals with brain senescence may be associated with various organ diseases. Interests in the induction of organ disease has become important to disease manifestation and medical research has invested billions of dollars in the diagnosis of various diseases with novel tests that are able to identify the importance of an organ that has malfunctioned early (brain, liver or pancreas) that leads to chronic disease progression with metabolic abnormalities.

The global diabetes epidemic in the developing and developed world has attracted considerable interest with the increased incidence in the global stroke epidemic [1-5]. Interests in early brain senescence has increased and possibly connected to obesity, Type 2 diabetes and Type 3 diabetes [6,7]. Individuals with Type 2 and Type 3 diabetes are induced early in life with nuclear and subcellular changes involved with cell membrane alterations linked to disorders of lipid metabolism with changes in several plasma analytes such as glucose, cholesterol, calcium (cell levels) with lowzinc levels that lead to diseases of the liver, kidney, heart, thyroid, brain and pancreas (Figure 1).

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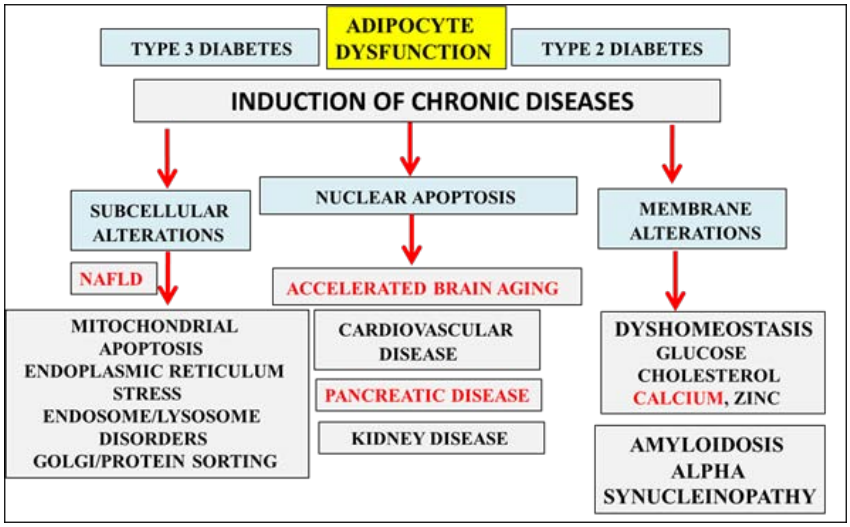

Figure 1 : The role of adipocyte dysfunction in the induction of chronic disease has been associated with subcellular and membrane alterations that involve nuclear apoptosis. Accelerated aging involves the diseases of the heart, brain, liver, kidney and thyroid and involve the dyshomeostasis of plasma glucose, cholesterol, calicium and zinc. Subcellular alterations in cells include mitophagy, endoplasmic reticulum stress, endosome/lysosome protein and lipid disorders and golgi associated protein disorders that may be associated with diabetes and Alzheimer'disease.

Induction of chronic diseases may be linked to adipocyte dysfunction [8,9] associated with the current global stroke epidemic [1,10] with multiple changes in brain function that effect an individuals cognition and behavior.Chronic diseases are associated with changes in the mitochondria (mitophagy), endoplasmic reticulum (ER)/golgi apparatus (ER stress/protein synthesis) and lysosomal disorders (lipid/protein metabolism). Unhealthy diets, environmental influences and lifestyle changes that lead to overnutrition with an excess of glucose, fats and proteins that enter the blood plasma from the gastrointestinal tract induce cell and nuclear alterations that lead to various subcellular abnormalities. Diseases such as gastroinstestinal disorders, cardiovascular disease, non alcoholic liver disease (NAFLD), thyroid, lung and diseases of the reproductive organs have increased in both the developing and developed world. Insulin resistance is possibly involved early in chronic disease progression and associated with inflammatory processes that alter nuclear, subcellular and cell membrane function (Figure 1) that leads to cell transformation without reversible changes with accelerated cell apoptosis.

a) Accelerated aging is associated with pancreatic dysfunction and chronic disease progression

The pancreas has been implicated in chronic disease progression and the pathogenesis of major organ diseases withincreased death rates in both the developing and developed world. Pancreatic disease is associated with the release of low levels of insulin as a result of pancreatic disturbances [7] or the release of insulin to peripheral and brain cells that do not respond to allow glucose to move into cells with overt hyperglycemia. The intimate association of the pancreas with various chronic diseases indicates a role for association with the brain and liver (Figure 2) to play an important part in the complications of the variousperipheral chronic diseases associated with dyslipidemia, neuroendocrine disease (stroke) and the metabolic syndrome.

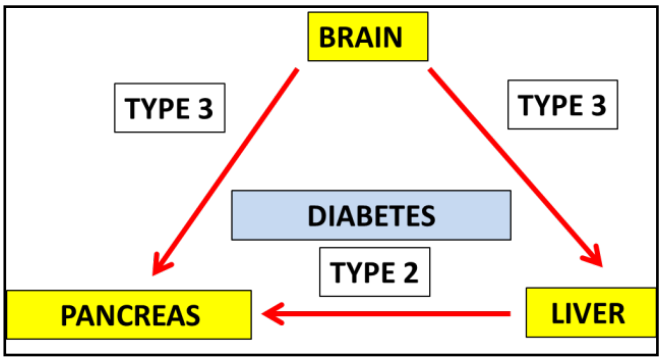

Figure 2 : In the current global epidemic individuals with insulin resistance involve early brain senescence (Type 3 diabetes) with NAFLD (Type 2 diabetes) and pancreatic dysfunction. Accelerated aging with pancreatic disease are linked to high fat diet with elevated palmitic acid levels that induce NAFLD, pancreatic disease and Alzheimer's disease.

In the global diabetic epidemic hyperglycemia and hyperlipidemia with pancreatic dysfunction may involve NAFLD linked to Type 2 diabetes [11-12] and Type 3 diabetes (Figure 2). Alzheimer disease (AD) is now referred to as Type 3 diabetes [6,7]with early brain senescence and insulin resistancethat involves other neurodegenerative diseases such as Parkinson's disease, Huntington's disease and Multiple Sclerosis [7]. Furthermorethe prevalence of Type 2 diabetes and AD increase with age and in the pancreas the islet of Langerhans in type 2 diabetes is characterized by β-cell

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loss and islet amyloid deposition that are associated with brain dysfunction in Alzheimer disease characterized by loss of neurons with brain amyloid deposits [13].

In Western countries the increased intake of fats, sugars and proteins may induce early liver disease with NAFLD with hyperglycemic/hyperlipidemia closely involved in pancreatic dysfunction in these individuals. Diets that are rich in fat (palmitic acid) induce NAFLD that release cytokines that are involved with pancreatic disease with increased palmitic acid in cells that may induce beta cell apoptosis in the pancreas [14-17].Calorie sensitive genes in the liver are sensitive to nutritional regulation [4,5] with downregulation of these nuclear receptor genes and proteins involved in early hepatocyte senescence [4,11]. NAFLD has increased in both the developed and developing world and induction of NAFLD may involve endrocine disruptors (environmental exposure) and xenobiotics that promote insulin resistance and pancreatic disturbances in these communities [4,18]. The complex interactions of Western diets, environmental and genetic factors may induce early liver and brain senescence that are linked to neuroendocrine disease that promote insulin resistance and pancreatic disease (Figure 2) with the development of various organ disease in global communities. Specific nutrients such as leucine and pyruvic acid are essential for insulin secretions [19-22] with phosphatidylinositol ingestion important to pancreatic function and survival.Cellular calcium channel dyshomeostasis in diabetes may be relevant to pyruvic acid levels with leucine and calcium important to energy metabolism in muscle and adipocytes [23-26].

b) Overnutrition leads to accelerated adipocyte senescence with diabetes and organ disease

Individuals with obesitydevelop circadian disorders linked to intracellular calcium suprachiasmatic nucleus fluctuations [27] and appetite dysregulation that are connected to diabetesand various organ diseases [10, 28].Adipocyte dysfunction has become of central importance to the development and treatment of diabetes (Figure 1) withabnormal transcriptional regulation of adipogenesis linked to several organ diseases in the Western world [28].Overnutrition and appetite dysregulation are closely linked to loss of adipocyte function with early adipocyte senescence linked to the severity of various metabolic events in diabetes associated with the cellular apoptosis in these organs.

Adiposity is the body fat tissue content and increases in adiposity is measured by body mass index (BMI). Obese individuals are defined as having a BMI of >30 (BMI=weight in kg/[height in m]2 whereas overweight is defined as having a BMI from 25-30 and ideal lean individuals to have a BM of 25 kg/m2. Visceral fat is more metabolically active than peripheral fat and is associated with type 2 diabetes, dyslipidemia, high blood pressure, and increased risk for atherosclerotic disease [29,30]. The waist-to-hip ratio helps to identify patients with excess visceral adiposity. Women with a waist-to-hip ratio > 0.8 and men with a ratio > 1.0 are considered to have excess central adiposity that confers risk for developing the metabolic syndrome. Morbid obesity classification is BMI of > 35 kg/m2 and severe obesity >40 kg/m2. In the United States children and young adults affected by type 2 diabetes has risen and childhood obesity [28] is now considered a major predictor of adult obesity and Type 2 diabetes.

In the current obesity and diabetes epidemic the anti-aging gene sirtuin 1 (Sirt1) is 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 various diseases [31-33]. Interests in Sirt 1 have increased since it may override the effects of genes and their cellular expression with importance to obesity, diabetes and accelerated neurodegenerative disease [31-33]. Sirt 1 is involved in gluconeogenesis in the liver, fat mobilization from white adipose tissue, cholesterol metabolism, mitochondrial biogenesis, adipocyte senescence and energy metabolism [1].

Adiposity is involved with Sirt1 dysregulation with adipocyte size negatively correlated with adiponectin levels and high density lipoprotein levels (HDL) levels. Adiponectin is mainly secreted from the adipose tissue into the bloodstream and inversely correlated with body fat in adults. Adiponectin like leptin is involved in appetite regulation with effects in the brain regulated by dietary fat intake [34]. Adiponectin is involved in the metabolic syndrome, NAFLD with excess calorie consumption involved with adipose tissue Sirt 1 downregulation. Adipose tissueSirt 1 effects on the release of adipokines (adiponectin, leptin) and cytokines (tumor necrosis factor alpha, interleukin-6 and C-reactive protein levels, Ang II) [1](Figure 1) are implicated in abnormal cellular processes involved in the development of early brain senescence (Type 3 diabetes) associated with cardiovascular diseaseand pancreatic disease.

c) LPS and Obesity linked Type 2 Diabetes are associated with pancreatic disease and neurodegeneration

Atherogenic diets that contain high fat contents have been discouraged in various communities to prevent obesity linked diabetes with the role of these fat diets relevant to the transport of gut microbiotica that increase plasma endotoxins such as lipopolysaccarides (LPS) in the blood plasma. LPS has been associated with metabolic diseases and diabetes [35]and have been shown to induce acute pancreatitis [36]. LPS are endotoxins and essential components of the outer membrane of all Gram-negative bacteria and consist of

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covalently linked segments, surface carbohydrate polymer, core oligosaccharide and acylated glycolipid (LIPID A) and can bind to cell membranes to alter membrane interactions [37,38].After absorption of fat chylomicrons that are produced contain the LPS binding protein (LBP) that bind LPS and interactions of LPS to apo B containing cholesterol-rich lipoproteins (chylomicrons/very low density lipoproteins) clearly implicate the role of dietary fat and LPS in the induction of pancreatic disease (Figure 3) and LPS-inflammatory processes associated with neurodegenerative diseases [39].

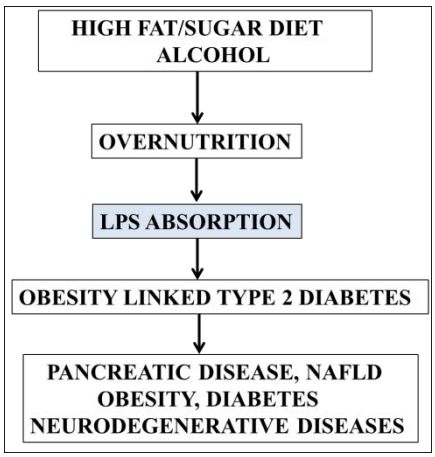

Figure 3 : Induction of pancreatic disease, NAFLD and neurodegenerative implicate LPS, dietary fat and alcohol consumption as factors involved in systemic inflammation. LPS alter hepatic lipid metabolism and adipocyte function with an increase hepatic cytokines and acute phase reactants (APP) that lead to pancreatic disease and neurodegeneration.

The role in LPS in lipoprotein interactions involve apolipoprotein E [37] and binding to lipoproteins prevent inflammatory processes associated with LPS.LPS has been shown to effect cholesterol metabolism by the modulation of the Sirt 1 regulationonliver X Receptors (LXR)and ATP-binding cassette transporter 1 (ABCA1) interactions [33]. In rodents LPS transport across the intestine has been shown to be increased by dietary fat and monitoring of dietary fat intake to reduce LPS induction of metabolic diseases and neurodegenerative diseases (Figure 3) has been indicated. In obese mice altered inflammatory responses were found with LPS administration when compared with control mice with intestinal microbiota linked to pancreatic disease, NAFLD (Figure 3) linked with connections to the systemic inflammation and abnormal lipoprotein production [37]. Furthermore, LPS alter hepatic lipid metabolism with anincrease in hepatic cytokines and APPs in plasma that are involved in pancreatic disease [35-38]. In adipose tissue LPS has been shown to effect adipocyte function with effects on systemic inflammation[39] and administration of adiponectin has been shown to reverse LPS induced inflammatory processes [40-42].

d) Diagnosis tests and relevance to diabetes and global organ diseases

In the obesity linked to diabetes epidemic various plasma tests have been conducted to diagnose various organ diseases induced by obesity. Measurements of glucose, insulin, cholesterol and triglyceride levels allow rapid diagnosis for insulin resistance associated with diseases of the liver, pancreas, heart and liver. Diagnosis of organ diseases by other plasma analysis (Figure 4) involve measurements of electrolytes (sodium, potassium, calcium) for kidney function tests, liver enzymes for liver function, hormones (neuroendocrine disease) and immunoglobulins (immune dysfunction).

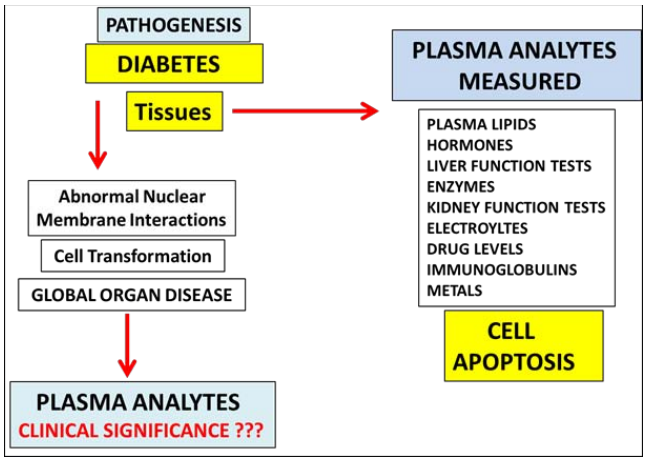

Figure 4 : Diagnostic tests that involve the assessment of early organ disease has become of major importance in global communities. Dyslipidemia, hyperglycemic and calcium and zinc dyshomeostasis indicate cell dysfunction but early events in cell transformation with the loss of rapid amyloid beta clearance with subcellular alterations may have been induced. Genomic tests for nuclear receptors such as Sirt 1 and transcription factors such as p53/microRNA may be important. Diagnositic tests that involve plasma analysis of APP, cytokines, adiponectin, apelin and LPS may be of significance to the detection of early cellular disease.

In the past 10 years links between obesity and Alzheimer's disease have indicated accelerated brain aging is associated with NAFLD and the global stroke epidemic [1]. Adipocyte dysfunction and its association with pancreatic disease has become of major concern with links between pancreatic cancer and diabetes [43,44]. Fat intake should be reduced in global communities with active lifestyles to reduce pancreatic fat to stabilize pancreatic beta-cell function [45,46]. LPS associated with adipocyte dysfunction also affect acinar pancreatic cells with the induction of acute pancreatitis and diabetes [36,47]. LPS in adipocyteshave shown to

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reduce adiponectin and apelin levelswith relevance to pancreatic function [48,49]. Tests for plasma adiponectin (adipose tissue) should be routinely performed to determine the relevance of low adiponectin levels [50] and abnormal apelin levels [51] on plasma insulin levels with relevance to pancreatic dysfunction.

In the current obesity epidemic induction of global diabetes involve abnormal nuclear and mitochondria interactions in various cells that may lead to early cell transformation with abnormal adipogenesis connected to NAFLD [11].Early cell transformation may involve incorrect interpretation of the significance of normal plasma analyte levels (cholesterol, glucose, calcium) in the presence of nuclear changes (Sirt 1 downregulation) that involve abnormalities in various cells such as the brain, liver and pancreas. Tests that involve the assessment of APP and cytokines [38] have become important as early events in cell transformation and apoptosis. The significance of the early interventions allow the maintenance of the peripheral sink amyloid beta hypothesis [7,10] that is now closely associated with adipose tissue transformation and liver disease [1,33]. Genetic cell tests that involve genomic markers [33] are required such as gene expression tests for Sirt 1, peroxisome proliferator-activated receptors, microRNA and transcription factors (p53, 5′-monophosphate-activated protein kinase,pregnane X receptor)may be important to determine the early reversal of the obese condition linked to the induction of diabetes.

Monitoring of dietary fat and alcohol intake to reduce LPS absorption with relevance to metabolic diseases and neurodegenerative diseases has become important with LPS linked to Sirt 1 dysregulation and mitochondrial apoptosis. LPS and its effects on mammalian cell transformation (nuclear, mitochondria, membrane) do not allow rapid reversal of chronic disease progression with internal cell dysregulation. Tests for plasma LPS determination may be important with early diagnosis linked to metabolic disease and neurodegeneration without misinterpretation for clinical diagnosis. Apoptotic cells may release cell analytes for clinical diagnosis and reversal of degenerative disease may not be prevented without accurate plasma LPS level determination. Early routine testing for xenobiotics such as bisphenol A and phthalates [18] may allow rapid reversal of pancreatic disease relevant to obesity and induction of diabetes. The synergistic effects of LPS and xenobiotics within cells may transform the cell (lack of peripheral amyloid beta clearance) and the routine plasma measurements may not allow early assessment of functional status with poor interpretations in relation to multiple organ disease associated with diabetes.

II. Conclusion

In the current global diabetes epidemic early cell transformation is possibly associated with accelerated aging and pancreatic disease induced by a high fat diet/alcohol diet that increases plasma LPS levels with reduced xenobiotic clearance. Accelerated aging with downregulation of the nuclear cell receptors such as anti-aging Sirt 1 is linked to insulin resistance (pancreatic disease)with the development of various organ diseases such as NAFLD, brain diseases (Type 3 diabetes), cardiovascular disease and kidney disease. Measurements from routine plasma tests (glucose/cholesterol/calcium) for clinical diagnosis of diseases do not test for functional peripheral sink amyloid beta clearance that is linked to maintenance of the cellular anti-aging processes. Genomic tests such as Sirt 1 expression and p53 analysis early in life may allow maintenance of adipocyte/liver function without irreversible adipocyte transformation that lead to elevated inflammation markers (APP, cytokines) with pancreatic disease and NAFLD. The recent failure of the anti-obese drugs to prevent adipocyte dysfunction now require urgent nutritional interventions with consumption of essential nutrients such as leucine, pyruvic acid and phosphatidylinositol that maintain organ function. Excessive metabolism of these nutrients in global populations inactivate Sirt 1to delay the clearance of LPS/xenobiotics that are connected to pancreatic disease, NAFLD and Alzheimer's disease.

III. Acknowledgements

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References Références Referencias

1. Martins I.J., (2014):The Global Obesity Epidemic is Related to Stroke, Dementia and Alzheimer's disease. JSM Alzheimer's Dis Related Dementia; 1(2): 1010.
2. Sander D, Sander K, Poppert H., (2008): Stroke in type 2 diabetes. Br J Diabetes Vasc Dis; 8: 222–229.
3. Martins I.J., Lim W.L.F., Wilson A., Laws S., Martins R.N., (2013): The acceleration of aging and Alzheimer's disease through the biological mechanisms behind obesity and type II diabetes. Health; 5:913-920.
4. Martins I.J., (2013): Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries. J Mol Genet Med; S1: 001.
5. Martins I.J., Wilson A.C., Lim W.L.F., Laws S.M., Laws S.M., et al, (2012): Sirtuin 1 mediates the obesity induced risk of common degenerative diseases: Alzheimer's disease, coronary artery disease and type 2 diabetes. Health; 4: 1448-1456.
6. De la Monte S.M. and Wands J.R., (2008):Alzheimer's disease is Type 3 diabetes-

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Evidence Reviewed. Journal of Diabetes and Science Technology;2(5):1101-1113.
7. Martins I.J., (2014): 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" Vol 3. edited by Prof. Atta-ur-Rahman.
8. Yoshino J, and Klein S., (2013): A novel link between circadian clocks and adipose tissue energy metabolism. Diabetes; 62(7):2175-7.
9. Martins IJ, Creegan R, Lim W.L.F., Martins R.N., (2013) Molecular insights into appetite control and neuroendocrine disease as risk factors for chronic diseases in Western countries. Special Issue. Molecular Mechanisms Involved in Inflammation and Insulin Resistance in Chronic Diseases and Possible Interventions. Open J Endocr Metab Dis; 3:11-33.
10. Martins I.J., Creegan R., (2014): Links between Insulin Resistance, Lipoprotein Metabolism and Amyloidosis in Alzheimer's Disease. Health; 6:1549-1579.
11. Martins I.J., (2014): Induction of NAFLD with Increased Risk of Obesity and Chronic Diseases in Developed Countries. Open J Endocr Metab Dis; 4:90-110.
12. Sander D., Sander K. and Poppert H., (2008): Stroke in type 2 diabetes. Br J Diabetes Vasc Dis; 8: 222–229.
13. Janson J, Laedtke T, Parisi J.E., O'Brien P, Petersen R.C. and Butler P.C., (2004): Increased risk of type 2 diabetes in Alzheimer disease. Diabetes; 53(2):474-81.
14. Liang H., Zhong Y., Zhou S. and Li Q.Q., (2011):Palmitic acid-induced apoptosis in pancreatic β-cells is increased by liver X receptor agonist and attenuated by eicosapentaenoate. In Vivo;25(5):711-8.
15. Maedler K, Spinas G.A., Dyntar D., Moritz W., Kaiser N., et al., (2001): Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function. Diabetes;50(1):69-76
16. Wang C., Guan Y., and Yang J., (2010): Cytokines in the Progression of Pancreatic β-Cell Dysfunction International Journal of Endocrinology;Volume 2010: 1-10.
17. Feurino L.W., Fisher W.E., Bharadwaj U., Yao Q., Chen C., et al., (2006): Current update of cytokines in pancreatic cancer: pathogenic mechanisms, clinical indication, and therapeutic values. Cancer Invest;24(7):696_703.
18. Ropero A.B., Alonso-Magdalena P., García-García E., Ripoll C., Fuentes E., et al., (2008): Bisphenol-A disruption of the endocrine pancreas and blood glucose homeostasis. Int J Androl;31(2):194-200.
19. Yang J., Chi Y., Burkhardt B.R., Guan Y., Wolf B.A., (2010): Leucine metabolism in regulation of insulin secretion from pancreatic beta cells. Nutr Rev;68(5):270-9.
20. Brouwer A.E., Carroll P.B., and Atwater I.J., (1991): Effects of leucine on insulin secretion and beta cell membrane potential in mouse islets of Langerhans. Pancreas; 6(2):221-8.
21. Zawalich W.S. and Zawalich K.C., (1997):Influence of pyruvic acid methyl ester on rat pancreatic islets, Effects on insulin secretion, phosphoinositide hydrolysis, and sensitization of the beta cell.J. Biol. Chem;272(6):3527-31.
22. MacDonald M.J., (1995): Feasibility of a mitochondrial pyruvate malate shuttle in pancreatic islets. Further implication of cytosolic NADPH in insulin secretion. J Biol. Chem;270(34):20051-8.
23. Bakowski D. and Parekh A.B., (2007):Regulation of store-operated calcium channels by the intermediary metabolite pyruvic acid. Curr Biol;17(12):1076-81.
24. Sun X. and Zemel M.B., (2007): Leucine and calcium regulate fat metabolism and energy partitioning in murine adipocytes and muscle cells. Lipids;42(4):297-305.
25. Dunn K.M and Nelson M.T., (2010): Calcium and diabetic vascular dysfunction. Focus on "Elevated Ca2+ sparklet activity during acute hyperglycemia and diabetes in cerebral arterial smooth muscle cells. Am J Physiol Cell Physiol; 298: C203–C205.
26. Parekh A.B., (2000):Calcium signaling and acute pancreatitis: specific response to a promiscuous messenger. Proc Natl Acad Sci U S A;97(24):12933-4.
27. Whalley K., (2011): Circadian rhythm: Calcium sets the tempo. Nature Reviews Neuroscience; 12:434-435.
28. Martins I.J., (2013): Appetite dysregulation and obesity in Western Countries. Ebook project. Editor. Emma Jones. Acquisition Editor LAP LAMBERT Academic Publishing is a trademark of: AV Akademikerverlag GmbH & Co. KG.
29. C.J. Lavie, M.R.Mehra and R.V.Milani., "Obesity and heart failure prognosis: paradox or reverse epidemiology?" European Heart Journal, (2005) Vol. 26, 2005, pp. 5–7
30. B. Mathew., "Obesity: Effects on Cardiovascular Disease and its Diagnosis," Journal American Board Family Medicine, Vol.21, 2008, pp.562– 8.
31. L.Guarente., "Sirtuins in aging and disease," Cold Spring Harbour Symposium Quantitative Biology, Vol.72, 2007, pp. 483-8.
32. M.K.Hansen and T.M. Connolly, "Nuclear receptors as drug targets in obesity, dyslipidemia and atherosclerosis," Current Opinion Investigational Drugs, Vol 9, No.3, 2008, pp. 247-55.

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33. Martins I.J., (2015): Unhealthy Nutrigenomic Diets Accelerate NAFLD and Adiposity in Global communities. J Mol. Genet. Med;(In Press) ID:JMGM-15-106R1.
34. Bullen JW, Bluher S, Kelesidis T, Mantzoros CS. Regulation of adiponectin and its receptors in response to development of diet-induced obesity in mice. Am J Physiol Endocrinol Metab. 2007, 292:E1079-86.
35. Al-Attas O.S., Al-Daghri N.M., Al-Rubeaan K., da Silva N.F, Sabico S.L., et al., (2009): Changes in endotoxin levels in T2DM subjects on anti-diabetic therapies. Cardiovascular Diabetology; 8:1-10.
36. Vaccaro M.I., Calvo E.L., Suburo A.M., Sordelli D.O., Lanosa G., et al., (2000) Lipopolysaccharide directly affects pancreatic acinar cells: implications on acute pancreatitis pathophysiology. Dig Dis Sci; 45(5):915-26.
37. Martins I.J., (2015): LPS regulates apolipoprotein E and Aβ interactions with effects on acute phase proteins and amyloidosis. Advances in Aging Research; (In Press)ID: 2420153
38. Martins I.J., Gupta V., Wilson A.C., Fuller S.J. and Martins R.N., (2014): Interactions Between Apo E and Amyloid Beta and their Relationship to Nutriproteomics and Neurodegeneration. Current Proteomics; 11(3): 171-183.
39. Murray C.L., Skelly D.T. and Cunningham C., (2011): Exacerbation of CNS inflammation and neurodegeneration by systemic LPS treatment is independent of circulating IL-1β and IL-6. J Neuroinflammation;17 (8):50.
40. Lee Y.H,, Magkos F., Mantzoros C.S., Kang E.S., (2011): Effects of leptin and adiponectin on pancreatic β-cell function. Metabolism;60(12):1664-72.
41. Wang L., Li L., Ran X., Long M., Zhang M., et al., (2013): Lipopolysaccharides reduce adipogenesis in 3T3-L1 adipocytes through activation of NF-κB pathway and downregulation of AMPK expression. Cardiovasc Toxicol;13(4):338-46.
42. Vatier C., Kadiri S., Muscat A., Chapron C., Capeau J., et al.,(2012):Visceral and subcutaneous adipose tissue from lean women respond differently to lipopolysaccharide-induced alteration of inflammation and glyceroneogenesis Nutrition and Diabetes; 2: e51
43. Wang F., Herrington M., Larsson J. and Permert J., (2003): The relationship between diabetes and pancreatic cancer. Molecular Cancer; 2:4
44. Morrison M., (2012) Pancreatic cancer and diabetes. Adv Exp Med Biol; 771:229-39.
45. Heni M., Machann J., Staiger H., Schwenzer N.F., Peter A., et al., (2010):Pancreatic fat is negatively associated with insulin secretion in individuals with impaired fasting glucose and/or impaired glucose tolerance: a nuclear magnetic resonance study. Diabetes Metab Res Rev;26(3):200-5
46. Pinnick KE1, Collins SC, Londos C, Gauguier D, Clark A, et al.m (2008): Pancreatic ectopic fat is characterized by adipocyte infiltration and altered lipid composition. Obesity (Silver Spring);16(3):522-30.
47. Ding S.P. , Li J.C. and Jin C., (2003): A mouse model of severe acute pancreatitis induced with caerulein and lipopolysaccharide. World J Gastroenterol; 9(3):584-9.
48. Taira R., Yamaguchi S., Shimizu K., Nakamura, K., Ayabe, T. and Taira., T (2015): Bacterial cell wall components regulate adipokine secretion from visceral adipocytes. J. Clinical Biochem Nutr; 1-6.
49. Obara, S., Akifusa S., Ariyoshi W., Okinaga T., Usui M., et al. (2014): Pyroglutamated Apelin-13 Inhibits Lipopolysaccharide-Induced Production of Pro-Inflammatory Cytokines in Murine Macrophage J774.1 Cells. Modern Research in Inflammation; 3:59-66.
50. Okamoto M., Ohara-Imaizumi M., Kubota N., Hashimoto S., Eto K., et al., (2008):Adiponectin induces insulin secretion in vitro and in vivo at a low glucose concentration. Diabetologia; 51(5):827-35.
51. Martins I.J., (2015):Nutritional diets accelerate amyloid beta metabolism and prevent the induction of chronic diseases and Alzheimer's disease. Photon;(In Press) ID (B-4646) Chapter.

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