We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Insulin Therapy and Autoimmune Disease with Relevance to Non Alchoholic Fatty Liver Disease

Ian James Martins

Abstract

The diabetes epidemic is now expected by the year 2050 to become a global pandemic with approx. 592 million affected in both the developed and developing world. The treatment of diabetes by insulin therapy has been the focus for many diabetics with the improvement and prevention of various diseases such as cardiovascular disease, kidney disease and neurodegeneration. The global nonalcoholic fatty liver disease (NAFLD) epidemic has now become of major concern to diabetes with critical interest in insulin therapy to reverse and stabilize autoimmune disease with relevance to NAFLD and the diabetes pandemic. Dietary components that activate anti-aging genes improve insulin therapy and should be assessed with specific amounts and doses of Indian spices consumed that may not interfere with insulin therapy and induce mitophagy in various diseases. Food quality, appetite control and core body temperature are critical to maintain insulin therapy with unhealthy diets linked to NAFLD and diabetes. Genomic medicine and dietary activators are essential to maintain insulin therapy and prevent toxic immune reactions with relevance to NAFLD and diabetes management.

Keywords: insulin therapy, genomic, autoimmune disease, diabetes, global, mitophagy, curcumin, cinnamon

1. Introduction

The diabetes epidemic is expected to affect approx. 592 people by the year 2035. The urgency to prevent the largest diabetes epidemic in history has now assessed multiple risk factors involved with induction of Type 3 diabetes connected to various chronic diseases. Insulin resistance and brain aging now indicate neuron vulnerability to mitophagy associated with the diabetes pandemic expected in 2050 [1, 2]. Diabetes and its connections autoimmunity [3] have become important to mitophagy, metabolic disease with relevance to the nonalcoholic fatty liver disease (NAFLD) epidemic.

An association between various genes and the immune system [4, 5] has been proposed to be involved with the regulation of life-span in various species. Immune gene activation has been associated with brain aging [6] with the critical involvement of inflammation in the development of neuro-degeneration. Autoimmune disease, drugs and immunosenescence are related to the chronic disease epidemic with uncontrolled release of inflammatory cytokines such as tumor necrosis factor

α and interleukin-6 [7, 8]. Major interests to determine human longevity require the assessment of nutrition and diet with relevance to the control of inflammatory cytokines that are associated with age-related changes in the immune system and the induction of diabetes, NAFLD and neurodegeneration.

Appetite control with relevance to immuno-metabolism has become critical to the treatment of NAFLD. The major defect in global chronic disease is autoimmune disease with defective adipose tissue and liver interaction involved with the release of inflammatory cytokines and adipo-cytokines relevant to toxic immune reactions that involve the pancreas, brain, heart, thyroid, kidneys and reproductive organs. Appetite control and autoimmune disease are connected to anti-aging genes with relevance to irreversible programmed cell death in various cells and tissues. Immune competence changes over a human's life span with a process known as immunosenescence [9, 10]. In man multiple theories of aging have been proposed with the immune theory of aging that involve abnormal inflammatory responses that contribute to the induction of chronic diseases [11].

In various communities in the developing and developed world the understanding of the ingestion of a healthy diet and hepatic fat metabolism has become of critical importance to the treatment diabetes that is now linked to various organ diseases. In the world [12] transition to healthy diets has become urgent to prevent insulin resistance, autoimmune disease and NAFLD. The liver is the major organ for the metabolism of dietary fat and after consumption of a meal in healthy individuals the fat is rapidly metabolized by the mitochondria in the liver.

A diet rich in fat and sugar that lead to fat deposition in the liver can be referred to as liver steatosis. The defect in the liver fatty acid metabolism is possibly related to mitochondrial dysfunction and a careful calorie controlled diet may reverse liver steatosis. As mitochondrial apoptosis occurs steatohepatitis may be associated with liver inflammation. Steatohepatitis may induce NAFLD that may then progress to severe inflammation and liver cirrhosis. In obesity and diabetes the metabolism of a fat meal by the liver is defective with associated hyperglycemia and hyperinsulinemia. Food restriction [13] and appetite control are vital to the treatment of NAFLD with hepatic fat metabolism connected to insulin resistance, autoimmune disease and mitophagy [14].

2. Diabetes and pathogenetic loop complications

Insulin treatment in diabetes has provided information that approx. 30% of patients are involved with insulin treatment or plan to start insulin with insulin regimens [15] associated with various insulin doses and failure of oral anti-diabetic medications. Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance, and impairment of insulin secretion [16]. The impairment of insulin secretion is related to hyperglycemia, high serum low-density lipoprotein cholesterol concentrations and low serum high-density lipoprotein cholesterol concentrations with relevance to cardiovascular disease [17]. The relative importance of impaired insulin release and insulin resistance in the pathogenesis of Type 2 diabetes has been evaluated and may be connected to NAFLD. NAFLD may be connected to autoimmune disease and mitophagy associated with impairment in insulin secretion and cardiovascular disease [18–20]. In Type 1 diabetes the use of insulin therapy has been assessed with the critical importance to reduce hyperglycemia, severe hypoglycemia and the development of long-term complications [21–23]. Insulin therapy should be carefully evaluated in Type 1 and Type 2 diabetes with relevance to reduction in plasma glucose levels [24]. Interference in hepatic glucose production [24, 25] or interference with increased glucose uptake by the liver may be sensitive to repression

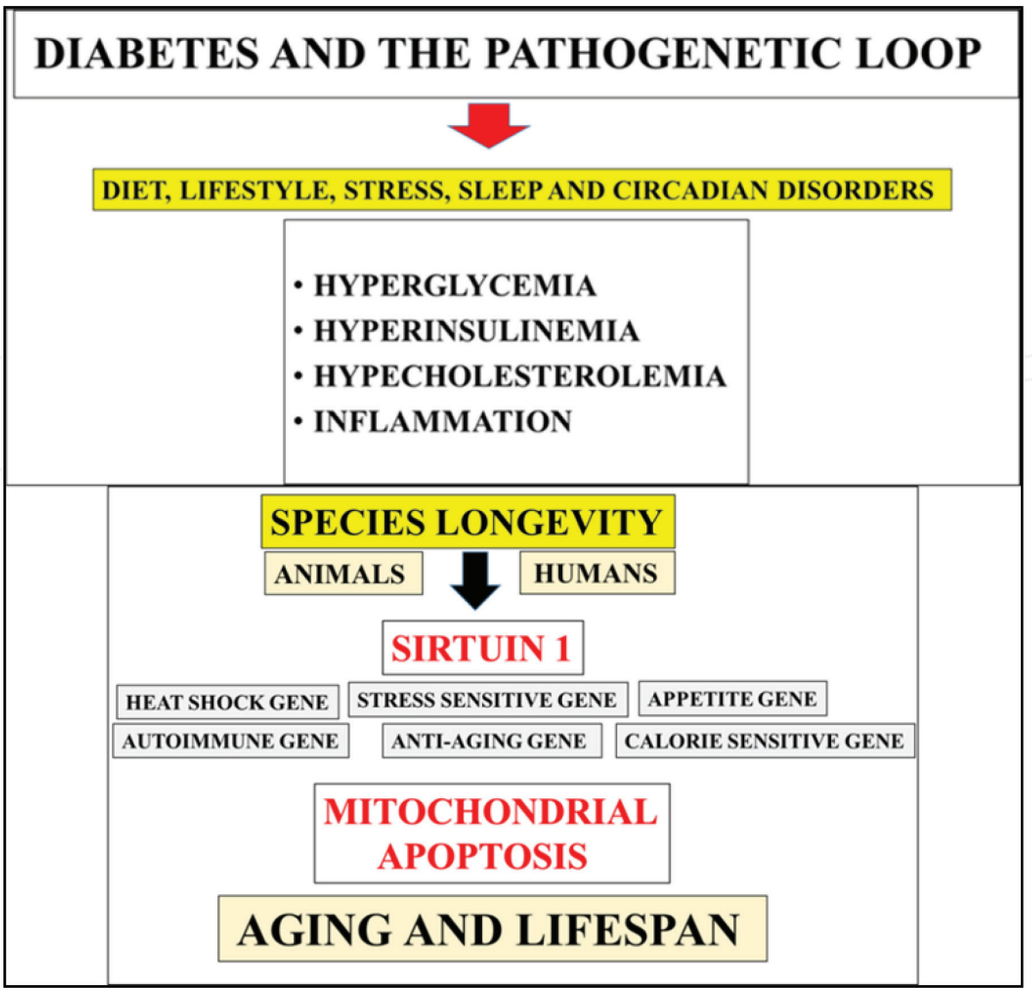


Figure 1.
Diabetes and the pathogenetic loop associated with inflammation, age related diseases and neurodegeneration involve inactivation of the anti-aging gene Sirtuin 1 (Sirt 1) associated with mitochondrial apoptosis in various species and man.

of glucose related genes associated with the induction of glucolipotoxicity, NAFLD and insulin resistance. Exercise and insulin therapy [26] may reduce glucolipotoxicity and NAFLD but with the aging process the pathogenetic loop [27–32] that involve hyperglycemia, hypercholesterolemia and hyperinsulinemia may be associated with autoimmune disease, mitophagy and programmed cell death of various cells and tissues [18–20]. The role of diet, lifestyle, stress, sleep and circadian disorders [33] may inactivate the anti-aging gene Sirtuin 1 (Sirt 1) with relevance to insulin therapy and induction of NAFLD associated with the pathogenetic loop (**Figure 1**) and uncontrolled inflammation of cells and tissues [18–20].

3. Anti-aging genes, mitochondrial apoptosis and programmed cell death

Insulin resistance is involved early in alterations of nuclear, subcellular and cell membrane function that lead to cell transformation without reversible changes with accelerated cell apoptosis [34]. In 2050 the predicted global diabetes pandemic [1, 2] has accelerated scientific research to determine the identification of novel genomic pathways such as the anti-aging gene Sirt 1 that may provide new knowledge with relevance to accelerated cell apoptosis and inactivated insulin therapy. In Type 2 diabetes and Type 1 diabetes various genes and genetic loci have been

reported to be involved in the development of diabetes [35]. Novel genes [36] have been identified that are involved with autoimmune disease [18, 19, 36, 37] and glucolipotoxicity with irreversible immune complications relevant to NAFLD, diabetes [3] and the pathogenetic loop. The discovery of the anti-aging gene Sirt 1 now has become important to the treatment of diabetes with insulin therapy in Type 1 and Type 2 diabetes connected to Sirt 1 activation in the pancreas with relevance to insulin release [38] with Sirt 1 associated with mitochondrial biogenesis (**Figure 1**) and cell survival in various tissues [38, 39]. The inactivation of Sirt 1 [39] in humans leads to the pathogenetic loop in diabetes and implicates nutritional and environmental factors in the induction of programmed cell death.

Sirt 1 is a nicotinamide adenine dinucleotide (NAD+) dependent class III histone deacetylase (HDAC) that targets transcription factors such as p 53 to adapt gene expression to metabolic activity and the deacetylation of nuclear receptors indicate its critical involvement in insulin resistance and autoimmune disease [18]. In situ hybridization analysis has localized the human Sirt 1 gene to chromosome 10q21.3 [18]. Calorie restriction is essential for Sirt 1 transcriptional regulation with other factors such as diet and lifestyle critical for the prevention of insulin resistance and NAFLD. Sirt 1 is an acute phase protein involved with neuron proliferation [18] and its regulation of the suprachiasmatic nucleus is involved with control of the circadian rhythm [18]. The circadian rhythm and immune system are closely connected to the immune response. Nutritional interventions that are controlled by the consumption of a low calorie diet indicate the maintenance of connections between Sirt 1 and other anti-aging genes such as Klotho, p66shc (longevity protein) and FOXO1/FOXO3a that are connected to programmed cell death [36]. Sirt 1 and transcriptional regulation of anti-aging genes are critical to mitophagy (**Figure 1**) and neurodegenerative disease with accelerated brain aging connected to NAFLD and diabetes [19, 36].

4. Insulin therapy and Indian spices with relevance to NAFLD and diabetes

The connections between NAFLD and diabetes have become of central importance to the expected diabetes pandemic by the year 2050 [1, 2]. NAFLD in diabetic individuals may completely inactivate insulin therapy with defective insulin dose regimens and failure of oral anti-diabetic medications. The defect in the liver fatty acid metabolism is possibly related to mitochondrial dysfunction associated with severe liver inflammation and steatohepatitis that may induce NAFLD that may then progress to severe inflammation (NASH) and liver cirrhosis. Insulin therapy has been used to improve liver function but with NAFLD, high dose insulin therapy may be unsuccessful with liver inflammation [40–42] associated with uncontrolled hyperglycemia and mitochondrial apoptosis (**Figure 2**). Insulin therapy with insulin dose and oral anti-diabetic medications should be re-evaluated to improve hepatocyte mitochondrial biogenesis with relevance to reversal of liver disease connected to hyperglycemia and NAFLD in various Type 1, Type 2 and Type 3 [35, 39] diabetics.

The connections between Sirt 1 and insulin resistance have accelerated in recent years with Sirt 1 as a calorie sensitive gene is now implicated in insulin resistance and to the important to glucose dependent insulin secretion with protection of pancreatic β-cell mass [43–46]. Sirt 1 may be involved in silencing insulin resistance by regulation of specific proteins involved in insulin action [47]. Anti-inflammatory actions in adipocytes involve Sirt 1 repression and inflammation [48, 49] associated with the adipose-liver defect [49, 50] and the induction of NAFLD. Sirt 1

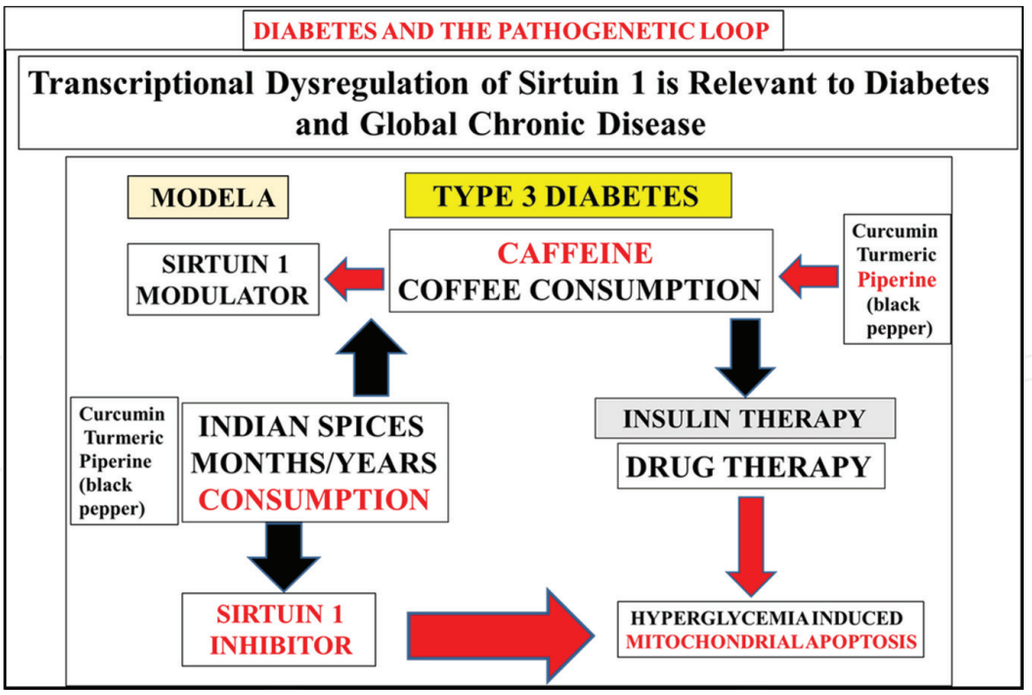


Figure 2.
Indian spices have become important as a diabetes technology and its use in diabetes has become of concern. Indian spices such as curcumin and cinnamon associated with glucose control in diabetics but excessive curcumin or piperine may inactivate insulin therapy associated with hyperglycemic induced mitochondrial apoptosis in the brain and the periphery.

dysfunction in the brain leads to systemic insulin resistance [51] with close links to Type 3 diabetes and NAFLD [52, 53]. In Sirt 1 knockout mice increased adipose tissue mass has been connected to NAFLD [33]. The expression of Sirt 1 protein has a molecular weight (Mol Wt) of 81 kda with Mol Wt variation (81–110 kda). Insulin therapy to prevent NAFLD requires insulin dose/antidiabetic medication calculation to release the Sirt 1 acute phase protein [18, 37]. Sirt 1 is essential to prevent inflammation and Sirt 1 inactivation may induce NAFLD that may corrupt pancreas function. Insulin therapy and plasma Sirt 1 levels may allow mitochondrial biogenesis to be assessed with relevance to therapeutic glucose control in Type 1, 2 and 3 diabetics. It is unclear if inactivation of insulin therapy is associated with mitophagy and the induction of NAFLD and various organ diseases [52]. Appetite control [13, 18] is now critical to the maintenance of mitochondrial biogenesis and insulin therapy with overeating [13] connected to inactivation of insulin therapy and linked to the severity of the diabetic condition.

Indian spices have become important as a diabetes technology [54] with Indian spices such as curcumin and cinnamon associated with glucose control in diabetics (**Figure 2**). The event of insulin therapy as the primary therapy in diabetes technology has raised concern with relevance to the consumption of Indian spices as a secondary technology [55]. Indian spices consumed over many years are not cleared from the body and may bind to cells and receptors with excess Indian spices that may associate with insulin receptors related to altered insulin actions and inactivated insulin therapy. In normal individuals consumption of cinnamon and curcumin may inactivate the biological activity of insulin [54, 55] with Indian spices as the secondary treatment for glucose control in the brain and the periphery. Drugs such as anti-obese drugs [56] and novel drugs [57] are now of critical importance to NAFLD and insulin therapy. Insulin therapy and the use of various therapeutic drugs in diabetes have been linked to the treatment of organ dysfunction [35, 57–59] in diabetes. The use of Indian spices should be reassessed in various populations to

prevent interference with drug/insulin therapy (**Figure 2**) or with caffeine effects [60] relevant to the treatment of NAFLD and diabetes. The mixing of spices such as curcumin, turmeric and black pepper in coffee should be discouraged and may contribute to the transcriptional dysregulation of Sirt 1 and induction of mitochondrial apoptosis relevant to diabetes and the pathogenetic loop [27–32].

5. Genomic medicine and Sirt 1 activators reverse immune reactions in global chronic disease

Genomic medicine in the treatment of cardiovascular disease and diabetes [19, 37] has now accelerated in various communities. Peripheral nutrition is essential early to prevent neurodegeneration (Type 3 diabetes) that lead to uncontrolled peripheral glucose homeostasis. Type 3 diabetes is associated with suprachiasmatic nucleus defects with the abnormal maintenance of brain and whole body glucose metabolism in various species and man [20]. Nutritional therapy in diabetics now need to involve the use of Sirt 1 activators [61] to prevent the effects of various Sirt 1 inhibitors that accumulate in the blood plasma that repress Sirt 1 expression in cells and tissues. A dose of 4 g/day of phosphatidylinositol [62] is essential with insulin therapy to prevent hyperglycemia, NAFLD and other neurodegenerative diseases. Sirt 1 inhibitors such as excess palmitic acid (cream, cheese), alcohol and drugs (suramin and sirtinol) should be carefully controlled to prevent inactivation of insulin therapy. Sirt 1 activators such as pyruvic acid, leucine and magnesium are critical with relevance to insulin therapy. Diabetic individuals with Indian spice consumption (**Figure 3**) over years need to be carefully evaluated with relevance to plasma Sirt 1 inhibitors, xenobiotics [63], caffeine content [60], drug therapy, bacterial lipopolysaccharides (LPS) and mycotoxins [62] that may interfere with insulin/oral medication therapy. The importance of genomic medicine may indicate that the immune system may malfunction [37] early with relevance to poor nutrition of food quality with irreversible organ disease manifestations. Biotherapy and the immune system [37, 61] may be critical to insulin therapy and connected to insulin resistance and NAFLD. Appetite control and essential food components [64] may be essential to maintain the immune system with autoimmune disease

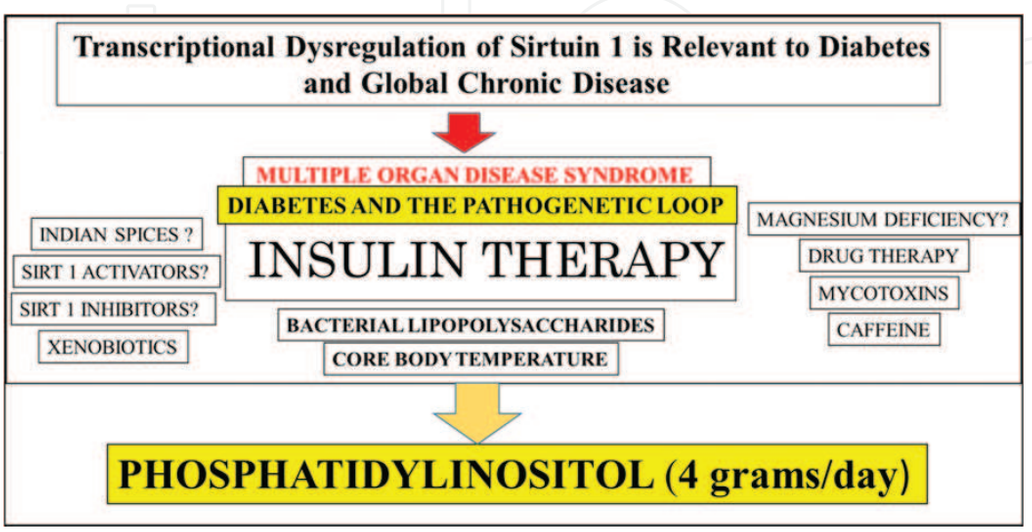


Figure 3.
Poor food quality and core body temperature defects will inactivate Sirt 1 and induce insulin resistance and NAFLD. Sirt 1 inhibitors such as xenobiotics, caffeine/Indian spice over-consumption and magnesium deficiency may lead to the diabetes pandemic with high doses of phosphatidylinositol essential to maintain insulin therapy and prevent the induction of NAFLD.

associated with appetite dysregulation and poor food quality. Specific mitochondrial nutrients [65] with insulin therapy need to be consumed to prevent severe mitophagy and organ disease.

Food quality with relevance to stroke, synaptic plasticity and neurological diseases has become important to diabetic individuals with essential maintenance and prevention of brain diseases by insulin therapy. Unhealthy diets that contain LPS, mycotoxins and xenobiotics can induce NAFLD with inactivation of insulin therapy. In the developing world increased plasma LPS levels (**Figure 3**) have raised concern with relevance to induction of metabolic and neurodegenerative diseases [66, 67]. Antibiotic resistance with relevance to antimicrobial drug use should be carefully controlled to prevent excessive release of LPS from the debris of gram negative bacteria [68]. Food preparation should be carefully assessed to prevent end products such as LPS and patulin that may persist in contaminated food [63, 69]. LPS and patulin may inactivate Sirt 1 [62] with relevance to insulin resistance and NAFLD. Xenobiotics [63] in air, food and water may inactivate insulin therapy (**Figure 3**) with increased xenobiotic levels associated with mitochondrial apoptosis.

Core body temperature (**Figure 3**) and insulin therapy are closely connected and dysregulation of core body temperature may induce NAFLD. The discovery of the heat shock gene Sirt 1 [70] has indicated that careful body temperature control is critical to prevent autoimmune disease and mitochondrial apoptosis. Sirt 1 and its inactivation are associated with increased heat shock protein 70 with relevance to natural killer cell activation and mitochondrial apoptosis. Nutritional therapy and core body temperature are essential to maintain insulin therapy in diabetics with relevance to mitophagy and programmed cell death. The event of heat shock protein 70 disturbances may lead to kidney injury [71] and associated with chronic kidney disease and neurodegeneration in diabetes.

6. Novel biomarkers and insulin therapy may reverse NAFLD and diabetes

The analysis of various plasma biomarkers with insulin therapy [72] has become of major interest to NAFLD development, therapeutic strategies [73–77] and diabetes research. Essential measurements of plasma Sirt 1 and heat shock protein levels need to be determined to indicate core body temperature defects with relevance to inactivation of insulin therapy. Tissue analysis of anti-aging genes [18, 33, 54] need to be conducted to determine the role of insulin therapy with relevance to reversal of NAFLD [18, 33, 35, 49, 55, 68, 69] with connections to inflammation and metabolic diseases. Plasma assays of inflammatory cytokines such as tumor necrosis factor alpha, interleukin-1 and interleukin-6 [10, 11] need to be assayed with effective insulin therapy. The major limitation with insulin therapy is to correlate the dose of insulin injected with plasma biomarkers [78] that maintain mitochondrial biogenesis associated with the prevention of NAFLD (**Figure 4**). The use of antimicrobials [79] with insulin therapy should be carefully controlled to prevent increased release of gram negative bacteria LPS end products that may interfere with glucose homeostasis and induce NAFLD. Plasma LPS should be measured with antimicrobial use in individuals on insulin therapy. The connections between the antimicrobial activity, immune system and nitric oxide homeostasis involve Sirt 1 and connected to toxic immune reactions [80].

The geriatric population in many communities is associated with insulin resistance, Sirt 1 repression and nuclear-mitochondria defects relevant to NAFLD. Sirt 1 measurement in the plasma, cytoplasm and nucleus are essential to determine

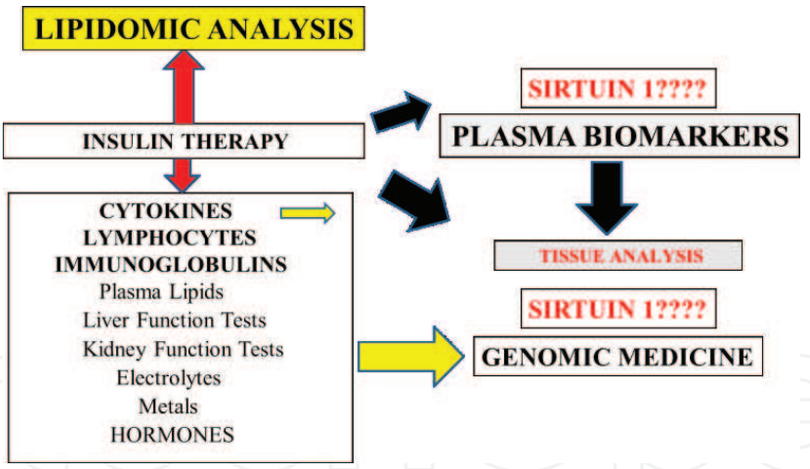


Figure 4.
Complications of insulin therapy in diabetes lead to irreversible mitophagy and programmed cell death with relevance to defective Sirt 1 expression in diabetic individuals. Conventional clinical biochemistry tests do not indicate nuclear-mitochondria defects associated with autoimmune disease and mitophagy but lipidomic tests may be relevant to insulin therapy and Sirt 1 analysis.

the relevance of insulin therapy and mitochondrial apoptosis when compared to the validity of various diagnostic tests and plasma analytic measurements. In many biomarker laboratories the comprehensive assessment of various biomarkers may not be correlated with insulin therapy with mitophagy the inevitable cellular defect in geriatric individuals. Analysis of plasma biomarkers (**Figure 4**) and tissue samples may indicate a primary autoimmune reaction related to a defective nuclear-mitochondria interaction.

Insulin therapy and its use should be carefully revised with relevance to conventional plasma tests that do not indicate cellular mitophagy and toxic immune reactions associated with diabetes [81, 82]. Previous studies [83, 84] with the assessment of the role of insulin on cytokines, lymphocytes and macrophages do not assess Sirt 1's role in toxic immune reactions and mitophagy. Recent studies have shown that molecular lipid biomarkers from lipidomic analysis [85–88] may determine diabetes severity. The role of insulin therapy with relevance to lipidomic biomarkers may integrate routine plasma biomarker testing with relevance to cellular Sirt 1 expression and plasma Sirt 1 analysis (**Figure 4**).

7. Conclusion

Insulin treatment has been evaluated in diabetes but the global NAFLD epidemic that is expected to reach between 20 and 30% of the worldwide communities will now be connected to diabetes pandemic and the pathogenetic loop. Insulin therapy has been assessed with relevance to improvement in inflammatory conditions but the defect in the anti-aging gene Sirt 1 and diabetic mitophagy still persists with the induction of NAFLD and various organ diseases. Insulin therapy with Indian spice consumption requires reassessment to avoid over-consumption of Indian spices that may inactivate insulin therapy and mitochondrial biogenesis. Food quality, appetite control and core body temperature are critical to maintain insulin therapy with unhealthy diets linked to NAFLD and diabetes. Genomic medicine and Sirt 1 activators are essential to maintain insulin therapy in the developing world with toxic immune reactions important to NAFLD. Insulin therapy may not reverse the nuclear-mitochondria defect that is relevant to global organ disease and various plasma biomarkers.

Acknowledgements

This work was supported by grants from Edith Cowan University, the McCusker Alzheimer's Research Foundation and the National Health and Medical Research Council.

Abbreviations

NAFLD	nonalcoholic fatty liver disease
Sirt 1	Sirtuin 1
LPS	bacterial lipopolysaccharides

Author details

Ian James Martins[1,2,3*]

1 Centre of Excellence in Alzheimer's Disease Research and Care, Sarich Neuroscience Research Institute, Edith Cowan University, Nedlands, Western Australia, Australia

2 School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Nedlands, Australia

3 McCusker Alzheimer's Research Foundation, Hollywood Medical Centre, Nedlands, Australia

*Address all correspondence to: i.martins@ecu.edu.au

IntechOpen

© 2018 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Zimmet PZ. Diabetes and its drivers: The largest epidemic in human history? Clinical Diabetes and Endocrinology. 2017;**3**:1

[2] Zimmet PZ, Alberti KG. Epidemiology of diabetes-status of a pandemic and issues around metabolic surgery. Diabetes Care. 2016;**39**:878-883

[3] Michels AW, Eisenbarth GS. Immunologic endocrine disorders. Journal of Allergy and Clinical Immunology. 2010;**125**:S226-S237

[4] Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. The Journal of Pathology. 2007;**211**:144-156

[5] Vasto S, Caruso C. Immunity and ageing: A new journal looking at ageing from an immunological point of view. Immunity and Ageing. 2004;**1**:1

[6] Fulop T, Witkowski JM, Pawelec G, Alan C, Larbi A. On the immunological theory of aging. Interdisciplinary Topics in Gerontology. 2014;**39**:163-176

[7] Passarino G, De Rango F, Montesanto A. Human longevity: Genetics or lifestyle? It takes two to tango. Immunity and Ageing. 2016;**13**:12

[8] Doria G, Frasca D. Genetic factors in immunity and aging. Vaccine. 2000;**18**:1591-1595

[9] Cribbs DH, Berchtold NC, Perreau V, Coleman PD, Rogers J, Tenner AJ, et al. Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: A microarray study. Journal of Neuroinflammation. 2012;**9**:179

[10] Kulmatycki KM, Jamali F. Drug disease interactions: Role of inflammatory mediators in disease and variability in drug response. Journal of Pharmacy and Pharmaceutical Sciences. 2005;**8**:602-625

[11] Lai Y, Dong C. Therapeutic antibodies that target inflammatory cytokines in autoimmune diseases. International Immunology. 2016;**28**:181-188

[12] Alam S, Mustafa G, Alam M, Ahmad N. Insulin resistance in development and progression of nonalcoholic fatty liver disease. World Journal of Gastrointestinal Pathophysiology. 2016;**7**:211-217

[13] Martins IJ. In: Jones E, editor. Appetite Dysregulation and Obesity in Western Countries. Saarbrucken, Deutschland/Germany: LAP LAMBERT Academic Publishing; 2013. ISBN: 978-3-659-40372-9

[14] Martins IJ. Autoimmune disease and mitochondrial dysfunction in chronic diseases. Research Chronic Diseases. 2017;**1**:10-12

[15] Davidson MB. Insulin therapy: A personal approach. Clinical Diabetes. 2015;**33**:123-135

[16] Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: A systematic review and meta-analysis. Lancet Diabetes and Endocrinology. 2013;**1**:28-34

[17] Silver B, Ramaiya K, Andrew SB, Fredrick O, Bajaj S, Kalra S, et al. EADSG guidelines: Insulin therapy in diabetes. Diabetes Therapeutics. 2018;**9**:449-492

[18] Martins IJ. Appetite control and biotherapy in the Management of Autoimmune Induced Global Chronic Diseases. Journal of Clinical Immunology and Research. 2018;**2**:1-4

[19] Martins IJ. Genomic medicine and acute cardiovascular disease progression

in diabetes. International Journal of Medical Studies. 2018;**3**:124-130

[20] Martins IJ. Insulin therapy inactivation is connected to NAFLD and diabetes severity index. Journal of Diabetes and Clinical Studies. 2017;**1**:001-003

[21] Campbell MD, Walker M, Bracken RM, Turner D, Stevenson RJ, Gonzalez JT, et al. Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: A randomized controlled trial. BMJ Open Diabetes Research and Care. 2015;**3**:e000085

[22] Yadav S, Parakh A. Insulin therapy. Indian Pediatrics. 2006;**43**:863-872

[23] Lechleitner M, Hoppichler F. Insulin therapy. Wiener Medizinische Wochenschrift. 2011;**161**:300-304

[24] DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: Scientific review. The Journal of the American Medical Association. 2003;**289**:2254-2264

[25] Mudaliar S, Edelman SV. Insulin therapy in type 2 diabetes. Endocrinology and Metabolism Clinics of North America. 2001;**30**:935-982

[26] Kourtoglou GI. Insulin therapy and exercise. Diabetes Research and Clinical Practice. 2011;**93**:S73-S77

[27] Kohei K. Pathophysiology of type 2 diabetes and its treatment policy research and reviews. Journal of the Japan Medical Association. 2010;**53**:41-46

[28] Leahy JL. Pathogenesis of type 2 diabetes mellitus. Archives of Medical Research. 2005;**36**:197-209

[29] Cersosimo E, Triplitt C, Solis-Herrera C, et al. Pathogenesis of type 2 diabetes mellitus. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth, MA: MDText.com, Inc.; 2000 Available from: https://www.ncbi.nlm.nih.gov/books/NBK279115/

[30] McCulloch DK. Pathogenesis of type 2 diabetes mellitus—UpToDate. 2016. Available from: https://www.uptodate.com/contents/pathogenesis-of-type-2-diabetes-mellitus

[31] DeFronzo RA, Ferrannini E, Zimmet P, George K, Alberti MM. Pathogenesis of type 2 diabetes mellitus. In: Chapter 25 Published Print: 17 April 2015 International Textbook of Diabetes Mellitus. 4th ed. United Kingdom: John Wiley & Sons, Ltd; ISBN: 9781118387658

[32] Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. Lancet. 2014;**383**:1068-1083

[33] 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

[34] Martins IJ. Diabetes and organ dysfunction in the developing and developed. World Global Journal of Medical Research: F Diseases. 2015;**15**:15-21

[35] 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

[36] Martins IJ. Anti-aging genes improve appetite regulation and reverse cell senescence and apoptosis in global populations. Advances in Aging Research. 2016;**5**:9-26

[37] Martins IJ. Genomic medicine and endocrine autoimmunity as key to mitochondrial disease. Global Journal of Endocrinological Metabolism. 2018;**2**:1-3

[38] Bordone L, Motta MC, Picard F, Robinson A, Jhala US, Apfeld J, et al. Sirt1 regulates insulin secretion by repressing UCP2 in pancreatic β cells. PLoS Biology. 2006;**4**:e31

[39] Martins IJ. Anti-aging gene linked to appetite regulation determines longevity in humans and animals. International Journal of Aging Research. 2018;**1**:1-4

[40] Jeschke MG, Klein D, Herndon DH. Insulin treatment improves the systemic inflammatory reaction to severe trauma. Annal of Surgery. 2004;**239**:553-560

[41] Chen Z, Yu R, Xiong Y, Du F, Zhu S. A vicious circle between insulin resistance and inflammation in nonalcoholic fatty liver disease. Lipids in Health and Disease. 2017;**16**:203

[42] Dal S, Jeandidier N, Seyfritz E, Bietiger W, Péronet C, Moreau F, et al. Featured article: Oxidative stress status and liver tissue defenses in diabetic rats during intensive subcutaneous insulin therapy. Experimental Biology and Medicine (Maywood). 2016;**241**:184-192

[43] Cao Y, Jiang X, Ma H, Wang Y, Xue P, Liu Y. SIRT1 and insulin resistance. The Journal of Diabetic Complications. 2016;**30**:178-183

[44] Liang F, Kume S, Koya D. SIRT1 and insulin resistance. Nature Reveiws in Endocrinology. 2009;**5**:367-373

[45] Yoshizaki T, Milne JC, Imamura T, Schenk S, Sonoda N, Babendure JL, et al. SIRT1 exerts anti-inflammatory effects and improves insulin sensitivity in adipocytes. Molecular and Cellular Biology. 2009;**29**:1363-1374

[46] Zabolotny JM, Kim YB. Silencing insulin resistance through SIRT1. Cell Metabolism. 2007;**6**:247-249

[47] de Luca C, Olefsky JM. Inflammation and insulin resistance. FEBS Letters. 2008;**582**:97-105

[48] Wieser V, Moschen AR, Tilg H. Inflammation, cytokines and insulin resistance: A clinical perspective. Archivum Immunologiae et Therapia Experimentalis (Warsz). 2013;**61**:119-125

[49] Martins IJ. Unhealthy Nutrigenomic diets accelerate NAFLD and adiposity in global communities. Journal of Molecular and Genetic Medicine. 2015;**9**:1

[50] Martins IJ. Defective interplay between adipose tissue and immune system induces non alcoholic fatty liver disease. Updates in Nutritional Disorders and Therapy. 2017;**1**:1-6

[51] Lu M, Sarruf DA, Li P, Osborn O, Sanchez-Alavez M, Talukdar S, et al. Neuronal Sirt1 deficiency increases insulin sensitivity in both brain and peripheral tissues. Journal of Biological Chemistry. 2013;**288**:10722-10735

[52] 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

[53] 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. International Journal of Diabetes and Clinical Diagnosis. 2016;**3**:20

[54] Martins IJ. Indian spices and insulin therapy in diabetes and neurodegenerative diseases. Journal of Diabetes and Clinical Studies. 2018;**1**:1-3

[55] Martins IJ. Indian spices and biotherapeutics in health and chronic disease. Health. 2018;**10**:374-380

[56] Martins IJ. Drug therapy for obesity with anti-aging genes modification. Annals of Obesity and Disorders. 2016;**1**:1001

[57] Cole BK, Feaver RE, Wamhoff BR, Dash A. Non-alcoholic fatty liver disease (NAFLD) models in drug discovery. Expert Opinion in Drug Discovery. 2018;**13**:193-205

[58] Martins IJ. Sirtuin 1, a diagnostic protein marker and its relevance to chronic disease and therapeutic drug interventions. EC Pharmacology and Toxicology. 2018;**6.4**:209-215

[59] Martins IJ. Indian spices and unhealthy diets interfere with drug therapy in diabetes and neurodegenerative diseases. Novel Approaches in Drug Designing and Development. 2018;**3**:555616

[60] Martins IJ. Indian spices and caffeine treatment for obesity and cardiovascular disease. Annals of Clinical Endocrinology and Metabolism. 2018;**2**:010-014

[61] Martins IJ. Biotherapy and the immune system in ageing science. Acta Scientific Nutritional Health. 2018;**2**(**4**):29-31

[62] Martins IJ. Overnutrition determines LPS regulation of mycotoxin induced neurotoxicity in neurodegenerative diseases. International Journal of Molecular Sciences. 2015;**16**:29554-29573

[63] Martins IJ. Chapter 01. Increased risk for obesity and diabetes with neurodegeneration in developing countries. In: Top 10 Contribution on Genetics. Book Chapter. Avid Science.2018. www.avid.science.com

[64] Martins IJ. Functional foods and active molecules with relevance to health and chronic disease: Editorial. Functional Foods in Health and Disease. 2017;**7**:833-836

[65] 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

[66] Martins IJ. Bacterial lipopolysaccharides and neuron toxicity in neurodegenerative diseases. Neurology and Neurosurgery. 2018;**1**:1-3

[67] Martins IJ. Bacterial lipopolysaccharides change membrane fluidity with relevance to phospholipid and amyloid Beta dynamics in Alzheimer's disease. Journal of Microbial and Biochemical Technology. 2016;**8**:322-324

[68] Martins IJ. Antibiotic resistance involves antimicrobial inactivation in global communities. SAJ Pharmaacy and Pharmacology. 2017;**2**:102

[69] Martins IJ. Food quality induces a miscible disease with relevance to Alzheimer's disease and neurological diseases. Journal of Food Research. 2016;**5**:45-52

[70] Martins IJ. Heat shock gene inactivation and protein aggregation with links to chronic diseases. Diseases. 2018;**6**:1-5

[71] Martins IJ. Heat shock protein aggregation and chronic kidney disease. Research on Chronic Diseases. 2018;**2**:42-44

[72] Martins IJ. Advances in biomarkers and insulin therapy with relevance to reversal of diabetes. Journal of Studies on Diabetes. 2018;**1**:9-14

[73] Kitade H, Chen G, Ni Y, Ota T. Nonalcoholic fatty liver disease and

insulin resistance: New insights and potential new treatments. Nutrients. 2017;**9**:pii: E387

[74] Mills EP, Brown KPD, Smith JD, Vang PW, Trotta K. Treating nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: A review of efficacy and safety. Therapeutic Advances in Endocrinology and Metabolism. 2018;**9**:15-28

[75] Issa D, Patel V, Sanyal AJ. Future therapy for non-alcoholic fatty liver disease. Liver International. 2018;**38**:56-63

[76] Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nature Medicine. 2018;**24**:908-922

[77] Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. Journal of Gastroenterology. 2018;**53**:362-376

[78] Lees T, Nassif N, Simpson A, Shad-Kaneez F, Martiniello-Wilks R, Lin Y, et al. Recent advances in molecular biomarkers for diabetes mellitus: A systematic review. Biomarkers. 2017;**22**:604-613

[79] Dos Reis SA, do Carmo Gouveia Peluzio M, Bressan J. The use of antimicrobials as adjuvant therapy for the treatment of obesity and insulin resistance: Effects and associated mechanisms. Diabetes/Metabolism Research and Reveiws. 2018 Apr 16:e3014. [Epub ahead of print]

[80] Martins IJ. Antimicrobial activity inactivation and toxic immune reactions induce epilepsy in human. Journal of Medical Discovery. 2017;**2**:jmd17040

[81] Itariu BK, Stulnig TM. Autoimmune aspects of type 2 diabetes mellitus—A mini-review. Gerontology. 2014;**60**: 189-196

[82] Hemminki K, Liu X, Försti A, Sundquist J, Sundquist K, Ji J. Subsequent type 2 diabetes in patients with autoimmune disease. Scientific Reports. 2015;**5**:13871

[83] Nell LJ, Thomas JW. The human immune response to insulin. I. Kinetic and cellular aspects of lymphocyte proliferative responses in diabetics. Journal of Immunology. 1983;**131**:701-705

[84] Watters C, Everett JA, Haley C, Clinton A, Rumbaugh KP. Insulin treatment modulates the host immune system to enhance *Pseudomonas aeruginosa* wound biofilms. Infection and Immunity. 2014;**82**:92-100

[85] Markgraf DF, Al-Hasani H, Lehr S. Lipidomics—Reshaping the analysis and perception of type 2 diabetes. International Journal of Molecular Sciences. 2016;**17**:1841

[86] Suvitaival T, Bondia-Pons I, Yetukuri L, Pöhö P, Nolan JJ, Hyötyläinen T, et al. Lipidome as a predictive. Tool in progression to type 2 diabetes in Finnish men. Metabolism. 2018;**78**:1-12

[87] Kopprasch S, Dheban S, Schuhmann K, Xu A, Schulte KM, Simeonovic CJ, et al. Detection of independent associations of plasma lipidomic parameters with insulin sensitivity indices using data mining methodology. PLoS One. 2016;**11**:e0164173

[88] Lydic TA, Goo Y-H. Lipidomics unveils the complexity of the lipidome in metabolic diseases. Clinical and Translational Medicine. 2018;**7**:4