

Type 3 diabetes with links to NAFLD and Other Chronic Diseases in the Western World

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Abstract

In the year 2015 it is now estimated that 30% of the Western World will now progress to non alcoholic fatty liver disease (NAFLD) and by the year 2050 if NAFLD remains untreated in the Western world the prevalence of the disease may rise to 40% of the global population. Type 3 diabetes and circadian rhythm disturbances may be involved in the induction of NAFLD that may promote insulin resistance and various chronic diseases such as cardiovascular disease, pancreatic disease, kidney disease and neurodegenerative disease. Multiple risk factors that induce Type 3 diabetes and NAFLD include stress, magnesium deficiency, bacterial lipopolysaccharide contamination, drug induced toxicity, xenobiotic levels, unhealthy diet/lifestyle factors and defective thermoregulation. Early diagnosis of Type 3 diabetes by multiple assessment techniques such as proteomics, genomics and lipidomics may allow reversal or stabilization of NAFLD that may progress slowly from simple non-alcoholic steatosis to non-alcoholic steatohepatitis and to hepatic fibrosis/cirrhosis of liver and hepatoma. Analysis of plasma constituents such as heat shock proteins (60,70, 90), amyloid beta, adiponectin, fibroblast growth factor 21, ceramide, sphingosine-1-phosphate, vasoactive intestinal peptide, thrombospondin 1, acute phase reactants may indicate progression of Type 3 diabetes and NAFLD and these results may not be consistent with normal plasma glucose and cholesterol levels. Early nutritional interventions with temperature regulation are required to reverse premature brain disease in diabetes (Type 3/Type2) that is connected to the rapid metabolism of heat shock proteins and amyloid beta oligomers that determine the severity of insulin resistance and NAFLD in individuals in the Western World.

Short Communication

Type 3 diabetes and circadian rhythm disturbances may be involved in the induction of non alcoholic fatty liver disease (NAFLD) that may promote insulin resistance and various chronic diseases such as cardiovascular disease, pancreatic disease, kidney disease, obesity and neurodegenerative disease [1,2]. The aging process involves the loss of neurons from the brain with relevance to Type 3 diabetes and NAFLD. After the age of 25 years neurons start to decrease in the brain [3] and may be associated with toxic adipokine release from adipocytes or liver dysfunction [1] that is linked to the increased concentration of drugs and xenobiotics that accumulate in the brain that become toxic to mitochondria and lead to the death of neurons [4-6].

Interests in the genetic regulation of diabetes has accelerated and now involves the nuclear receptor Sirtuin 1 (Sirt 1) that is associated with insulin resistance and involves neuron senescence in the brain with hepatic steatosis linked to the induction of

NAFLD [7]. Hypothalamic neurons involve Sirt 1 regulation of the suprachiasmatic nucleus (SCN) with the maintenance of brain and whole body glucose homeostasis in various species and man [8-10]. In the year 2015 it is now estimated that 30% of the Western World will now progress to NAFLD [11-13] and interests in brain Sirt 1 and its transcriptional dysregulation involves circadian disturbances relevant to Type 2 or Type 3 diabetes and now identify combined Type 3 and Type 2 diabetes as individuals that are extremely sensitive to accelerated NAFLD [5,7]. Multiple risk factors that involve Sirt 1 dysregulation in combined Type 3 and Type 2 diabetes that induce various chronic diseases and include stress [14], magnesium deficiency [15], bacterial lipopolysaccharides [16,17], drug induced toxicity, xenobiotic levels [5], unhealthy diet/lifestyle factors and defective thermoregulation (Figure 1).

Stress as a factor for the induction of Type 3 diabetes and NAFLD has become of major concern with alterations in the autonomic

nervous system [18] and hypothalamic pituitary axis in Western communities. In recent years the apelinergic pathway [14] has been connected to insulin resistance and NAFLD with apelin regulated stress pathways associated with defective autonomic pathways in neuroendocrine and various chronic diseases. Interests in apelinergic defective pathways with relevance to Type 3 diabetes [14] have escalated and thermoregulation dysfunction in Type 2 diabetes [19,20] involved in the early induction of NAFLD in these individuals. Furthermore thermoregulation dysfunction, apelinergic defective pathways and diabetes has rapidly become an important factor in the induction of metabolic and cardiovascular disease with interests in temperature regulation and circadian rhythm disturbances [21,22] involved in the induction of the combined effects of Type 3 diabetes and Type 2 diabetes in various chronic diseases (Figure 1).

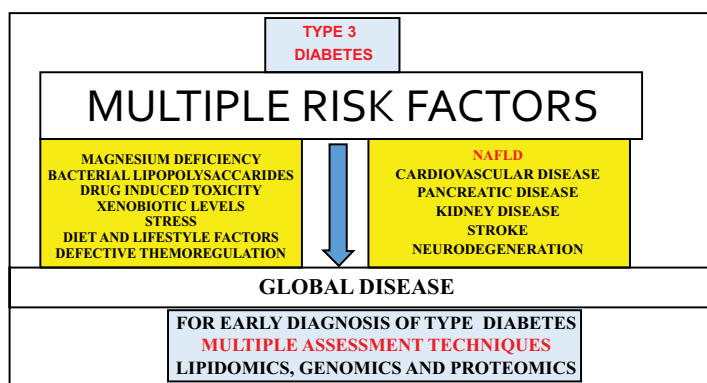


Figure 1: Prevention of Type 3 diabetes involves the consideration of many risk factors that include stress, diet, lifestyle, thermoregulation, neuron xenobiotic toxicity and bacterial contamination. The risk factors associated with Type 3 diabetes may induce various chronic diseases and with the global Type 2 diabetes accelerate the early induction of NAFLD in these individuals. Multiple tests are required to diagnose Type 3 diabetes and with diet and lifestyle changes [2] the severity of global Type 2 diabetes and NAFLD may be reduced.

Thermoregulation dysfunction now identifies the anti-aging gene Sirt 1 as the temperature sensitive gene that is linked to defective apelinergic pathways, NAFLD and various chronic diseases. Research in Sirt 1 and its involvement in temperature regulation [23-29] has escalated to prevent the induction of chronic diseases such as NAFLD with Sirt 1 dysregulation observed in both individuals with Type 3 and Type 2 diabetes [5,7,14,30,31]. Temperature regulation of Sirt 1 (NAD⁺ dependent class III histone deacetylase) has become important to the deacetylation of heat shock factor 1 (HSF1) [26,28,29] that protect neurons from protein-damaging stress associated with misfolded proteins such as heat shock protein 70 (HSP70) [32-37] and the Alzheimer's disease amyloid beta involved with the regulation of the insulin-receptors pathways [38,39].

Sirt 1 is involved with the circadian regulation of cellular heat shock protein (HSP) 60, 70 and 90 with temperature regulation closely associated with Sirt 1 activity/HSP levels in cells [23-29,32-37,40-42] and may be relevant to the heat shock response in Type

2 diabetes [43-45]. Interests in peripheral HSP 70 and amyloid beta metabolism (Figure 2) have escalated with thermoregulation important to the peripheral sink amyloid beta model [7] with relevance to HSP 70 in neuron amyloid beta metabolism and insulin receptor interactions. Temperature regulation of Sirt 1 is now relevant to abnormal transcriptional regulation of the transcription factor p53 with heat shock protein associated with p53 accumulation [46] with relevance to mitochondrial apoptosis, cholesterol/amyloid beta metabolism and NAFLD [7,45,47]. LPS has been shown to induce HSPs in various cells [48-50] and LPS in various species has been shown induce thermoregulatory dysfunction [51,52]. The role of LPS in thermodyregulation involves Sirt 1 dysregulation [53] and neuron apoptosis determined by interactions between HSPs and amyloid beta with relevance to magnesium levels in the brain and periphery [54-57].

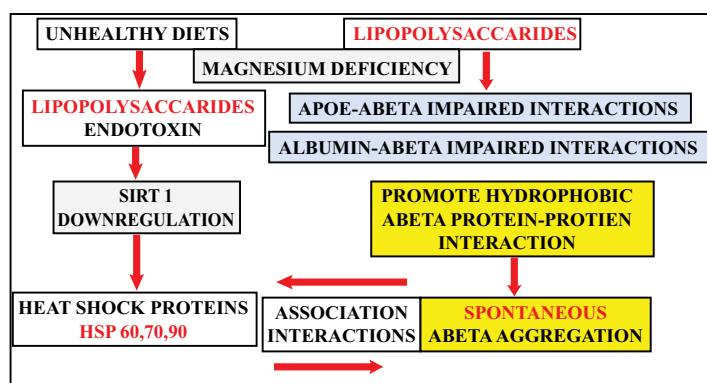


Figure 2: The nuclear receptor Sirt 1 is responsible for the metabolism of HSP (60,70,90) and amyloid beta oligomers. Sirt 1 dysregulation has been linked with Type 3 and Type 2 patients with relevance to plasma and brain HSP and amyloid beta metabolism. LPS reduces magnesium levels with relevance to the metabolism of HSPs and amyloid beta oligomers in the blood plasma and brain. Magnesium deficiency may be relevant to abnormal membrane interactions that involve HSP and amyloid beta interactions with the insulin receptor in the brain and the periphery.

Diets that are low in calories (low fat/sugar diets) and without inhibitors activate Sirt 1 with relevance to prevention of neuron senescence and Type 3 diabetes/NAFLD [58]. Brain temperature dysregulation connected to liver dysfunction may markedly delay the metabolism of saturated fats versus monounsaturated oils such as olive oil and associated with the development of insulin resistance in man [59,60]. Consumption of fats such as palm oil (palmitic acid rich) and virgin coconut oil (saturated fatty acids) that are solid (20-24C) versus the consumption of olive oil (monounsaturated) that is liquid to temperature (4C) may be sensitive to abnormal body temperature dysregulation with the induction of NAFLD. Diets that contain alcohol and fat promote the absorption of LPS with relevance to neuron membrane fluidity and body temperature dysregulation involve the abnormal metabolism of HSPs/amyloid beta oligomers [35-37,61-66] (Figure 2). In individuals with early neuron senescence in Western communities early diagnosis of Type 3 diabetes by multiple assessment techniques such as proteomics, genomics and lipidomics may allow reversal or stabilization of NAFLD that may progress slowly from simple non-alcoholic

steatosis to non-alcoholic steatohepatitis and to hepatic fibrosis/cirrhosis of liver and hepatoma. Analysis of plasma constituents such as LPS, HSP 60, HSP 70, adiponectin, fibroblast growth factor 21, ceramide, sphingosine-1-phosphate, vasoactive intestinal peptide, thrombospondin 1, acute phase reactants may indicate the progression of Type 3 diabetes to the severity to NAFLD (Figure 1) and these results may not be consistent with normal plasma glucose and cholesterol levels [67-72]. Furthermore, early nutritional interventions and brain temperature regulation to reverse premature neuron senescence and Type 3/Type 2 diabetes may delay the stages and progression to NAFLD that may be connected to irreversible hepatic fibrosis, brain insulin resistance and severity of chronic diseases in individuals in the Western World.

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References

1. Martins IJ (2015) Diabetes and Organ Dysfunction in the Developing and Developed World. *Global Journal of Medical Research: F Diseases* 15: 1.
2. Martins IJ (2016) Diet and Nutrition reverse Type 3 Diabetes and Accelerated Aging linked to Global chronic diseases. *Journal of Diabetes Research Therapy* 2: 1-6.
3. Morrison JH, Hof PR (1997) Life and death of neurons in the aging brain. *Science* 278: 412-419.
4. Hung CW, Chen YC, Hsieh WL, Chiou SH, Kao CL (2010) Ageing and neurodegenerative diseases. *Ageing Res Rev* 9 Suppl 1: S36-46.
5. Martins IJ (2013) Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries. *Journal of Molecular Genetic Medicine* S1: 001
6. Rosen ED, Spiegelman BM (2006) Adipocytes as regulators of energy balance and glucose homeostasis. *Nature* 444: 847-853.
7. Martins IJ (2015) 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* 35:158-192.
8. Rahman AU1 (2014) Foreword. *Mini Rev Med Chem*.
9. Nakagawa H, Okumura N (2010) Coordinated regulation of circadian rhythms and homeostasis by the suprachiasmatic nucleus. *Proc Jpn Acad Ser B Phys Biol Sci* 86: 391-409.
10. Kalsbeek A, la Fleur S, Fliers E2 (2014) Circadian control of glucose metabolism. *Mol Metab* 3: 372-383.
11. Bailey SM, Udoh US, Young ME2 (2014) Circadian regulation of metabolism. *J Endocrinol* 222: R75-96.
12. Ahmed M1 (2015) Non-alcoholic fatty liver disease in 2015. *World J Hepatol* 7: 1450-1459.
13. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, et al. (2015) Global Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of Prevalence, Incidence and Outcomes. *Hepatology*.
14. Martins IJ (2014) Induction of NAFLD with Increased Risk of Obesity and Chronic Diseases in Developed Countries. *Open Journal of Endocrine and Metabolic Diseases* 4: 90-110.
15. Martins IJ (2016) Magnesium Therapy Prevents Senescence with the Reversal of Diabetes and Alzheimer's disease. *Health* 8: 694-710.
16. Martins IJ (2015) Nutritional diets accelerate amyloid beta metabolism and prevent the induction of chronic diseases and Alzheimer's disease. *Photon ebooks* UBN: 015-A94510112017
17. Martins IJ (2015) Unhealthy Diets Determine Benign or Toxic Amyloid Beta States and Promote Brain Amyloid Beta Aggregation. *Austin Journal of Clinical Neurology* 2: 1060-1066.
18. Martins IJ (2015) Overnutrition Determines LPS Regulation of Mycotoxin Induced Neurotoxicity in Neurodegenerative Diseases. *International Journal of Molecular Science* 16: 29554-29573.
19. Frith J, Newton JL (2009) Autonomic dysfunction in chronic liver disease. *Liver Int* 29: 483-489.
20. Scott AR, Bennett T, Macdonald IA (1987) Diabetes mellitus and thermoregulation. *Can J Physiol Pharmacol* 65: 1365-1376.
21. Rutkove SB, Veves A, Mitsa T, Nie R, Fogerson PM, et al. (2009) Impaired distal thermoregulation in diabetes and diabetic polyneuropathy. *Diabetes Care* 32: 671-676.
22. Van Someren EJW (2003) Thermosensitivity of the circadian timing system. *Sleep and Biological Rhythms* 1: 55-64.
23. Tokizawa K, Uchida Y, Nagashima K (2009) Thermoregulation in the cold changes depending on the time of day and feeding condition: physiological and anatomical analyses of involved circadian mechanisms. *Neuroscience* 164: 1377-1386.
24. Thompson JW, Dave KR, Saul I, Narayanan SV, Perez-Pinzon MA (2013) Epsilon PKC increases brain mitochondrial SIRT1 protein levels via heat shock protein 90 following ischemic preconditioning in rats. *PLoS One* 8: e75753.
25. Sánchez-Hidalgo AC, Muñoz MF, Herrera AJ, Espinosa-Oliva AM, Stowell R, et al. (2016) Chronic stress alters the expression levels of longevity-related genes in the rat hippocampus. *Neurochemical International* 97:181-192.
26. Liu DJ, Hammer D, Komlos D, Chen KY, Firestein BL, et al. (2014) SIRT1 knockdown promotes neural differentiation and attenuates the heat shock response. *J Cell Physiol* 229: 1224-1235.
27. Westerheide SD, Anckar J, Stevens SM Jr, Sistonen L, Morimoto RI (2009) Stress-inducible regulation of heat shock factor 1 by the deacetylase SIRT1. *Science* 323: 1063-1066.
28. Teigen LE, Orczewska JI, McLaughlin J, O'Brien KM. Cold acclimation increases levels of some heat shock protein and sirtuin isoforms in threespine stickleback. *Comparative Biochemistry Physiology A Molecular Integrative Physiology* 188:139-147.
29. Wang HY, Fu JC, Lee YC, Lu PJ (2013) Hyperthermia stress activates heat shock protein expression via propyl isomerase 1 regulation with heat shock factor 1. *Mol Cell Biol* 33: 4889-4899.

30. Reinke H, Saini C, Fleury-Olela F, Dibner C, Benjamin IJ, et al. (2008) Differential display of DNA-binding proteins reveals heat-shock factor 1 as a circadian transcription factor. *Genes Development* 22:331-345.
31. Kitada M, Koya D (2013) SIRT1 in Type 2 Diabetes: Mechanisms and Therapeutic Potential. *Diabetes Metab J* 37: 315-325.
32. Han J, Wei M, Wang Q, Li X, Zhu C, et al. (2015) Association of Genetic Variants of SIRT1 With Type 2 Diabetes Mellitus. *Gene Expr* 16: 177-185.
33. Magrané J, Smith RC, Walsh K, Querfurth HW (2004) Heat shock protein 70 participates in the neuroprotective response to intracellularly expressed beta-amyloid in neurons. *J Neurosci* 24: 1700-1706.
34. Yenari MA, Giffard RG, Sapolsky RM, Steinberg GK (1999) The neuroprotective potential of heat shock protein 70 (HSP70). *Mol Med Today* 5: 525-531.
35. Ou JR, Tan MS, Xie AM, Yu JT, Tan L4 (2014) Heat shock protein 90 in Alzheimer's disease. *Biomed Res Int* 2014: 796869.
36. Wilhelmus MM, de Waal RM, Verbeek MM (2007) Heat shock proteins and amateur chaperones in amyloid-beta accumulation and clearance in Alzheimer's disease. *Mol Neurobiol* 35: 203-216.
37. Kakimura J, Kitamura Y, Takata K, Umeki M, Suzuki S, et al. (2002) Microglial activation and amyloid-beta clearance induced by exogenous heat-shock proteins. *FASEB J* 16: 601-603.
38. Wang H, Tan MS, Lu RC, Yu JT, Tan L4 (2014) Heat shock proteins at the crossroads between cancer and Alzheimer's disease. *Biomed Res Int* 2014: 239164.
39. Sawa T, Imamura T, Haruta T, Sasaoka T, Ishiki M, et al. (1996) Hsp70 family molecular chaperones and mutant insulin receptor: differential binding specificities of BiP and Hsp70/Hsc70 determines accumulation or degradation of insulin receptor. *Biochem Biophys Res Commun* 218: 449-453.
40. Zacharyus JL, Benatmane S, Plas C (1996) Role of Hsp70 synthesis in the fate of the insulin-receptor complex after heat shock in cultured fetal hepatocytes. *J Cell Biochem* 61: 216-229.
41. Tomita T, Hamazaki J, Hirayama S, McBurney MW, Yashiroda H, et al. (2015) Sirt1-deficiency causes defective protein quality control. *Sci Rep* 5: 12613.
42. Rensing L, Monnerjahn C (1996) Heat shock proteins and circadian rhythms. *Chronobiol Int* 13: 239-250.
43. Fukuyama T, Doi M, Matsuo M, Nishinaga H, Miyake S, et al. (2008) Circadian expression of 86- and 84-kDa heat shock proteins in the mouse suprachiasmatic nucleus. *Biomed Res* 29: 93-98.
44. Märker T, Sell H, Zillessen P, Glöde A, Kriebel J, et al. (2012) Heat shock protein 60 as a mediator of adipose tissue inflammation and insulin resistance. *Diabetes* 61: 615-625.
45. Padmalayam II (2014) The heat shock response: its role in pathogenesis of type 2 diabetes and its complications, and implications for therapeutic intervention. *Discov Med* 18: 29-39.
46. Martins IJ (2015) Unhealthy Nutrigenomic Diets Accelerate NAFLD and Adiposity in Global communities. *Journal of Molecular and Genetic Medicine* 9: 1.
47. Han J, Xu X, Qin H, Liu A, Fan Z, et al. (2013) The molecular mechanism and potential role of heat shock-induced p53 protein accumulation. *Mol Cell Biochem* 378: 161-169.
48. Goldstein I, Rotter V (2012) Regulation of lipid metabolism by p53 - fighting two villains with one sword. *Trends Endocrinol Metab* 23: 567-575.
49. Jaiswal MK, Agrawal V, Jaiswal YK (2013) Lipopolysaccharide drives alternation of heat shock proteins and induces failure of blastocyst implantation in mouse. *Biol Reprod* 88: 162.
50. Triantafilou M, Triantafilou K (2004) Heat-shock protein 70 and heat-shock protein 90 associate with Toll-like receptor 4 in response to bacterial lipopolysaccharide. *Biochem Soc Trans* 32: 636-639.
51. Stulík J, Hernychová L, Macela A, Krocová Z, Kroca M (1999) Production of stress-inducible form of heat-shock protein 70 in mouse peritoneal adherent cells after in vivo infection by *Francisella tularensis*. *Folia Microbiol (Praha)* 44: 306-310.
52. Merchant M, Fleury L, Rutherford R, Paulissen M (2008) Effects of bacterial lipopolysaccharide on thermoregulation in green anole lizards (*Anolis carolinensis*). *Vet Immunol Immunopathol* 125: 176-181.
53. do Amaral JP, Marvin GA, Hutchison VH (2002) The influence of bacterial lipopolysaccharide on the thermoregulation of the box turtle *Terrapene carolina*. *Physiol Biochem Zool* 75: 273-282.
54. Martins IJ (2016) Anti-Aging Genes Improve Appetite Regulation and Reverse Cell Senescence and Apoptosis in Global Populations. *Advances in Aging Research* 5:9-26.
55. Martins IJ (2016) Magnesium Therapy Prevents Senescence with the Reversal of Diabetes and Alzheimer's Disease. *Health* 8:694-710.
56. Garnier C, Protasevich I, Gilli R, Tsvetkov P, Lobachov V, et al. (1998) The two-state process of the heat shock protein 90 thermal denaturation: effect of calcium and magnesium. *Biochem Biophys Res Commun* 249: 197-201.
57. Xiao B, Ma LL, Xiao CL, Lu M, Xu W, et al. (2011) [Protective effect of heat shock protein 70 and magnesium sulfate supplementation on renal ischemia reperfusion injury]. *Beijing Da Xue Xue Bao* 43: 525-530.
58. Rembold CM, O'Connor M (2000) Caldesmon and heat shock protein 20 phosphorylation in nitroglycerin- and magnesium-induced relaxation of swine carotid artery. *Biochim Biophys Acta* 1500: 257-264.
59. Martins IJ (2016) Drug Therapy for Obesity with Anti-Aging Genes Modification. *Ann Obes Disord* 1: 1001.
60. Riccardi G, Giacco R, Rivellese AA (2004) Dietary fat, insulin sensitivity and the metabolic syndrome. *Clin Nutr* 23: 447-456.
61. Lovejoy JC, Smith SR, Champagne CM, Most MM, Lefevre M, DeLany JP, Denkins YM, Rood JC, Veldhuis J, Bray GA. Effects of diets enriched in saturated (palmitic), monounsaturated (oleic), or trans (elaidic) fatty acids on insulin sensitivity and substrate oxidation in healthy adults.

- Diabetes Care. 2002;25:1283-8.
62. Martins IJ (2016) Bacterial lipopolysaccharides change membrane fluidity with relevance to phospholipid and amyloid beta dynamics in Alzheimer's disease. *Journal of Microbial & Biochemical Technology* 8: 322-324.
 63. Tsvetkova NM, Horváth I, Török Z, Wolkers WF, Balogi Z, et al. (2002) Small heat-shock proteins regulate membrane lipid polymorphism. *Proc Natl Acad Sci U S A* 99: 13504-13509.
 64. Armijo G, Okerblom J, Cauvi DM, Lopez V, Schlamadinger DE, et al. (2014) Interaction of heat shock protein 70 with membranes depends on the lipid environment. *Cell Stress Chaperones* 19: 877-886.
 65. Bakthisaran R, Tangirala R, Rao ChM2 (2015) Small heat shock proteins: Role in cellular functions and pathology. *Biochim Biophys Acta* 1854: 291-319.
 66. Hanazono Y, Takeda K, Yohda M, Miki K (2012) Structural studies on the oligomeric transition of a small heat shock protein, StHsp14.0. *J Mol Biol* 422: 100-108.
 67. Delbecq SP, Rosenbaum JC, Klevit RE1 (2015) A Mechanism of Subunit Recruitment in Human Small Heat Shock Protein Oligomers. *Biochemistry* 54: 4276-4284.
 68. Ye J, Zhu R, He X, Feng Y, Yang L, et al. (2014) Association of plasma IL-6 and Hsp70 with HRV at different levels of PAHs metabolites. *PLoS One* 9: e92964.
 69. Kimura F, Itoh H, Ambiru S, Shimizu H, Togawa A, et al. (2004) Circulating heat-shock protein 70 is associated with postoperative infection and organ dysfunction after liver resection. *Am J Surg* 187: 777-784.
 70. Shamaei-Tousi A, Steptoe A, O'Donnell K, Palmen J, Stephens JW, et al. (2007) Plasma heat shock protein 60 and cardiovascular disease risk: the role of psychosocial, genetic, and biological factors. *Cell Stress Chaperones* 12: 384-392.
 71. Bernabucci U, Basiricò L, Morera P, Lacetera N, Ronchi B, et al. (2009) Heat shock modulates adipokines expression in 3T3-L1 adipocytes. *J Mol Endocrinol* 42: 139-147.
 72. Martins IJ (2016) The Role of Clinical Proteomics, Lipidomics, and Genomics in the Diagnosis of Alzheimer's disease *Proteomes* 4:14.
 73. Miller MH, Walsh SV, Atrih A, Huang JT, Ferguson MA, et al. (2014) Serum proteome of nonalcoholic fatty liver disease: a multimodal approach to discovery of biomarkers of nonalcoholic steatohepatitis. *Journal of Gastroenterology Hepatology*. 29: 1839-1847.

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