Defective Glucose Metabolism: An Underlying Cause of Cognitive Decline

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30-Min, Non-CME Research Presentation

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FEATURED SPEAKER

Eric Dorninger

ND, LAc

FOUNDER, OWNER
Roots and Branches
Integrative Health Care

DOCTOR OF NATUROPATHIC MEDICINE
MASTERS OF SCIENCE IN ACUPUNCTURE
BASTYR UNIVERSITY

PRE-MED
University of Colorado, Boulder

CERTIFIED
Shoemaker Practitioner
survivingmold.com

EMT
Cranford First Aid Squad
Cranford, NJ

Healthcare
drdorninger.com

Roots and Branches
Integrative Health Care

@drericdorninger

The Vitality Hour

Is Health Care "Winning the War" on Cognitive Decline, Dementia, and Alzheimer's?

"The global prevalence of dementia is reported to be as high as 24 million and is predicted to increase 4 times by the year 2050. The estimated healthcare cost of Alzheimer's disease is $172 billion per year in the United States alone. In 2011, the United States had an estimated 4.5 million people age sixty-five and above living with clinical Alzheimer's disease."

Review

Alzheimer Disease

Kumar A, Sidhu J, Goyal A, et al. Alzheimer Disease. [Updated 2021 Aug 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499922/

Are There Pharmaceutical Solutions?

"Currently, there are only two classes of approved drugs to treat AD, including inhibitors to cholinesterase enzyme and antagonists to N-methyl d-aspartate (NMDA), which are effective only in treating the symptoms of AD, but do not cure or prevent the disease."

Review

Comprehensive Review on Alzheimer's Disease: Causes and Treatment

Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's Disease: Causes and treatment. *Molecules*. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789

Are There Any Exciting Therapeutic Options in the Pipeline?

The drug, Aduhelm, a monthly infusion priced at $56,000 per year, was approved despite weak evidence that it helps patients.

The New York Times

"This might be the worst approval decision that the F.D.A. has made that I can remember," said Dr. Aaron Kesselheim, a professor of medicine at Harvard Medical School and Brigham and Women's Hospital, who submitted his resignation Thursday after six years on the committee.

He said the agency's approval of the drug, aducanumab, which is being marketed as Aduhelm, a monthly intravenous infusion that Biogen has priced at $56,000 per year, was wrong "because of so many different factors, starting from the fact that there's no good evidence that the drug works."

Newspaper Article

Three F.D.A. Advisers Resign Over Agency's Approval of Alzheimer's Drug

Belluck P, Robbins, R. Three FDA health advisers resign over agency's approval of Alzheimer's drug. *New York Times*. June 10, 2021. https://www.nytimes.com/2021/06/10/health/aduhelm-fda- resign-alzheimers.html?campaign_id=2&emc=edit_th_20210611&instance_id=32732&nl=todaysheadli. Accessed February 16, 2022.

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Remove Obstacles to Brain Health and Healing: Follow the Fuel

"In this prospective cohort study of 10,095 participants, younger age at onset of type 2 diabetes was significantly associated with higher risk for incident dementia; at age 70, the hazard ratio for every 5-year earlier age at type 2 diabetes onset was 1.24."

HumanStudy

Association Between Age at Diabetes Onset and Subsequent Risk of Dementia

Barbiellini Amidei C, Fayosse A, Dumurgier J, et al. Association between age at diabetes onset and subsequent risk of dementia. *JAMA*. 2021 Apr 27;325(16):1640-1649. doi: 10.1001/jama.2021.4001

Remove Obstacles to Brain Health and Healing: Follow the Fuel (cont.)

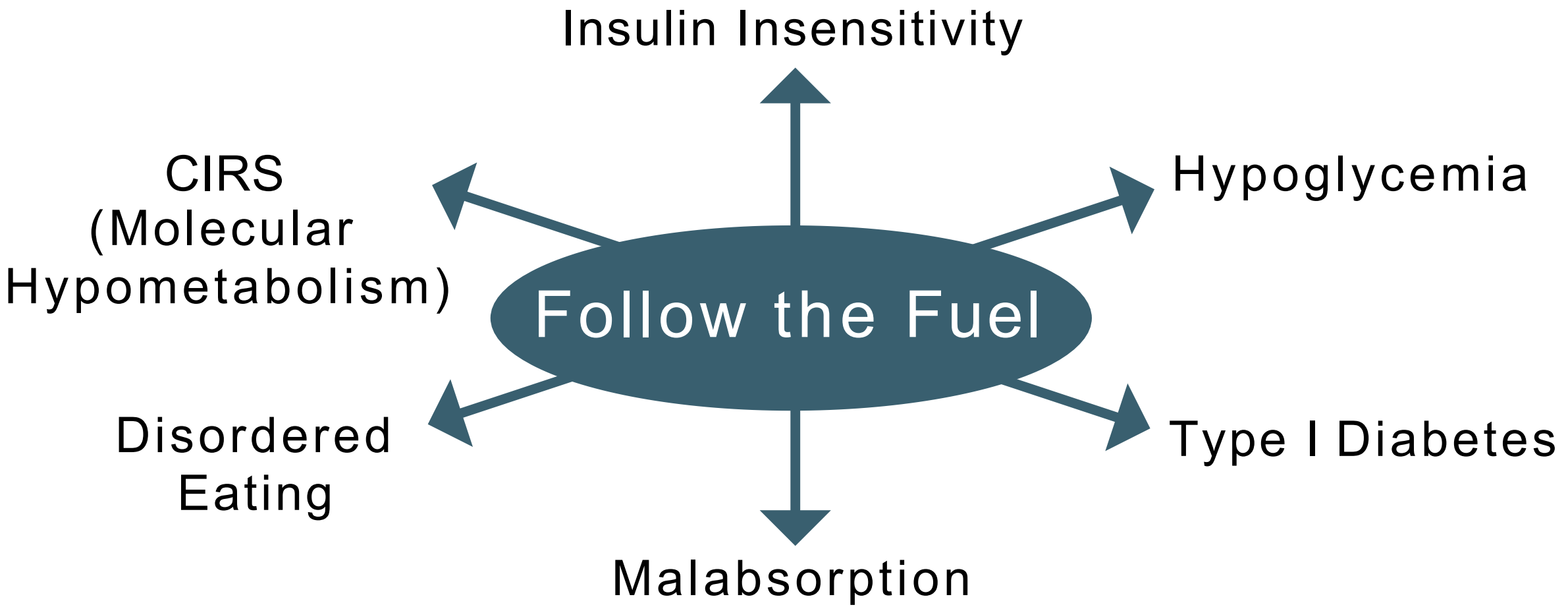
"In this longitudinal cohort study with a median follow-up of 31.7 years, younger age at onset of diabetes was significantly associated with higher risk of subsequent dementia."

HumanStudy

Association Between Age at Diabetes Onset and Subsequent Risk of Dementia

Barbiellini Amidei C, Fayosse A, Dumurgier J, et al. Association between age at diabetes onset and subsequent risk of dementia. *JAMA*. 2021 Apr 27;325(16):1640-1649. doi: 10.1001/jama.2021.4001

Follow the Fuel



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Insulin Insensitivity

- Excessive refined carbohydrates
- Sedentary lifestyle
- Sleep apnea
- Vitamins D and K deficiency
- Omega-3 (EPA/DHA fish oil) deficiency
- CIRS (biotoxin illness)
    - » IRS2 (Insulin Receptor Substrate 2) downregulated, resulting in impaired GLUT1 and GLUT4 transport

Type III Diabetes

"The present work demonstrates extensive abnormalities in insulin and insulin-like growth factor type I and II (IGF-I and IGF-II) signaling mechanisms in brains with AD, and shows that while each of the corresponding growth factors is normally made in central nervous system (CNS) neurons, the expression levels are markedly reduced in AD. These abnormalities were associated with reduced levels of insulin receptor substrate (IRS) mRNA, tau mRNA, IRS-associated phosphotidylinositol 3-kinase, and phospho-Akt (activated), and increased glycogen synthase kinase-3beta activity and amyloid precursor protein mRNA expression. The strikingly reduced CNS expression of genes encoding insulin, IGF-I, and IGF-II, as well as the insulin and IGF-I receptors, suggests that AD may represent a neuro-endocrine disorder that resembles, yet is distinct from diabetes mellitus. Therefore, we propose the term, 'Type 3 Diabetes' to reflect this newly identified pathogenic mechanism of neurodegeneration."

Review

Impaired Insulin and Insulin-Like Growth Factor Expression and Signaling Mechanisms in Alzheimer's Disease – Is This Type 3 Diabetes?

Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease–is this type 3 diabetes? *J Alzheimers Dis*. 2005 Feb;7(1):63-80. doi: 10.3233/jad-2005-7107

Follow the Fuel: Insulin Insensitivity's Effect on the Brain

"Herein, we review the evidence that (1) T2DM causes brain insulin resistance, oxidative stress, and cognitive impairment, but its aggregate effects fall far short of mimicking AD; (2) extensive disturbances in brain insulin and insulin-like growth factor (IGF) signaling mechanisms represent early and progressive abnormalities and could account for the majority of molecular, biochemical, and histopathological lesions in AD; (3) experimental brain diabetes produced by intracerebral administration of streptozotocin shares many features with AD, including cognitive impairment and disturbances in acetylcholine homeostasis; and (4) experimental brain diabetes is treatable with insulin sensitizer agents, i.e., drugs currently used to treat T2DM."

Review

Alzheimer's Disease Is Type 3 Diabetes–Evidence Reviewed

de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. *J Diabetes Sci Technol.* 2008;2(6):1101-1113. doi:10.1177/193229680800200619

Follow the Fuel: Insulin Insensitivity's Effect on the Brain (cont.)

"We conclude that the term 'type 3 diabetes' accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type 1 diabetes mellitus and T2DM."

Review

Alzheimer's Disease Is Type 3 Diabetes–Evidence Reviewed

de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. *J Diabetes Sci Technol*. 2008;2(6):1101-1113. doi:10.1177/193229680800200619

Follow the Fuel: Sedentary Behavior

"The total daily time that people sit, stand, and accumulate non-exercise steps is independent of traditionally recommended moderate-vigorous physical activity (MVPA). The large amount of sedentary time associated with risk for disease can only be reduced significantly with safe and non-fatiguing LIPA, especially in the most at risk proportion of the population."

Review

Sedentary Behavior as a Mediator of Type 2 Diabetes

Hamilton MT, Hamilton DG, Zderic TW. Sedentary behavior as a mediator of type 2 diabetes. *Med Sport Sci*. 2014;60:11-26. doi:10.1159/000357332

Follow the Fuel: Vitamin D

"Through a before-after study, 100 patients with T2DM, 30–70 years old, were recruited from an Arak diabetes clinic as consecutive attenders. Participants were assessed for clinical and biochemistry. Serum insulin and, 25(OH)D concentration, and HOMA-IR was calculated. All measurements were performed at the beginning and the end of the study. Patients received 50,000 units of vitamin D_3 orally per week for eight weeks."

"Our data showed significant improvements in serum FPG, insulin and in HOMA-IR after treatment with vitamin D, suggesting that vitamin D supplementation could reduce insulin resistance in T2DM."

HumanStudy

The Effect of Vitamin D on Insulin Resistance in Patients with Type 2 Diabetes

Talaei A, Mohamadi M, Adgi Z. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. *Diabetol Metab Syndr* 5, 8 (2013). https://doi.org/10.1186/1758-5996-5-8

Follow the Fuel: Vitamin K1

"This was an ancillary study of a 36-month, randomized, double-blind, controlled trial designed to assess the impact of supplementation with 500 microg/day phylloquinone on bone loss."

"Conclusions: Vitamin K supplementation for 36 months at doses attainable in the diet may reduce progression of insulin resistance in older men."

HumanStudy

Effect of Vitamin K Supplementation on Insulin Resistance in Older Men and Women

Yoshida M, Jacques PF, Meigs JB, et al. Effect of vitamin K supplementation on insulin resistance in older men and women. *Diabetes Care*. 2008 Nov;31(11):2092-6. doi: 10.2337/dc08-1204

Follow the Fuel: Vitamin K2

"To summarize, we have demonstrated for the first time that vitamin K2 supplementation for 4 weeks increased insulin sensitivity in healthy young men, which seems to be related to increased cOC rather than modulation of inflammation. Small sample size limits firm interpretation on β-cell function. Our results are consistent with previous studies that demonstrated improved glucose intolerance or relieved insulin resistance by treatment with vitamin K or vitamin K2, respectively. We conclude that unlike in rodents, cOC rather than ucOC may be the endocrine hormone that increases insulin sensitivity in humans."

HumanStudy

Vitamin K2 Supplementation Improves Insulin Sensitivity via Osteocalcin Metabolism: A Placebo-Controlled Trial

Choi HJ, Yu J, Choi H, et al. Vitamin K2 supplementation improves insulin sensitivity via osteocalcin metabolism: a placebo-controlled trial. *Diabetes Care*. 2011;34(9):e147. doi:10.2337/dc11-0551

Follow the Fuel: EPA/DHA

"We assessed whether omega-3 index [red blood cell concentrations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] was associated with insulin sensitivity and other metabolic outcomes in 47 overweight men aged 46.5 ± 5.1 years."

"In conclusion, higher omega-3 index is associated with increased insulin sensitivity and a more favourable metabolic profile in middle-aged overweight men."

HumanStudy

Higher Omega-3 Index is Associated with Increased Insulin Sensitivity and More Favourable Metabolic Profile in Middle-Aged Overweight Men

Albert B, Derraik J, Brennan C, et al. Higher omega-3 index is associated with increased insulin sensitivity and more favourable metabolic profile in middle-aged overweight men. *Sci Rep* 4, 6697 (2014). https://doi.org/10.1038/srep06697

Hypoglycemia

- Patients tend to be “thin and lanky”
- Should avoid meal skipping, intermittent fasting, and caloric restriction
- Do well with anti-inflammatory diet
- Sensitive to blood sugar swings from refined carbs, caffeine, alcohol, and THC
- Overtraining

Screening for Type I Diabetes

High fasting blood sugar in a "thin and lanky" patient?

- Often lean with elevated fasting glucose
- GAD antibodies (also called GAD65) are predictive of Type 1
- Pancreatic islet cell autoantibodies
- Insulin autoantibodies
- GAD, islet cell, insulin antibodies

Screening for Type I Diabetes

"One of the hallmarks of autoimmune diabetes is the presence of adaptive responses directed to neuroendocrine proteins. One of these proteins is glutamic acid decarboxylase (GAD). While GAD is widely distributed in neuroendocrine tissues, its specific significance in diabetes has paralleled the advances in understanding humoral and cellular immunity in Type 1 diabetes (T1D) and in a subset of Type 2 diabetes (T2D), going from the seminal discoveries of islet autoantibodies to the development and standardization of bioassays as diagnostic tools, to studies on the structure of GAD and its antigenic determinants."

Meta-Analysis

GAD65 Autoantibodies and its Role as Biomarker of Type 1 Diabetes and Latent Autoimmune Diabetes in Adults (LADA)

Towns R, Pietropaolo M. GAD65 autoantibodies and its role as biomarker of Type 1 diabetes and latent autoimmune diabetes in adults (LADA). *Drugs Future*. 2011 Nov;36(11):847. doi: 10.1358/dof.2011.036.11.1710754

Screening for Type I Diabetes (cont.)

"GAD65 autoantibodies can accurately predict T1D development in combination with other surrogate humoral biomarkers and they are considered the most sensitive and specific biomarker which identifies a subset of clinically diagnosed T2D termed Latent Autoimmune Diabetes in Adults (LADA). We and others provided evidence indicating that GAD65 autoantibody detection should be part of the diagnostic assessment for clinically diagnosed T2DM mainly because it predicts the rate of progression to insulin requirement in patients affected by LADA."

Meta-Analysis

GAD65 Autoantibodies and its Role as Biomarker of Type 1 Diabetes and Latent Autoimmune Diabetes in Adults (LADA)

Towns R, Pietropaolo M. GAD65 autoantibodies and its role as biomarker of Type 1 diabetes and latent autoimmune diabetes in adults (LADA). *Drugs Future*. 2011 Nov;36(11):847. doi: 10.1358/dof.2011.036.11.1710754

Is Type 1 Diabetes Genetic?

"Type 1 diabetes (T1D) is one of the most widely studied complex genetic disorders, and the genes in HLA are reported to account for approximately 40% to 50% of the familial aggregation of T1D. The major genetic determinants of this disease are polymorphisms of class II HLA genes encoding DQ and DR."

Review

Genetics of the HLA Region in the Prediction of Type 1 Diabetes

Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. *Curr Diab Rep.* 2011 Dec;11(6):533-42. doi: 10.1007/s11892-011-0223-x

Is Type 1 Diabetes Genetic? (cont.)

"The DR-DQ haplotypes conferring the highest risk are DRB1*03:01-DQA1*05:01-DQB1*02:01 (abbreviated "DR3") and DRB1*04:01/02/04/05/08-DQA1*03:01-DQB1*03:02/04 (or DQB1*02; abbreviated "DR4"). The risk is much higher for the heterozygote formed by these two haplotypes (OR = 16.59; 95% CI, 13.7–20.1) than for either of the homozygotes (DR3/DR3, OR = 6.32; 95% CI, 5.12–7.80; DR4/DR4, OR = 5.68; 95% CI, 3.91)."

Review

Genetics of the HLA Region in the Prediction of Type 1 Diabetes

Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. *Curr Diab Rep*. 2011 Dec;11(6):533-42. doi: 10.1007/s11892-011-0223-x

Is Type 1 Diabetes Genetic? (cont.)

"In addition, some haplotypes confer strong protection from disease, such as DRB1*15:01-DQA1*01:02-DQB1*06:02 (abbreviated "DR2"; OR = 0.03; 95% CI, 0.01–0.07)."

"Not surprisingly, current approaches for the prediction of T1D in screening studies take advantage of genotyping HLA-DR and HLA-DQ loci, which is then combined with family history and screening for autoantibodies directed against islet-cell antigens. Inclusion of additional moderate HLA risk haplotypes may help identify the majority of children with T1D before the onset of the disease."

Review

Genetics of the HLA Region in the Prediction of Type 1 Diabetes

Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. *Curr Diab Rep*. 2011 Dec;11(6):533-42. doi: 10.1007/s11892-011-0223-x

Malabsorption

- Elevated fecal fat
  - » Liver function (bilirubin, lipids, AST, ALT, ALK Phos, GGTP)
  - » Liver imaging (abdominal ultrasound, CT, HIDA, MRI)
  - » Pancreatic function (fasting lipase, fasting amylase)
  - » Pancreatic imaging (abdominal ultrasound, CT, MRCP, ERCP)
  - » Celiac, Crohn's, SIBO
- Elevated fecal protein
  - » Hypochlorhydria
  - » PPI, H2 blockers
  - » Anti-parietal cell antibodies
  - » Atrophic gastritis
- Slow down and chew your food; chew 30 times per bite

Disordered eating

- Anorexia, bulimia, orthorexia, overeating

Sleep Apnea a Cause of Fuel Problems?

"This study investigated the relationship between sleep-disordered breathing and insulin resistance, indicated by fasting serum insulin level and insulin resistance index based on the homeostasis model assessment method (HOMA-IR). A total of 270 consecutive subjects (197 male) who were referred for polysomnography and who did not have known diabetes mellitus were included, and 185 were documented to have OSA defined as an apnea–hypopnea index (AHI) ⩾ 5. OSA subjects were more insulin resistant, as indicated by higher levels of fasting serum insulin ($p = 0.001$) and HOMA-IR ($p < 0.001$); they were also older and more obese."

Review

The Relationship Between Obstructive Sleep Apnea and Alzheimer's Disease

Andrade AG, Bubu OM, Varga AW, Osorio RS.
The Relationship between obstructive sleep apnea and Alzheimer's Disease. *J Alzheimers Dis*. 2018;64(s1):S255-S270. doi:10.3233/JAD-179936

Sleep Apnea a Cause of Fuel Problems? (cont.)

"Stepwise multiple linear regression analysis showed that obesity was the major determinant of insulin resistance but sleep-disordered breathing parameters (AHI and minimum oxygen saturation) were also independent determinants of insulin resistance (fasting insulin: AHI, $p = 0.02$, minimum O_2, $p = 0.041$; HOMA-IR: AHI, $p = 0.044$, minimum O_2, $p = 0.022$); this association between OSA and insulin resistance was seen in both obese and nonobese subjects. Each additional apnea or hypopnea per sleep hour increased the fasting insulin level and HOMA-IR by about 0.5%. Further analysis of the relationship of insulin resistance and hypertension confirmed that insulin resistance was a significant factor for hypertension in this cohort. Our findings suggest that OSA is independently associated with insulin resistance, and its role in the atherogenic potential of sleep disordered breathing is worthy of further exploration."

Review

The Relationship Between Obstructive Sleep Apnea and Alzheimer's Disease

Andrade AG, Bubu OM, Varga AW, Osorio RS. The Relationship between obstructive sleep apnea and Alzheimer's Disease. *J Alzheimers Dis*. 2018;64(s1):S255-S270. doi:10.3233/JAD-179936

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CIRS Biotoxin Illness

- IRS2 (Insulin Receptor Substrate 2)
  - » Downregulated IRS2 resulting in impaired GLUT1 and GLUT4 transport
- VDAC (Voltage Dependent Anion Channels)
  - » Biotoxins close the VDAC “tunnel” or pore that allows pyruvate passage into the mitochondria
  - » Metabolic acidosis
  - » Chronic fatigue
  - » Shoemaker Protocol

Follow the Fuel: CIRS Biotoxin Illness

Clinical Pearl:

Biotoxin Illness can drive Molecular Hypometabolism (Chronic Fatigue) due to closure of the VDAC (Voltage Dependent Anion Channel). When pyruvate cannot enter the mitochondria the patient gets stuck in Metabolic Acidosis.

Review

Metabolism, Molecular Hypometabolism and Inflammation: Complications of Proliferative Physiology Include Metabolic Acidosis, Pulmonary Hypertension, T Reg Cell Deficiency, Insulin Resistance and Neuronal Injury

Shoemaker R. Metabolism, molecular hypometabolism and inflammation: Complications of proliferative physiology include metabolic acidosis, pulmonary hypertension, T reg cell deficiency, insulin resistance and neuronal injury. *Trends in Diabetes and Metabolism*. 2020;vol 3:2-15. doi: 10.15761/TDM.1000118

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with Eric Dorninger, ND, LAc

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