Advances

In Orthomolecular Research

Blood Sugar Management

Celebrating

30

1991 | Years | 2021

Advanced Orthomolecular Research

Thank you.

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Research **Collaborations**

Anti scarring

University of British Columbia
Dr. Aziz Ghahary

This project developed and formulated a topical formula to improve the healing process of burns, and to be used as an anti-scarring treatment for other conditions such as fibrosis.

Bone Health

Washington University School of Medicine
Dr. Brian Gage

This study evaluated the effects of the various forms of vitamin K2 and Vitamin K epOxide Reductase Complex (a key enzyme in the vitamin k cycle) as a treatment for osteoporotic features.

Bonutti Technologies
Dr. Peter Bonutti

This study explored novel venous thromboemboloic disease (VTED) prophylaxis in hip and knee arthroplasties, using novel nutraceutical formulations.

Blood Sugar / Diabetes

Albert Einstein Medical College
Dr. Brownlee

This study evaluated the effects of benfotiamine and R-lipoic acid on blood glycating indices HbA1c, as a marker of diabetes.

Cancer

Canadian College of Naturopathic Medicine and Ottawa Hospital Research Institute - Ongoing
Dr. Dugald Seely

This project is exploring the impact of advanced integrative care in a pilot clinical research trial, the TPOISE study.

University of Windsor
Dr. Siyaram Pandey

This study evaluated the role of dandelion root extract in various human cancers.

Cardiovascular Health

University of Manitoba
Dr. Rotimi Aluko

This research project focused on using pea protein to reduce blood pressure while maintaining health kidney function by decreasing the activity of renin (an aspartic protease protein and enzyme secreted by the kidneys.

University Health Network, University of Toronto - Ongoing
Dr. Michael Sole and Dr. Kevin Kuo

This research project focused on using pea protein to reduce blood pressure while maintaining health kidney function by decreasing the activity of renin (an aspartic protease protein and enzyme secreted by the kidneys.)

University Health Network, University of Toronto
Dr. Christopher Low

This project aims to determine if taurine has a role in reducing the abnormal flux of calcium ions and ferrous ions to minimize oxidative and inflammatory damage caused by an iron level overload in heart muscle cells and other tissues.

Cognition/Neurological Health

University of Victoria / Victoria General Hospital
Dr. Patrick Macleod

This study investigated the role of nutritional ingredients in various neurological conditions, including Parkinson's disease.

University of Alberta - Ongoing
Dr. Jerome Yager

This project is focusing on the effects of broccoli sprout supplementation in preventing perinatal brain injury in pregnant females.

Weill Cornell School of Medicine, Cornell University
Dr. Gary Gibson

This project focused on the use of nutraceuticals in reducing the symptoms and/or progression of Alzheimer's Disease.

Drug Delivery Systems

Rutgers University
Dr. Qingrong Huang

This study examined methods for improving bioavailability through a variety of drug delivery systems and formulations.

Extraction and Scale up Production Methods

Agri-food Discovery Place, University of Alberta - Ongoing
Dr. Robert Ippolito

This study will attempt to formulate a natural health product made up of fermented buckwheat sprouts that can effectively reduce blood pressure without side effects.

Agri-Food Discovery Place, University of Alberta - Ongoing
Dr. Robert Ippolito

This study is developing an extraction method to isolate and produce large scale amounts of lunasin from legumes, which has shown to have anticarcinogenic effects for prostate, breast and colorectal cancers.

Immunity

Queen's University
Dr. John Muscedere

This clinical study evaluated the role of lactoferrin (a glycoprotein found in breast milk) in the prevention of nosocomial infections (e.g., UTIs and respiratory pneumonia) in the critically ill.

University of Toronto/Sunnybrook Research Institute
Dr. Elizabeth Asztalos

This study evaluated the role of oral bovine lactoferrin (a glycoprotein found in breast milk) in reducing the rate of mortality, or major morbidity, in very low birth weight preterm infants.

University of Sydney - Initiated
Dr. Michael Dibley

This study is evaluating the effect of bovine lactoferrin (a glycoprotein found in breast milk) in reducing neonatal sepsis, mortality rates and anemia in women of reproductive age.

University of Montréal
Dr. Keith Barrington

This study tested the effects of Lactoferrin, a milk glycoprotein with anti-inflammatory, immunomodulatory and antimicrobial properties, as a treatment for neonatal sepsis.

Inflammation / Gastrointestinal Health

University of Alberta
Dr. Thava Vasanthan

This study worked to create a flour with a low glycemic index, high fibre and low caloric content to optimize the production of molecules with anti-hypertensive properties.

North Carolina Agricultural & Technical State University.
Dr. Shengmin Sang

This study focused on the health impact that phenolic lipids (present in the outer parts of wheat and rye grains) have on IBD, colorectal cancer, diabetes and obesity.

University of Manitoba
Dr. Rotimi Aluko

This project aimed to develop a process for extracting an iron-protein complex found in plant chloroplasts in order to counter iron-deficiency.

University of Alberta
Dr. Gurmeet Singh and Dr. Sean Bagshaw

This clinical study assessed the use of glutamine in reducing inflammation in the gastrointestinal tract in patients following cardiac surgery.

Metabolic Disorders / Health & Weight Loss

University of Guelph
Dr. Paul Spagnuolo

This study investigated the effects of an avocado derived lipid in regards to healthy weight loss, while simultaneously working on a process to develop a supplement containing this lipid for weight loss and diabetes.

University of Calgary
Dr. Praasanth Chelikani

This study mainly evaluated the role of two components found in whey protein have in reference to weight loss and diabetic improvement.

Rutgers University
Dr. Qingrong Huang

This project focused on the use of potent flavonoids derived from citrus peels to reduce high cholesterol, obesity and cancer causing agents.

Academic Medical Center, University of Amsterdam
Dr. Maarten Soeters

This study focused on the effects that gamma butyro betaine has on lipid and acyl carnitine metabolism in healthy adults.

Personalized Nutrition / Cardiovascular Health

University of Ulster
Dr. Helene McNulty

This study analysed the effects that riboflavin has on blood pressure in regards to individuals lacking a specific enzyme that helps the body utilize folate.

University College Dublin
Dr. Michelle Clark

This study evaluated the beneficial effects of B vitamins in older adults who are at risk of low B vitamin intake due to genetics and diet.

University of Gambia / London School of Hygiene & Tropical Medicine
Dr. Jobe Modou and Dr. Andrew Prentice

This study evaluated the use of riboflavin as a measure to counter high blood pressure associated with pregnancy.

Women's Health

University of Toronto
Dr. Robert Casper

This study evaluated the effect of coenzyme Q10 in women undergoing in-vitro fertilization.

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Innovation Track Record

1991 — AOR Founded

1993 — Glucosamine Sulfate — *First in Canada*

1996 — Pantethine — *First in Canada*

1998 — D-Ribose — *First in the World*

1999 — R-Lipoic Acid — *First in the World*

2000 — SAMe 400™ — *First in Canada*

2001 — Complete Vitamin E Complex (Total E®) — *First in North America*

2001 — Benfotiamine — *First in North America*

2002 — Strontium Citrate — *First in the World*

2005 — Nattokinase — *First in Canada*

2005 — Sustained Release R-Lipoic Acid — *First in the World*

2007 — Oxaloacetate (benaGene®) — *First in Canada*

2008 — Fucoidan — *First in North America*

2009 — Curcumin Nanoparticles — *First in the World*

2009 — Lactoferrin — *First in Canada*

2011 — Longvida Curcumin — *First in Canada*

2011 — nanoVAILABLE Boswellia — *First in the World*

2012 — NOx3,2,1 Technology — *First in the World*

2014 — Univestin (Arthritease) — *First in Canada*

2015 — Vegan soft gels — *First in North America*

2016 — Epicatechin — *First in the World*

2016 — XOS — *First in North America*

2016 — PCOS — *First in Canada*

2016 — Red Rice Yeast — *First in North America*

2017 — CurQFen® and Turmacin combination — *First in the World*

2018 — Carageenan-free vegan softgels — *First in the World*

2019 — Tri B12 Synergy — *First in Canada*

2019 — Palmitoylethanolamide (PEA) — *First in Canada*

- 1991 - 1999
- 2000 - 2009
- 2010 - Now

Managing Glycemia

A No-Brainer!

In humans, the brain accounts for approximately 2% of the body weight, but it consumes approximately 20% of glucose-derived energy, making it the main consumer of glucose (Glc).[1] Brain functions such as thinking, memory, and learning are intricately linked to Glc levels and how efficiently the brain uses this fuel source.[2] Conversely, excess Glc consumption is associated with memory and cognitive deficiencies.[3] Consistent with its critical role for physiological brain function, disruption of normal Glc metabolism as well as its interdependence with cell death pathways forms the pathophysiological basis for many brain disorders.[1] Hyperglycemia and the constant fluctuation between low blood sugar and high blood sugar leads to the activation of microglia and of an inflammatory cascade in the brain.[4] The neuroinflammation results in immediate and long-term effects. Chronic brain inflammation will lead to sustained microglial activation and eventually, to neuronal death.[4] High Glc concentrations can also result in an increase of beta amyloid plaques and tau tangles,[5] suggesting that Alzheimer's disease may be a third form of diabetes.[6] In this article, we will explore natural ways to support proper blood sugar levels and dampen or prevent brain inflammation.

Brain Metabolism

The importance of brain energy metabolism has been recognized and investigated for decades. Glucose metabolism provides the fuel for physiological brain function through the generation of adenosine triphosphate (ATP), the foundation for neuronal and non-neuronal cellular maintenance. Glucose is also required to provide the precursors for neurotransmitter synthesis and the ATP needed to perform their actions.[1] Hence, tight regulation of Glc metabolism is paramount for brain physiology and its disturbances bolsters several diseases, affecting both the brain itself as well as the entire system.

The Role of Glucose for Brain Function

Specialized centers in the brain and neurons in the hypothalamus sense central and peripheral glucose levels and regulate glucose metabolism. This tight regulation occurs through the vagal nerve as well as neuroendocrine signals.[6] Blood glucose enters the brain by crossing the blood-brain barrier (BBB) through glucose transporter 1 (GLUT1). Glucose and other metabolites are then rapidly distributed through a tightly linked metabolic network of brain cells. Most of the energy in the brain is consumed for neuronal computation and information processing.[6] In contrast with muscles and the liver, the brain cannot metabolize alternate energy sources such as fatty acids and amino acids because their entry is highly restricted by the BBB. However, glucose can be supplemented in certain situations. For example, when blood levels of ketone bodies are elevated and BBB monocarboxylic acid transporter (MCT) levels are upregulated during prolonged fasting, diets such as ketogenic or starvation.[7]

Since the brain uses Glc as its primary energy source, dysfunction in its metabolism can have physiological and pathophysiological consequences, leading to debilitating brain diseases.[1]

Glucose, Cognitive Decline, and Alzheimer's Disease

Several studies have linked chronically elevated blood sugar levels to cognitive decline and even Alzheimer's disease. For example, a 2018 study published in Diabetologia by a team of researchers from the Imperial College London clearly establishes significant longitudinal associations between glycated hemoglobin (HbA1c) levels, diabetes status and long-term cognitive decline.[8] The study, comprised of 5189 participants over a 10-year follow-up period, showed that the multivariable-adjusted rate of global cognitive decline associated with prediabetes and diabetes was increased by −0.012 SD/year and −0.031 SD/year respectively compared with the participants with normoglycemia. Similarly, memory, executive function and orientation z scores showed an increased rate of cognitive decline with diabetes. Conversely, several fluoro-2-deoxy-D-glucose (FDG–PET) studies have shown that cerebral glucose hypometabolism within key brain regions accurately distinguishes normal aging from Alzheimer's disease (AD), precedes cognitive decline and the onset of dementia among normal elderly and pre-symptomatic familial AD (FAD) individuals.[9]

Advanced Glycation End Products

One of the most damaging effects of chronic hyperglycemia is the formation of advanced glycation end products (AGEs). AGEs are created through a nonenzymatic reaction between sugars molecules and oxidation (glycoxidation) of proteins, lipids, and nucleic acids. Additionally, AGEs are also present in uncooked animal-derived foods and cooking results in the formation of new AGEs within these foods.[10] Although AGEs accumulation is part of the normal aging process, excessively high levels of AGEs detrimentally affect nearly every type of cell and molecule in the body. AGEs play a role in the development and progression/aggravation of many degenerative diseases, including diabetes and AD.[11] Essentially, AGEs promote oxidative stress and inflammation by binding with cell surface receptors or cross-linking with body proteins, altering their structure and function.[10] Balancing blood sugar levels through an appropriate diet and the use of targeted nutritional supplements can protect the body from the harmful effects of AGEs and prevent the damage they could do to blood vessels and the brain.

Natural strategies

In the light of this new paradigm which considers AD as a third form of diabetes, all nutritional interventions and lifestyle modifications geared at improving glucose metabolism, reducing AGEs production, oxidative stress and inflammation may help protect the brain and contribute to reducing the progression of cognitive decline. Targeted nutritional supplements addressing the same parameters such as alpha-lipoic acid, acetyl-L-carnitine and vinpocetine have been shown to delay cognitive decline.[12]

B vitamins supplementation has been shown to improve metabolic control in diabetic patients[13] and their intake is also important in preventing cognitive decline.[14] Of particular interest in this group of crucial vitamins, thiamine deserves our attention.

Natural strategies

Thiamine (vitamin B1) is an absolute requirement for vital metabolic processes and normal cellular growth and function. It also plays a key role in the maintenance of healthy brain function because of the coenzyme role of thiamine diphosphate (ThDP) in glucose and energy metabolism.[15] Benfotiamine is a highly bioavailable form of thiamine[16] which prevents the formation of AGEs, can neutralize oxidative stress[17] and exhibits anti-inflammatory properties.[18]

In a clinical study, benfotiamine has been shown to simultaneously inhibit three major biochemical pathways implicated in the pathogenesis of hyperglycemia induced vascular damage, and might be clinically useful in preventing the development and progression of diabetic complications.[19] In another ground-breaking study, supplementation with oral benfotiamine (300 mg mg/day) over 18 months significantly improved the cognitive abilities of mild to moderate AD patients, independently of brain amyloid accumulation.[20]

Conclusion

The new and evolving integrative paradigm which considers the brain and cognitive impairments as part of the whole system broadens our therapeutic options. This model is also particularly well suited to the naturopathic/functional medicine models and tools. While certain targeted drugs are useful in our arsenal of options, our increasing understanding of the importance of optimizing the different underlying biochemical processes at play in the etiology of various chronic conditions – such as the interplay between glucose metabolism and cognitive decline - is opening the door to new, more comprehensive strategies which are proving to be beneficial on various levels.

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Clinical Protocol:

Diabetes Management

This information is intended for educational purposes only and should not be followed without clinical direction from a qualified health care practitioner. Please consult with a practitioner if you are taking hypoglycemic medication prior to taking any supplements. If you are taking insulin or other hypoglycemic medications, ensure you are monitoring your blood glucose levels regularly when beginning a new diet or exercise regimen. If blood glucose levels are continuously low after implementing your new regime, your practitioner may need to adjust your medications.

Diet (from Duke University Medical Center)

The aim of this diet is to keep total carbohydrates to less than 20 g per day. Make sure to read labels to ensure proper tracking of carbohydrates.

Eat ANY of the Following Whenever:

- Meat: beef, pork, lamb, veal or other meats
- Poultry: chicken, turkey, duck or other fowl
- Fish and Shellfish: all types of fish (avoid farmed fish and try and choose smaller fish as they will contain less contaminants)
- Eggs: all types

Foods that MUST be Eaten EVERYDAY:

- Salad Greens (minimum two cups per day): arugula, bok choy, cabbage, chard, chives, endive, lettuce (all varieties), greens (all variety), kale, parsley, spinach, radicchio, radishes, scallions, watercress
- Vegetables (one cup uncooked): artichokes, asparagus, broccoli, Brussel sprouts, cauliflower, celery, cucumber, eggplant, green beans, leeks, mushrooms, okra, onions, pumpkin, shallots, snow peas, sprouts, tomatoes, rhubarb, wax beans, zucchini

Eat in LIMITED Quantities:

- Cheese (up to four oz per day): avoid processed cheeses - read the label as carb count should be less than 1 g per serving
- Cream (up to four Tbsp per day): includes all types (heavy, light, sour cream)
- Mayonnaise (up to four Tbsp per day): read the labels and choose low carb brand
- Olives (black or green): up to six/day
- Avocado: up to half a fruit per day
- Lemon/Lime Juice: up to four tsp a day
- Soy Sauce: up to four Tbsp per day (check carb count on label)
- Pickles (dill or sugar free): up to two a day

Fats and Oils

All are allowed. However, try and avoid margarine and other hydrogenated oils that contain trans fats.

For salad dressings, olive oil and vinegar is recommended, but if you are using a prepared dressing, ensure you check the label and that it contains less than one to two g of carbs.

Because, you are already following a diet low in carbohydrates, do not attempt to also eat a low-fat diet, or you will be hungry. Fats will help to make you feel full.

Beverages

Drink at least two litres of water per day. Carbonated water with flavour is also permitted, as long as it does not contain sugar. Up to three cups of caffeinated coffee or tea per day. Unlimited herbal tea.

Alcohol

Avoid alcohol consumption for the five to six weeks. Eventually, after dietary habits have been formed and weight loss has occurred, low carbohydrate alcohol may be added back.

Quantities

This is not about counting calories. Eat when you are hungry and stop when you are full. However, ensure you are choosing foods and limiting foods according to the guidelines above.

REMINDER: This is not about counting calories. Eat when you are hungry and stop when you are full. However, ensure you are choosing foods and limiting foods according to the guidelines above.

Sample Menu

Breakfast:

Meat or other protein source

Fat source- may already be in your protein (ex. bacon, eggs, cheese, etc)

Low carbohydrate vegetable: breakfast quiche or omelette

Lunch:

Meat or other protein source

Fat source- olive oil, avocado, cheese

1 1/2 cups of salad or cooked greens

½ to 1 cup of vegetables

Snack:

Low carb snack that has protein and/or fat

Dinner:

Meat or other protein source

Fat source

½ cup to 1 cup of vegetables

Reading a label

- Note serving size, total carbohydrates and fibre
- You may subtract fiber from total carbohydrates to get "net carbs." Ex. 10 g of carbs and three g of fibre = seven g of net carbs
- Make sure net carbs stay below 20 g for the day
- Don't worry about calories or fat
- Net carbohydrate count of vegetables should be five g or less
- Net carbohydrate count of protein sources should be one g or less
- Avoid any food that has any form of starch or sugar in the first five ingredients

Names of hidden sugars (AVOID)

Sucrose, dextrose, fructose, maltose, lactose, glucose, honey, agave syrup, high-fructose corn syrup, maple syrup, brown-rice syrup, molasses, evaporated cane juice, cane juice, fruit-juice concentrate, corn sweetener.

Exercise

Must:

- Walk 10,000 steps per day
- Aerobic exercise that elevates heart rate to 60 to 70 HRMAX for 30 mins three to four times per week

Recommended:

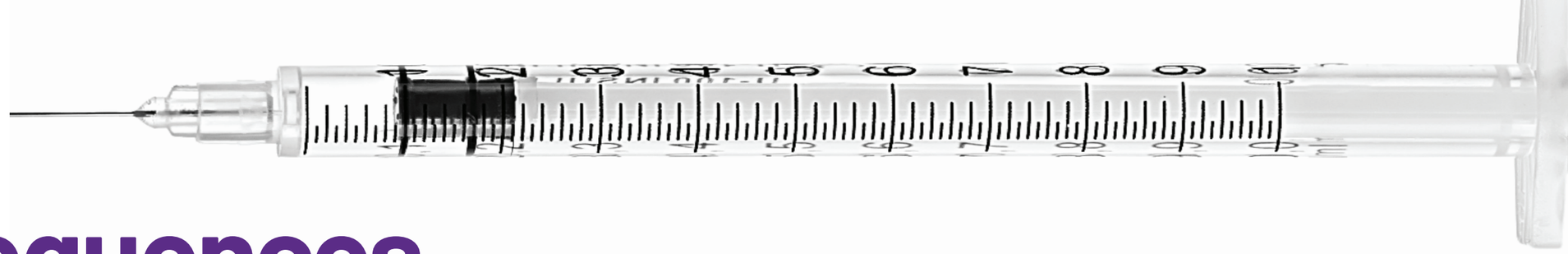
- Strength training three times per week (consult with a personal trainer to develop a routine)

Supplements:

- ***Gymnema sylvestre*:** 400-600 mcg (25% gymnemic acids) per day. Helps to lower glucose levels, improves HbA1c, as well as benefiting the pancreatic insulin-secreting cells.
- **Berberine:** 1 g per day. Helps to lower blood glucose, HbA1c, cholesterol and blood pressure.
- **Chromium picolinate:** 500 mcg twice per day. Increases insulin sensitivity.
- **Magnesium glycinate:** 500 mg per day. Magnesium is often deficient in patients with diabetes.
- **Fibre (please see diet section for use of fibre in calculation of net carbs):** 20-30 g per day. Helps to inhibit intestinal absorption of glucose after eating.
- **Alpha Lipoic Acid:** 600 mg per day. Antioxidant and also helpful for peripheral neuropathy.

Insulin Resistance and Neurocognitive Disease:

The Consequences of Unheeded Signs



Key discussion points

- Insulin resistance (IR) occurs when the glucose uptake into the cell is inhibited despite the presence of elevated insulin
- IR is a progressive, reversible state and can result in the formation of disruptive reactive oxidative species leading to mitochondrial dysfunction and impacts many systems in the body from cardiovascular, endocrine and cognitive function
- Insulin resistance in the central nervous system has been linked to mood and behavioural disorders, anxiety, depression, cognitive impairment as well as neurodegenerative diseases such as Alzheimer's disease, Parkinson's
- Therapeutic approaches relate to early identification and reversal and adaptation: exercise, diet(low GI/GL), and supplements or ingredients

Key Terms

Hyperglycemia
an excess of glucose in the bloodstream, often associated with diabetes mellitus

Hyperinsulinemia (HI)
the amount of insulin in your blood is higher than what's considered normal

Insulin Resistance (IR)
when cells in your muscles, fat, and liver don't respond well to insulin and can't easily take up glucose from your blood

HOMA-IR
the homeostasis model assessment-estimated insulin resistance is a method used to quantify insulin

Blood sugar fluctuations occur throughout the day in response to consumption, and our bodies have developed a highly regulated system to ensure that fuel is efficiently directed to cells rather than lingering in circulation. Blood sugar dysregulation refers to the inability for the body to properly regulate to changes in blood glucose levels and can have profound effects on the body such as the development of diabetes, cardiovascular and other metabolic diseases.[1] In a complex chicken or the egg scenario, this dysregulation can both exacerbate and result from impaired insulin output by the pancreas or responses by cells. Insulin resistance (IR) is the term specifically used to describe the impairment in the ability for insulin to adequately communicate with receptors for the uptake of glucose into the cell.[2] IR is progressive and can be reversible. It has genetic, modifiable and non-modifiable risk factors associated with it. Suffice to say this is a complex and important concept that has significant systemic impacts when left unmanaged. We will be exploring the role of IR in the pathophysiology of neurodegenerative disorders as well as cognitive disorders as this area of health is often overlooked in diabetic and insulin resistant patients despite the profound impact on quality of life for patients.

Understanding How Insulin Resistance Develops

Before we can thoroughly assess the relationship between IR and cognitive and neurodegenerative conditions, we must understand the role of oxidative stress and mechanisms that give rise to IR.

In the simplest terms: consider that every cell contains insulin receptors such as the GLUT family of receptors. Ingested glucose triggers the release of insulin from the beta islet cells of the pancreas which then chaperones the glucose into the cell via these insulin receptors. This response is meant to be temporary and pulsed as a response to food. Trouble can arise when there from several causes including[2]:

- chronic elevations in blood sugar (frequent overeating of high glycemic index and high glycemic load foods)
- pre-receptor defect abnormalities in insulin molecules or with the insulin receptor structure itself
- deficiencies in post receptor intracellular signalling or insulin production in the pancreas
- Medications such as glucocorticoids and niacin

Further, there does seem to be a strong genetic component to developing pre and post receptor defects. Resulting in an impaired glucose response to a specific amount of insulin or IR3.

Altered sensitivity of insulin receptors to insulin ramps up cellular metabolism, which can yield reactive oxidative species (ROS). Depending on where (i.e., what kind of cell and which cellular compartment) and how much ROS are formed, will determine the progression and impact of the IR[3]. For example, insulin resistance in fat cells or adipocytes leads to an increase in free fatty acids. As these free fatty acids accumulate in the blood stream there is a higher risk of lipoprotein lipases flooding the coronary arteries, heart, and liver.[3]

Because pancreatic function attempts to compensate for this desensitisation by secreting more insulin this elevation is detected before fasting blood glucose levels, or HbA1C are altered.[2,3] Therefore, early clinical indicators of IR can be detected with fasting serum insulin levels and elevated levels of circulating free fatty acids.

How Does it Impact the Body?

The biochemical changes resulting from IR and hyperinsulinemia have been well characterised particularly in regard to cardiovascular function.[3] IR disrupts processes such as: aldose reductase (AKR1B1), formation of advanced glycation end products (AGEs), mitochondrial fatty acid oxidation in arterial endothelial cells, macrophages, and cardiomyocytes, oxidation of tetrahydrobiopterin (BH 4 the essential cofactor of endothelial nitric oxide synthase). All of which explain how insulin resistance itself is a major cause of cardiovascular disease in type 2 Diabetes mellitus (T2DM). While this relationship may be clear, many of these same mechanisms help explain why diabetes and insulin resistance are associated with altered brain imaging, depression, and increased rates of age-related cognitive impairment[3]. These mechanisms include an increased ROS production in immune cells (specifically macrophages) which drives chronic inflammation. When fatty acids are oxidized in the mitochondria the ratio of key intermediates NADH and FADH 2 is shifted from 5:1 (favourable) to 2:1 (unfavourable.) What this results in is an overall reduction in the coenzyme Q10 pool available in the mitochondrial electron transport chain. Things then begin to move backwards in the reverse electron transport (RET) resulting in significant ROS production and a build-up of overoxidation of cysteine thiols which can then go on to damage proteins, cause aggregation and even proteolysis.

IR progression contributes to diseases such as diabetes, neuropathy, atherosclerosis, cardiomyopathy, PCOS, and metabolic syndrome.[1] This means that early detection and management can have profound impacts. It is also worth noting that IR is not always bad. In fact, throughout our lives there are several periods of development (puberty or pregnancy) where a transient IR occurs. For example, IR during puberty is linked to increased fat oxidation which increases serum IGF1 levels thought to increase growth hormone secretion explaining those pubertal growth spurts.[4] This type of IR is normal and not sustained as the body begins to adapt however, a combination of genetics and environmental exposure may interfere with these adaptive processes.

How can we detect insulin RESISTANCE?

- Hyperinsulinemic-euglycemic clamp technique:[5] This is considered the gold standard for assessing insulin sensitivity and is often used in clinical trials but still remains difficult to monitor in practice
- Signs and Symptoms:[3] skin tags, acanthas nigrans (dark patches of skin on neck and armpits), excessive thirst, abdominal weight gain, fatigue, excessive urination
- HOMA-IR[3] is calculated using fasting blood glucose and fasting blood insulin levels
- QUICKI[6] stands for Quantitative Insulin Sensitivity Check Index

Neurodegenerative Diseases?

Because of the high metabolic requirements of the central nervous system, blood sugar requirements for the brain are prioritized.[7] Meaning that in a starvation state any sugars will be preferentially shuttled to the brain to ensure survival. The body can do this through several mechanisms including the receptor mediated transport of insulin across the blood brain barrier.[2-6] Selective concentration of insulin to hypothalamus and olfactory bulb, and receptors located in the hippocampus and frontal cortex.[7] Given the importance of insulin and glucose uptake in the brain it stands to reason that any insulin resistance in the body will impact the brain early in progression. In fact, scientists have been able to link the mitochondrial and dopaminergic dysfunction[8] directly resulting from insulin resistance to behavioural disorders such as anxiety and depression and bipolar disorder.[9] In another study, 1759 patients with metabolic syndrome (with IR) were studied over 15 years and were found to be three to four times more likely to develop cognitive dysfunction than those with no other risk factors.[10]

Abbatecola et al.[11] examined the relationship between cognitive decline of the elderly and insulin levels and found that regarding memory and executive functions HI and IR are important risk factors for cognitive decline of the elderly. This was reaffirmed in 2017 where researchers looked at the metabolic profiles of elderly Dutch women and found impaired fasting plasma glucose levels and IR, or those with poor metabolic profiles, have an increased risk of the development of cognitive dysfunction.[3]

Neurodegenerative diseases such as sporadic Parkinson's disease[12] (PD), and Alzheimer's disease[13] (AD), demonstrate uncharacteristic glucose metabolism through a pathway that depletes antioxidant capacity leaving cells vulnerable to oxidative stress. IR downregulated the enzymes that are normally involved in shuttling glucose away from this pathway and thus increases risk of early pathological changes that occur in PD.

The association between T2DM and increased risk of dementia[14] – vascular dementia; mild cognitive impairment, and cognitive decline, further demonstrates the necessity of preventing, detecting, and correcting aberrant IR to prevent progression into more serious sequelae.

Therapies

An important consideration in management of health blood sugar is understanding the impact food will have. The glycemic index (GI) and the glycemic load (GL) are two concepts that help us predict this response in metabolically healthy individuals.[15] Ideally when consuming foods we are mindful of extremes, avoiding overconsumption of either very high GI or GL foods. Further, unless specifically recommended you needn't exclusively consume foods with low GL and low GI.

- GI = how fast the carbohydrates in a food are broken down into sugars and enter your bloodstream
- GL = the amount of carbohydrates (i.e. sugars) in a serving of that particular food
- Some GI guidelines also get a little carried away suggesting whole foods such as carrots would be excluded due to a medium to high GI. But the glycemic load (GL) is typically a more accurate indicator of health impact of the food because it gives us insight into how much sugar is available. In our carrot example this is a lower GL food meaning that while the sugars that exist are quickly absorbed, there isn't a high sugar content to begin with. High GI foods will rapidly increase blood glucose levels and the subsequent insulin response[15]
- Therefore, both must be taken in context
- Soluble fibres are also necessary in the diet as these avoid sharp frequent blood sugar bombs, rather allowing for a more sustained response[16]

Supplementation

While many supplements tout blood sugar regulation claims, the schedule for supplementation is important. The multifactorial nature into the development of IR indicates that a personalised approach is required.

Based on the described oxidative stress that occurs because of IR, it stands to reason that individuals with advanced IR such as those with T2DM may benefit from antioxidant therapy. A randomized double-blind placebo-controlled trial published in 2017 followed patients with type II diabetes mellitus who were assigned 300mg/day of ALA or placebo for two months. Results after two months of supplementation showed a statistically significant reduction in "FBG and PPG levels, IR-Homeostasis Model Assessment (IR-HOMA index) and GH-Px level in the ALA group".

As the relationship between IR and cognitive health are made clearer with research, so too will therapeutic strategies,– bringing hope to many struggling to address the root cause of their disease.

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Research Spotlight:

The Effects of Benfotiamine and Alpha-lipoic Acid on Complication-causing Pathways in Type 1 Diabetes

This study evaluated the effects of AOR's Benfotiamine and R-lipoic acid on blood glycating indices HbA1c, as a marker of diabetes in partnership with the International Center for Diabetic Complications Research at Albert Einstein College of Medicine.

What's Already Known on this Topic?

Numerous studies have shown the beneficial effects of benfotiamine on the formation of advanced glycation end products for individuals with diabetes. Alpha-lipoic acid has also been studied for its ability to be a possible treatment option for diabetes type 1 and 2. What had yet to be discovered was the potential of combining these two nutrients for a more comprehensive approach.

What's New About our Research?

We determined whether fixed doses of benfotiamine in combination with slow-release alpha-lipoic acid normalise markers of reactive oxygen species-induced pathways of complications in humans. Male participants with and without type 1 diabetes were studied in the General Clinical Research Centre of the Albert Einstein College of Medicine. Glycaemic status was assessed by measuring baseline values of three different indicators of hyperglycaemia. Intracellular AGE formation, hexosamine pathway activity and prostacyclin synthase activity were measured initially, and after two and four weeks of treatment.

Why our Findings are Important

In the nine participants with type 1 diabetes, treatment had no effect on any of the three indicators used to assess hyperglycaemia. However, treatment with benfotiamine plus alpha-lipoic acid completely normalised increased AGE formation, reduced increased monocyte hexosamine-modified proteins by 40% and normalised the 70% decrease in prostacyclin synthase activity from 1,709 +/- 586 pg/ml 6-keto-prostaglandin F(1alpha) to 4,696 +/- 533 pg/ml.

These results show that the previously demonstrated beneficial effects of these agents on complication-causing pathways in rodent models of diabetic complications also occur in humans with type 1 diabetes. While more research is needed in this field, these initial results show promise for future treatment options.

Key Terms

Advanced Glycation End Products (AGEs)
Advanced glycation end products are proteins or lipids that become glycated as a result of exposure to sugars. They are a bio-marker implicated in aging and the development, or worsening, of many degenerative diseases, such as diabetes, atherosclerosis, chronic kidney disease, and Alzheimer's disease.

Hexosamine Pathway
The Hexosamine Biosynthetic Pathway (HBP) is a branch of glycolysis responsible for the production of a key substrate for protein glycosylation.

Hyperglycaemia
Hyperglycaemia is an excess of glucose in the bloodstream, often associated with diabetes mellitus.

Prostacyclin Synthase
Prostacyclin synthase (PCS) is an enzyme with dilatory functions in the normal vasculature.

Reactive Oxygen Species
A type of unstable molecule that contains oxygen and that easily reacts with other molecules in a cell. A build up of reactive oxygen species in cells may cause damage to DNA, RNA and proteins, and may cause cell death.

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Gestational Diabetes

Gestational diabetes mellitus (GDM) occurs when there is abnormal glucose metabolism and tolerance during pregnancy, leading to a hyperglycemic state. It typically resolves after delivery, however, having GDM increases many health risks for mom and baby including the development of type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and obesity.[1]

In pregnancy, multiple body systems undergo modifications to support the needs of a growing fetus. Changes occur in circulation, respiration, metabolism, and insulin sensitivity. In early pregnancy, insulin sensitivity is greater in order to facilitate greater uptake of glucose to be stored by adipose tissue. This energy reserve will be necessary and used in later pregnancy.

Meanwhile, surging hormones in both mother and placenta drive a more insulin resistant state to keep blood glucose levels elevated so that glucose can easily cross the placenta for the fetus' growth. In order to compensate for these changes, maternal pancreatic beta-cells undergo hypertrophy and hyperplasia, and the levels of glucose-stimulated insulin secreted (GSIS) increases.[1]

There are many negative effects for both the mother and baby exposed to GDM. GDM can lead to macrosomia (abnormally high birth weight babies based on increased infant adipose tissue), preterm birth, fetal malformations, neonate respiratory distress, neurodevelopment changes and obesity - the onset of which can occur during early childhood or may be delayed until puberty.[2]

There is a consistent relationship between the development of GDM and overweight/obesity (BMI>25kg/m2), standard western diet, specific genetic polymorphisms, advanced maternal age, excessive gestational weight (adipose tissue) gain, pre-pregnancy insulin resistance and PCOS.[1] Diets high in saturated fat, refined sugars, red meat and processed meat are especially associated with GDM.[1]

Many risk factors can be modified by addressing diet and lifestyle, and therefore these changes need to be employed pre-conception. Obesity, glucose management and insulin resistance should be addressed as early as possible to benefit both mother and baby.[3]

Fetal Hyperinsulinemia and Increased Ketone Body Concentrations

When a mother has GDM, the fetus responds to excessive amounts of glucose by producing more insulin. This alone can perpetuate excessive fetal growth, but it also alters the production of surfactant in the lungs, increasing the risk of respiratory distress syndrome.[2]

Pregnancy with or without GDM increases the risk of ketosis, but ketosis is more easily reached in pregnancy when fasting for longer durations, and/or in women who suffer from hyperemesis gravidarum.[4]

Ketone bodies such as acetoacetate, β-hydroxybutyrate and acetone occur as natural metabolic products from the breakdown of fatty acids in the liver. Levels of ketone bodies can increase in pregnancy from prolonged exercise, poor diet, and/or from following a ketogenic diet.[4]

When available glucose is insufficient for energy production, the body increases the breakdown of fat into fatty acids which can form ketone bodies. In some cases when excessive ketone bodies are produced, this can result in ketosis and ketonuria and eventually into diabetic ketoacidosis. This dangerous state results in systemic acidosis, electrolyte imbalance, circulatory, renal and central nervous system failure.[4]

Increased concentrations of ketones can have negative consequences on offspring even at the conception phase as it negatively affects embryonic brain development and affects the uptake of glucose by cardiomyocytes. Animal studies have shown that exposing mouse embryos to β-hydroxybutyric acid can lead to interference with development and abnormal neural tube closure.[4] Animals exposed to high levels of ketones during pregnancy also demonstrate malformations such as myocardial hypertrophy and impaired brain development compared to controls.[4]

In human studies high levels of ketone bodies are associated with fetal malformations such as cleft lip, cleft palate, spina bifida and digestive system malformations.[4]

Even after delivery there are lasting effects of GDM. After the umbilical cord is cut, the infant will have a dramatic drop in glucose which was previously flowing continuously from mother to placenta. But when the infant is still in a state of hyperinsulinemia, this can result in infant hypoglycaemia.

Treatment in Preconception and Pregnancy

Most important in the prevention of GDM and its consequences is to maintain proper glucose and insulin regulation as early on as possible. This includes addressing overweight/obese status and high body adipose tissue percentage and is done using diet and lifestyle interventions.

GDM and obesity are associated with both increased pro-inflammatory cytokine concentrations as well as increased ROS production.[1,3] Certain pro-inflammatory cytokines can also impair insulin signalling and inhibit beta-cell release of insulin.[2] Therefore specific nutrient interventions play a role in both the management of glucose and insulin, but also address the associated concerns in these cases, including inflammatory status and increased oxidative stress.

Dietary

Dietary recommendations are very similar to the Mediterranean Diet as they contain higher amounts of mono- and poly-unsaturated fatty acids (MUFAs and PUFAs) and focus on whole, minimally processed foods which contribute antioxidant and anti-inflammatory activities associated with obesity and insulin resistance, as well as increased fiber for better glucose management and digestive elimination.

Natural strategies

1. Eat three small to moderate sized meals and two to three snacks that are balanced with whole grain carbohydrates, protein and unsaturated fats.
2. Breakfasts should be lower in carbohydrates (<30g) compared to other meals of the day.
3. Meals in general should consist of low-glycemic index foods.
4. Dietary carbohydrates should be paired with lean protein and/or healthy fats such as MUFAs and PUFAs to decrease postprandial glycemic load.
5. Avoid consumption of foods with pro-inflammatory activities including red or processed meat, processed foods, refined sugars and alcohol.
6. Meanwhile, fruits, vegetables, and anti-inflammatory foods should be increased.

Flavonoids

Flavonoids such as quercetin, procyanidins, catechins, proanthocyanidins, and stilbenes such as resveratrol have anti-inflammatory and antioxidant properties. Resveratrol in particular has been shown to decrease circulating leptin and therefore improve leptin sensitivity in obesity.[3]

Polyphenols found in olives and olive leaves have similar antioxidant and anti-inflammatory properties, but they also have hypoglycaemic effects and can down-regulate leptin mRNA levels in epididymal adipose tissue, thereby protecting against obesity- and diabetes-associated oxidative stress.[3]

Grape seed extract is another substance that has been shown to improve oxidative status in obesity.[3]

Omega 3 Fatty Acids

Omega 3 fatty acids are known for their anti-inflammatory actions but they also have effects on transcription factors involved in inflammation. Consuming PUFAs and supplementing with Omega 3 fatty acids during pregnancy can help reduce inflammation, prevent increased pro inflammatory cytokine release (including leptin) and overall reduces the risk of complications during pregnancy.[3]

Probiotics

The composition of the gut microbiome can directly affect systemic inflammation and metabolism. Low fiber diets in particular favour poorer microbiome compositions and more species associated with T2DM and inflammation.[3] Therefore supplementation with probiotics may help to restore beneficial gut bacteria function.

In a meta-analysis and systematic review, women with GDM given a combination probiotic supplement for six to eight weeks had significantly decreased fasting blood glucose and HOMA-IR scores.[5] Strain combinations included: *L. acidophilus*, *L. casei*, and *B. Bifidum*; *L. Acidophilus LA-5*, *Bifidobacterium BB-12*, *S. thermophilus* STY-31; and VSL#3 which includes *S. thermophilus*, *B. Breve*, *B. longum*, *B infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei* and *L. delbrueckii* subs. Bulgariscus.

Exercise

Exercise can improve both fasting and postprandial glucose levels in GDM. It's recommended for women with GDM to participate in 30 minutes of moderate-intensity aerobic exercise five to six days a week (or a minimum of 150 minutes per week).[2] Additionally, going for a moderate-intensity walk after a meal can improve postprandial glucose in GDM.[2]

Insulin Therapy

If diet and exercise alone fail to control glucose regulation, pharmaceutical interventions are often used, starting with insulin therapy. Insulin is the preferred treatment over other glucose-lowering drugs as it doesn't significantly cross the placenta compared to drugs such as glyburide and metformin. When transferred to the placenta, these drugs can increase the incidence of neonatal hypoglycemia and macrosomia.[2] Additionally, up to 50% of women with GDM who are given metformin will still require the addition of insulin to manage blood glucose properly.[2]

Insulin is also efficacious in removing ketone bodies by inhibiting lipolysis and the production of ketones in the liver, and increasing tissue use of ketone bodies.[2]

Although the development of GDM can be an isolated incidence of hyperglycemia, it's short-term and long-term effects warrant treatment and prevention as early as possible. Major risk factors such as pre-conception obesity, insulin resistance and poor diet can be addressed, however when dietary and lifestyle interventions are inadequate to regulate glucose levels in pregnancy, insulin therapy is the treatment of choice.

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