
Nutrition, Diabetes, and Cancer

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Abstract

The progression of inflammatory signaling to the metabolomic complications of diabetes usually occurs slowly and creates cellular shifts in biochemistry. Individual nutrigenomics, chronic stress, environmental intoxication (such as exposure to chemical preservatives or heavy metals), poor dietary choices, gut health, sleep patterns, and other factors can trigger inflammation signaling and as a consequence alter blood sugar homeostasis, leading to insulin resistance and accumulation of visceral fat. Likewise, repeated dietary insult leads to blood glucose alterations, insulin resistance, and increase in visceral fat deposition and thus enhancing inflammatory pathways that trigger the downward spiral to chronic illness that eventually may lead to type 2 diabetes and its complications. A movement toward intracellular fermentative metabolism creates intracellular acidity and heightened risk for other chronic disease, including cancer. Proper nutrition and the use of targeted nutritional supplements can have a significant impact on slowing the progression of diabetes as well as the progression of cellular shifts toward the Warburg effect. Diet and dietary supplements targeted at glycemic regulation based on individual needs, including those improving insulin resistance, immunity, inflammatory responses, gut health, and chronic stress, are important in decreasing the metabolic spiral to type 2 diabetes and eventually cancer.

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In all likelihood, the metabolic progression to cancer in a patient with type 2 diabetes is promoted by multiple vectors of inflammation. In the most basic construct, the physiology of those individuals with type 2 diabetes is more efficient at creating a cascade of inflammatory signaling that leads them to a complex milieu of comorbid symptoms, conditions, and pathologies including cancer. This is supported by the fact that in some type 2 diabetics, chronic conditions of autoimmunity and/or immune bystander effect are present.

What triggers inflammatory chemistry in the person with type 2 diabetes? Does diabetes trigger inflammatory chemistry or does the combination of genetics, environmental factors, and individual choices ignite the fires of inflammation, with diabetes simply being a more complete expression of the longstanding organic disruptions in metabolism? Several interesting developments are leading to a new level of understanding the dynamic aspects of diabetic chemistry. Individual nutrigenomic predisposition

and expression, chronic stress, environmental intoxication, poor dietary choices, sleep patterns, use of drug therapy, and poor or absent exercise habits among other factors can trigger inflammation signaling and as a consequence blood sugar and insulin homeostasis is altered. However, the converse can be true, where repeated dietary insults, such as excessive intake of refined carbohydrates, sugars, ω -6 oils, and partially hydrogenated oils, lead to blood glucose alterations, insulin resistance and visceral fat deposition, thus enhancing cytokines and other inflammatory pathways. The most intriguing model, and one that is the most diverse, is that the expression of symptoms and the complications of diabetes is being influenced by individual choices and environmental exposures that start from gestation and continue throughout one's lifetime. These choices and influences result in biochemical changes that lead individuals to illnesses, such as type 2 diabetes and cancer, and the resulting health consequences.

There is a growing realization that the effects of nutrition on health and diseases cannot be understood without a profound understanding of how nutrients work at the molecular level. The completion of several large genome projects early in this century has markedly altered the research agenda by drawing attention to the importance of genes in human nutrition, and has provided a wealth of new genetic information to be explored. There has been a growing recognition that micro- and macronutrients can be potent dietary signals that influence the genetic expressions of cells and play an important role in homeostasis. The fact that our diseases are actually less about our genes and more about the influences on the genes was one of the great surprises of the human genome project. Researchers have increasingly begun to recognize that genetic predisposition, environmental, and lifestyle choices are both important contributors to the main causes of mortality that are linked to diet, such as cardiovascular disease, type 2 diabetes, and cancer [1].

To date, the majority of research into disease progression in most conditions has not linked the multiple vectors or triggers of these disease progressions. Similarly, cancer may arise within the diabetic from a number of circumstances; however with cancer we know that inflammation is a primary component, which can both initiate and promote cancerous cell growth and division. In examining type 2 diabetes, there are multiple factors that assemble to create tremendous levels of inflammatory signaling – chronic imbalances in blood sugar, increases insulin growth factor-1, increases in cellular anaerobic metabolism, and alterations in immune vigilance occur. In this chapter we will discuss how nutritional support cannot only modulate those with phenotypes predisposed to biochemical imbalances that lead to type 2 diabetes and eventually cancer, but that can also redirect pathogenesis back to homeostatic function.

The Cascade of Inflammatory Signaling

Inflammation is the physiological response to biological, mechanical, or chemical stressors. In people with diabetes, increased risk of cardiovascular disease, kidney disease,

peripheral vascular disease, autoimmune disorders, obesity, and cancer as well as neurological disorders like Alzheimer's and Parkinson's disease are triggered at least in part from the inflammatory signaling that is chronically upregulated. The inflammatory state is closely related to obesity and insulin resistance, yet other vectors may lead to chronic inflammation, including chronic stress, gut-brain miscommunication, neuroendocrine-immune shifts, dietary choices (including artificial sweeteners), exercise frequency, drug use (prescription, non-prescription, and recreational), and environmental stressors (such as heavy metals and chemical preservatives in foods). Population-based studies have reported strong relationship between inflammatory markers and metabolic disturbances, obesity, atherosclerosis, and inflammation has been considered a 'common thread' between these conditions and type 2 diabetes [2, 3].

Cells are regularly exposed to stress, which mainly consists of inflammatory stress and metabolic stress. Inflammatory stress is exerted by cytokines that are released in large quantities by immune cells in response to invading microorganisms or other pathophysiological signals. The main cytokines involved in the pathogenesis of type 2 diabetes are interleukin (IL)-1 β , tumor necrosis factor- α (TNF- α), NF- κ B, and IL-6, IL-18 and adipokines, which are considered as the main regulators of inflammation; leptin, more recently introduced, and several others, such as monocyte chemoattractant protein-1, suppressors of cytokine signaling proteins, resistin, angiotensinogen, and aromatase also are present with deleterious effects in diabetic pathogenesis. The characterization of these molecules helps to identify targeted diabetes treatment beyond the conventional interventions (lifestyle changes and pharmaceutical agents), and move toward the controlling of specific molecular pathways to greatly reduce inflammation.

Chronic stress has negative effects on inflammatory signaling, serum glucose, serum cortisol levels, serum thyroid hormone levels, and body weight. Chronic stress, through hyperexcitation of the hypothalamic-pituitary-adrenal axis and microglial cell activation of the immune system, directly affects fat storage and weight gain in stressed individuals. Elevated serum cortisol is associated with diabetes and its complications as well as being a known initiator of insulin resistance. This could be the clue to why so many type 2 diabetics have evidence of autoimmunity. Elevations of cortisol and depletion of dehydroepiandrosterone (DHEA) pools are associated with memory loss and atrophy of the hippocampus combined with the known defect in glucose utilization in Alzheimer's disease could offer an important insight into neurodegeneration found in individuals with type 2 diabetes.

Oxidative stress in the diabetic, due to depleted levels of nitric oxide, can increase the pathways that lead to inflammatory signaling by upregulation of peroxyl nitrite free radicals. These processes accelerate pathological changes in endothelial tissues. Another vector associated with inflammatory signaling is obstructive sleep apnea syndrome. Sleep apnea produces more inflammatory signaling, which leads to more accumulation of visceral fat – cycles of the downward metabolic spiral. Surgical removal of visceral fat can reverse sleep apnea in a substantial number of patients,

demonstrating the role played by adipokines in this disorder. Even restricted sleep can induce insulin resistance and progression toward type 2 diabetes. Alterations in leptin, ghrelin, growth hormone, and body mass index have been found with sleep deprivation (approx. 4–5 h per night).

The quality of an individual's adaptive immune system can be evaluated through the balance of inflammatory cytokines it is producing. A healthy immune system is both balanced and dynamic – it should be balanced between Th1 and Th2 activity, switching back and forth between the two as needed. A failure of the Th1 arm of the immune system and an overactive Th2 arm is implicated in a wide variety of chronic illnesses, including autoimmune conditions, acquired immunodeficiency syndrome, chronic fatigue syndrome, candidiasis, allergies, multiple chemical sensitivities, blood sugar regulatory problems (including diabetes), and cancer. Likewise, overexpression of Th1- and cell-specific immunity can occur, leading to a subset of autoimmune disturbances.

Exposure to environmental chemicals, such as pesticides and heavy metals, may also disrupt the neuroendocrine-immune system, leading to upregulation of inflammatory signaling. Endocrine disruptors include dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, and plasticizers such as phthalates and bisphenol A (BPA). Endocrine disruptors may be found in many everyday products – including plastic bottles, metal food cans, detergents, flame retardants, food, toys, cosmetics, and pesticides and have been linked to insulin resistance. Exposure to BPA has been found to cause biological effects, and its mode of action appears to mimic that of the female hormone, estrogen. Studies have found that BPA does increase the risk of developing cancer [4]. Phthalates are another compound commonly found in cosmetics and personal care items such as shampoos. Phthalates are reported to also affect neuroendocrine-immune balance. A recent study reported that approximately 75% of the US population has measurable levels of phthalates in their bodies [5]. Chronic heavy metal exposure, including lead, mercury, aluminum, and cadmium, may lead to the upregulation of inflammatory signaling pathways. Mercury, commonly found in dental amalgam fillings, can cause microglial activation and lead to localized flora disturbances and immune activation in the gut. Mercury, commonly found in dental amalgam fillings, may leak into the gut, causing imbalances in the natural gut flora. This may lead to an increase in inflammatory signaling and neuroendocrine-immune imbalances. Similarly, chronic lead exposure can damage the neuroendocrine-immune system, leading to inflammatory signaling.

A disturbed gastrointestinal terrain can serve as an unseen 'motor' of inflammation, leading to a cycle of inflammatory signaling. There is a complex balance that exists between the indigenous flora and the adjacent immune system of the gut mucosa and liver. Evidence supports that impairment of normal gut barrier function, through environmental stressors (such as heavy metals and chemical preservatives), poor dietary habits (such as high in refined sugars and fructose), food allergies, various drug therapies, and chronic stress, results in the loss of the counterinflammatory flora balance and

leads to the expression of uncontrolled inflammation [6]. Food and bacterial proteins, such as dairy lectins, can act together to damage the gut and allow toxic protein complexes to get through the tight junction glycoprotein and toll receptor network that is normally supposed to be resistant to such a breach – termed ‘leaky gut’. When there is an imbalance in the natural flora of the gut, bacterial lipopolysaccharide released by increasing populations of pathogenic bacteria, such as *Escherichia coli* and *Candida* sp., causing oxidation that leads to gut ischemia. Downregulation of immunologic activation is an active, energy-requiring process, therefore gut ischemia may impair this normal anti-inflammatory function, and promote a state of systemic inflammation.

Symptoms such as gas and bloating, abdominal pain and diarrhea, can occur with imbalances in gut flora. As these imbalances continue they can progress to more profound symptoms such as headaches, nerve pain, skin rashes, and joint pain. The disorders that result or could be aggravated by an unhealthy gut include are celiac disease, Crohn’s disease and irritable bowel syndrome, multiple sclerosis, migraines, attention deficit, autism, depression, eczema, acne, rheumatoid arthritis, fibromyalgia, diabetes, chronic fatigue, and others. Many people are being diagnosed with multiple conditions, including type 2 diabetes, without the obvious connection of the overload in inflammatory signaling of the gut with certain foods that may be a driving force in the disease process in many of these illnesses.

Insulin Resistance and Cancer

The cycle of inflammatory chemistry that is activated through chronic stress and cortisol release, leaky gut, environmental stressors (such as chemical preservatives, plastics, and heavy metals), obesity, thyroid dysfunction, and immune system imbalances causes chronic imbalances in blood glucose homeostasis, eventually lead to type 2 diabetes. This progression to diabetes and its metabolic consequences has also been linked in clinical studies with the development of cancer [7, 8]. Researchers have known for decades that cancer cells consume more glucose than normal cells. All cells use both oxidative phosphorylation and glycolysis pathways for energy (ATP) but rely overwhelmingly on oxidative phosphorylation, switching to glycolysis at times of oxygen deprivation. Cancer cells, however, have been reported to exhibit increased glycolysis due in part to mitochondrial respiration injury and hypoxia. A shift in energy production from oxidative phosphorylation to glycolysis – the so-called ‘Warburg effect’ – is a fundamental property of cancer cells, not just a by-product of the cell’s transformation into cancer. Warburg [9] reported that many tumors relied on glycolysis even in the presence of oxygen. Certain nutrients are now focused on decreasing this intracellular shift to glycolysis (the Warburg effect) through improving insulin regulation and decreasing cellular oxidation. Elevated intra- and extracellular glucose concentrations also result in oxidative stress, leading to an increase in inflammatory signaling.

Studies have also reported that high levels of insulin decrease the production of insulin-like growth factor-1 (IGF-1) binding proteins and hence increase levels of free IGF-1 [10]. It is well established that bioactivity of free IGF-1 increases tumor turnover rate and can lead to various types of cancer.

Drug-Nutrient Depletion

Many of the side effects from drug therapies may not be directly due to the drug itself, but rather the result of nutritional deficiencies caused by the drug when taken over time. Drugs given to treat conditions such as type 2 diabetes or cardiovascular disease, such as diuretics for hypertension, statins for hypercholesterolemia, or metformin for blood sugar regulation, may actually be causing a cascade of biochemical changes in the body due to drug/nutrient depletion, further complicating the metabolomic chemistry of the individual. These biochemical changes can imbalance the homeostatic body system, leading to the cascade of inflammatory signaling.

Sulfonylurea medications, including glipizide (Glucotrol®), tolazamide (Tolinase®), chlorpropamide (Diabinese®), and glyburide (Diabeta®, Micronase®) have been reported in the literature to deplete coenzyme Q10 from the body [11]. A deficiency of CoQ10 may be associated with long-term conditions including heart disease and high blood pressure. Symptoms of deficiency include gingivitis, muscle weakness, reduction in neuroprotective functions and mitochondrial energetics, decreased insulin production, memory loss, loss in stamina, and weakened immune function.

Biguanide medications, including metformin (Glucophage®) have been reported to deplete folic acid and vitamin B₁₂ from the body [12]. Studies indicate that long-term metformin therapy significantly decreases serum vitamin B₁₂ levels. Additional studies suggest that short-term treatment with metformin increases homocysteine levels, and supplementation with B vitamins or folic acid can moderate this response [13]. More specifically, serum folic acid levels have been reported to decrease 7% and vitamin B₁₂ levels decrease by 14% while using metformin therapy in type 2 diabetic individuals [14]. Homocysteine is implicated as a risk factor for development of cardiovascular disease, kidney disease, and Alzheimer's disease.

Nutrient Intervention

So what can be done for the individual that is metabolically spiraling toward type 2 diabetes and cancer? Today the molecular profile of the diabetic is becoming clearer, which leads us to an opportunity to target the various biomarkers through novel approaches. Replenishing nutrients that may be insufficient due to genetic variances or poor dietary choices is of utmost importance for an individual's health. Controlling inflammatory signaling by factors such as decreasing stress, controlling

visceral fat weight accumulation, improving sleep patterns, eating a proper diet, decreasing environmental stressors, balancing immunity, decreasing *Candida* overgrowth, balancing adrenal, thyroid and sex hormones, and exercising regularly can reduce and even reverse the metabolic spiral to a state of chronic blood sugar imbalances. Although the nutrigenomics and nutrigenetics of each individual can vary, this chapter has included some of the most common nutrients that have been reported to help decrease inflammatory signaling, decrease oxidation, balance neuroendocrine-immune signaling pathways, and help maintain blood sugar homeostasis and reduce the Warburg effect in cancer metabolism.

ω -3 Essential Fatty Acids

ω -3 fatty acids are a group of polyunsaturated fatty acids (including α -linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA)) that come from food sources or dietary supplements. Food sources include fish and fish oils (including salmon, rainbow trout, mackerel, krill, anchovy, and sardines), flaxseed oil, berries (such as lingonberry and black raspberry), walnuts, and wheat germ. However, ω -3 sources that are not from fish require conversion in the body and are therefore not a preferred source.

A high ω -6/ ω -3 ratio, as is found in today's Western diets, promotes the pathogenesis of many chronic diseases, including cardiovascular disease, diabetes, asthma, and possibly cancer. Increased dietary intake of linoleic acid leads to oxidation of low-density lipoprotein (LDL), platelet aggregation, and interferes with the incorporation of essential fatty acids (EFA) in cell membrane phospholipids. Both ω -6 and ω -3 fatty acids influence gene expression. ω -3 fatty acids have strong anti-inflammatory effects via the suppression of inflammatory cytokines IL-1, TNF- α , and IL-6. ω -6 fatty acids tend to be proinflammatory. Because inflammation is at the base of many chronic diseases, including coronary heart disease, imbalances in the ω -6/ ω -3 ratio plays an important role in the manifestation of disease, particularly in persons with genetic variation, as for example in individuals with genetic variants at the 5-lipoxygenase genes. Increased dietary arachidonic acid significantly enhances the apparent atherogenic effect of the genotype, whereas increased dietary intake of ω -3 fatty acids EPA and DHA blunts this effect. The diet-gene interaction further suggests that dietary ω -6 fatty acids promote, whereas marine ω -3 fatty acids EPA and DHA inhibit leukotriene-mediated inflammation that leads to atherosclerosis.

Carotenoids

Carotenoids are the pigments that give fruits and vegetables such as carrots, cantaloupe, sweet potato, and kale their vibrant orange, yellow, and green colors. β -Carotene,