MINI-REVIEW ARTICLE

A More Complete Treatment of Prediabetes (Metabolic Syndrome) and Diabetes 1 and 2 for Humans - A Minireview

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ABSTRACT

Recent research has indicated the different forms of diabetes are most likely caused by oxidative and nitrosative stresses. But prediabetes, diabetes 1 and 2 are treated with drugs that lower blood glucose or increase release of insulin directly or indirectly. Since increases in fasting blood glucose and decreases in the release, production or activity of insulin do cause various types of diabetic damage they decrease the action of peroxynitrite which is the basic cause of different types of diabetes. But the action from chronic inflammation is not being addressed and therefore damage continues despite a tight control of blood glucose. The missing piece in preventing chronic excessive peroxynitrite is to use nitration and oxidative targets in a sustained form so the body's tissues and vasculature are continuously maintained and protected. A listing of supplements is included so that readers can constantly protect themselves from the ravages of diabetes. Hopefully the list is complete enough to be added to prescribed diabetic regimens or can be used almost as a standalone treatment. People with type 2 diabetes which are about 90% of total diabetics should be able to use berberine instead of or in addition to metformin. But type 1 diabetics should use insulin and the combination of short and long acting insulin is usually quite effective.

Key words: Oxidative and nitrosative stresses, insulin, inosine, berberine hydrochloride, antioxidant supplements

INTRODUCTION

The scope of the multiple types of diabetes in the title would encompass approximately about 30% of the population of the United States which would be about 100 million people in the United States alone. We believe that it could be described as the mother of all diseases. The reality of this statement is that diabetes is often associated with hypertension, cancer, kidney damage, vascular damage, liver and eye diseases, heart diseases, and more recently diseases of the brain, for example, Alzheimer's disease, which has recently been called diabetes 3 (since there is a frequent association of the two diseases).

Different types of diabetes become chronic inflammatory diseases.

What kind of disease is prediabetes and the other types of diabetes? These diseases can be characterized as chronic inflammatory diseases. How do chronic inflammatory diseases occur? The DNA of inflammatory cells such s macrophages is wrapped around structures that appear like spools (actually composed of histone proteins). When acute inflammation begins, these proteins become acetylated by the enzyme histone acetyltransferase. This eliminates the positive charge of the histones, while the negative DNA becomes loosened from the histones which allows for transcription of the inflammatory genes. This causes the production of inflammatory gene products and products of oxidative and nitrosative (O/N) stress. In particular, macrophages become activated and they generate a highly toxic peroxide called peroxynitrite which can react with carbon dioxide to produce an even more reactive product called peroxynitrite carbonate

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(which is a strong nitrating compound). If this inflammatory condition continues for weeks to months and to years and beyond, excessive peroxynitrite is produced by an increased number of macrophages which damage the off switch for acute inflammation called histone deacetylase 2. This creates continuous signaling for chronic inflammation, namely peroxynitrite or its carbonate. When acute inflammatory type 1 diabetes begins, T lymphocytes become stimulated which generate interleukins and chemokines which activate continuous inflammatory chemistry in macrophages mentioned above which is toxic to the insulin-producing and releasing beta cells in the pancreas. The excessive peroxynitrite kills the beta cells, so insulin is not produced. Alpha cells replace the dead beta cells and begin to produce excessive glucagon which when released increases glucose in the blood. Without insulin's ability to allow glucose to enter certain organs and tissues such as muscle and fat, the excessive glucose in the blood becomes very toxic to the tissues and blood vessels. In type 1 diabetes, insulin must be given to maintain life and healthy blood glucose levels. The insulin that is often given is a combination of short- and long-acting glucose which is fairly effective at maintaining correct glucose levels. However, nothing is given to control the O/N stresses, which is toxic to mitochondria; the cellular particle responsible for correct glucose and fat metabolism type 2 diabetes is the vast majority of actual diabetes (90–95%) and it is associated with insulin resistance. This means that insulin is not as effective as before the disease occurs. The key question to ask regarding what causes diabetes was originally addressed by Dr. Theodore Banting, the discoverer of insulin. In his 1920's Nobel address he said," Insulin is not the cure for diabetes." Since insulin helps control glucose levels in blood and tissues, a logical inference from this idea is that glucose is not totally responsible for diabetes since it is controlled by insulin. In addition, many children eat considerable amounts of candy and sugary sweets, so if sugars which contain glucose do not cause diabetes, how is glucose involved with the disease? Certainly, diabetes is involved with metabolic pathways that control carbohydrate and lipid metabolism. Essentially, all of the many drugs used to treat either type 1 or type 2 diabetes basically either control the metabolism of carbohydrates or lipids such as cholesterol and triglycerides or the release or action of insulin and some of them control both. The problem is that none of these antidiabetic substances actually cure the disease or completely prevent the damage from the disease. If diabetes is actually caused by O/N stresses, which we[1-5] and others have demonstrated[6-7], what is done to control O/N stresses? The many type 2 antidiabetic drugs are partially effective to control symptoms but not the total disease. If we control glucose and insulin what does that accomplish? It partially prevents some of the damage because excessive blood glucose and insufficient insulin actually increase the O/N stresses, and therefore, the drugs for type 1 and particularly type 2 diabetes lower some of the damage from O/N stresses but not all of it. Often, people with type 2 diabetes eventually develop such resistance to insulin that only very large doses of insulin can help them. We have shown that, if you nitrate insulin with peroxynitrite, it can nitrate some of the four key tyrosines of the insulin molecule and the receptor for insulin also has tyrosines in the structure of its active site which can be easily nitrated by peroxynitrite. These chemical actions of peroxynitrite cause the insulin to be less effective in lowering blood levels of glucose. Unquestionably, the drug which is most often used to control diabetes 2 is metformin, originally produced from plants. It is thought to control AMP kinase which is called a master-switch which controls carbohydrate and lipid metabolism in the mitochondria. The drug is available in sustained release form which is even more effective. However, metformin is often toxic to some people since it causes kidney damage to more elderly diabetic patients. Some people experience stomach problems from this drug. Over the past 5–6 years, another natural plant supplement called berberine has been often used to treat diabetes 2, in many countries including the USA. Berberine in the form of a salt has been demonstrated to activate or stimulate AMP kinase similar to metformin and can even be given with metformin, and the combination controls blood glucose extremely well. Berberine lowers cholesterol and triglycerides equally as well as metformin but without the known toxicity and expense of metformin. The usual dose of berberine hydrochloride is 400 mg taken every 8 h. Many people who had difficulty controlling their blood glucose properly with standard type 2 antidiabetic drugs found that berberine-HCl treatment worked very well without noticeable side effects. It has been used effectively in many thousands of people around the world. At present, we are working with a company in Portland, Oregon, called Endurance Products to produce an enhanced or sustained released products which are to be taken only once or twice per day. This will allow the blood levels of this supplement to be better absorbed and maintained for longer periods of time. In addition, we have developed a variety of sustained released supplements that control excessive peroxynitrite levels. This peroxide targets DNA, RNA, proteins, and lipids of cells causing O/N damage. These key cellular components can be protected using sustained-release antioxidants such as Vitamin C, tocotrienols (form of plant-based Vitamin E), and omega 3 fatty acids from krill oil and flaxseed oil. Coenzyme Q10 which is part of the electron transport and metabolism is important for healthy mitochondria. Another really excellent target of nitration is the supplement cannabidiol (CBD) from hemp oil. The advantages of these combinational treatments are to lessen O/N stress as well as to control carbohydrate and lipid metabolism. This will produce a more complete and effective treatment for the various forms of diabetes and prediabetes in humans. All of the substances in this narrative have been used in humans for years and have been shown to be safe and effective and less toxic than currently used antidiabetic drugs. Most of these effective supplements are natural substances from plants and have been used in humans

for years. Many of the supplements currently available which are used as antioxidants are not in the most utilizable form. They have short half-lives in the body. Our approach is to use sustained release forms of supplements which are helpful to maintain constant blood and tissue levels for maximum effectiveness. These supplements must be consistently maintained to provide continuous protection since chronic diseases generally do not relent.

Treatment with various sustained release supplements including berberine hydrochloride taken 1–2 times per day - 600 mg capsules. The berberine is 98% pure and prepared to pharmaceutical grade standards (USA).

List of daily supplements for the treatment of prediabetes and diabetes 1 and 2

- Sustained release inosine* - in split doses taken orally - 3 g/day. This generates urate in the body which is a target for peroxynitrite which it destroys.
- Sustained release niacinamide* in split doses - 1 g/day. This is the precursor for the cofactor nicotinamide adenine dinucleotide used in metabolism studies to prevent or slow type 1 diabetes.
- Sustained release Vitamin C* - in split doses taken orally - 4 g/day - destroys peroxynitrite.
- Tocotrienols - taken orally - peroxynitriite target
- Flaxseed oil* - omega 3 fatty acids - peroxynitrite target - 1 capsule/day taken orally.
- Krill oil* capsule - omega 3 fatty acids - peroxynitrite targets - 1 capsule/day taken orally.
- Sustained release multivitamin* without iron taken orally twice/day in split doses.
- Curcumin-black pepper combination - 1 capsule/day taken orally antioxidant peroxynitrite target.
- Vitamin D3 taken orally 3000 IU/day.
- CBD taken orally twice/day 100 mg per split dose-peroxynitrite target.
- PQQ - natural quinone - taken twice orally per day - 20mg/day – stimulates production of mitochondria
- Coenzyme Q10 - a key ingredient for electron transport of mitochondria 100 mg/day - taken orally.
- Magnesium chloride - 400 mg/day - taken orally.
- Calcium carbonate 1 gram/day
- Dehydroepiandrosterone - 50 mg/day - taken orally.
- Berberine hydrochloride sustained release 600 mg –given twice per day orally.
- If a person has type 1 diabetes - insulin should be used to control blood sugar levels. Insulin is available in many different forms. However, often, a combined insulin product is used which utilizes both short-and long-acting insulins together which generally gives better glucose control than any single product utilizing a single insulin type.
- The asterisk = *indicates that the product is available from Endurance Products - suburb of Portland, Oregon, or from the website = enduranceproducts.com.

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