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Short Commentary Open Access

New Concepts in Prevention and Treatment of Diabetes 1 and 2

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Introduction

Almost without question diabetes is the queen mother of all diseases. When active insulin was discovered in the 1920's by Banting and Best (B&B) from Canada it almost appeared that a complete cure for diabetes was soon to follow. In his Nobel Prize acceptance speech, Frederick Banting (1925-1) stated clearly that insulin was not the cure for diabetes [1]. Years later, the Queen of England, at the town active insulin was first discovered, lit a torch in Canada which she called the Flame of Hope which will remain lit until a cure is found. For the first time the flame is beginning to flicker and grow dimmer.

The fundamental problem with all chronic diseases is that science has not clearly explained how chronic diseases operate and this is why we have not until recently-began to understand how to correct or prevent the damage caused by diabetes and other chronic diseases.

Almost all chronic diseases arise first as an acute inflammatory response and later as a chronic inflammatory response which becomes essentially untreatable. These mechanisms of acute inflammation have been beautifully explained by Peter Barnes [2]. The DNA of inflammatory cells is coated with histones so the DNA is quiescent. But, when inflammation occurs, the DNA transcription factor nuclear factor kappa b becomes activated and stimulates histone acetyl transferase (HAT) which acetylates amino groups on the histones which changes the charge association between the DNA and the histones covering the inflammatory genes. Then these inflammatory genes are free to be activated- therefore stimulating production of larger amounts of inflammatory proteins and consequently the products of acute then eventually chronic inflammation.

The best treatment for acute inflammation is the timely use of anti-inflammatory steroids. These steroids activate histone deacetylase 2 (HDAC-2) which snips off the acetate groups from the acetylated histones thus restoring the charge difference of histones and DNA and the inflammatory genes are covered again by the histones and inflammation is stopped.

It is also well known that chronic use of anti-inflammatory steroids causes type 2 diabetes because they inhibit both the release of insulin and the induction of nitric oxide synthase 2 which could produce a deficiency of nitric oxide and concomitant hypertension. However, if steroids were used early in type 1 or type 2 diabetes it is likely they could prevent these diseases. The problem with treating type 1 diabetes with steroids early in the disease state is there is presently no recognized method for detecting diabetes 1 in an early stage.

Step 1: Acute Inflammation is turned on by acetylation of histones and turned off by deacetylation of histones stimulated by steroids. In addition- in acute inflammation-nitric oxide synthase which produces nitric oxide from L-arginine and oxygen which by reacting with available superoxide which produces relatively small amounts of peroxynitrite (OONO-). The small amounts of peroxynitrite do not affect the epigenetic inflammatory mechanism to a meaningful extent in this acute, early stage of inflammation.

Step 2: Chronic Inflammation is activated by similar mechanisms and produces similar products but in higher amounts. In particular, after weeks of acute inflammation which eventually turns chronic that causes the production of excessively large amounts of peroxynitrite (OONO-). Excessive peroxynitrite nitrates the active site tyrosines in HDAC-2 which prevents HDAC-2 from causing deacetylation of histones thus preventing steroid action. Chronic inflammation is resistant to the anti-inflammatory action of steroids.

Therefore, chronic inflammation becomes almost untreatable, even though use of steroidal anti-inflammatory drugs is the gold standard of care for acute inflammation. Diabetes is first an acute and then a chronic inflammatory disease regardless of whether it is type 1 or 2. The overriding idea regarding the cause of diabetes is uncontrolled blood sugar which causes vascular damage. Certainly this is important but treating with insulin for type 1 or 2 or using various drugs to control insulin resistance is helpful but not completely successful in combatting the disease. Why is this case?

It is because the real cause of diabetes in the general sense is oxidative stress and even more directly to the point it is mostly nitrosative or nitrative stress which really creates the damage linked to the disease [3].

Therefore treatment to control sugar to normal levels probably decreases oxidative and nitrosative stress somewhat, but the underying disease continues regardless of the quality of blood glucose control.

Furthermore, recent data suggests that when beta cells of the pancreas- which make and release insulin die, they are replaced with alpha cells which produce glucagon which raises blood sugar. But even more recently, amylin, and glucagon–like peptide-1 have become an important portion of glucose regulation [4]. Therefore, the rise in blood sugar after the demise of beta cells in type 1 diabetes is a combination of multiple factors besides insulin and all are important in glucose regulation. But if nitrosative stress continues, even if glucose is well controlled, so does diabetes and its damage. What is nitrosative or nitrative stress? It is caused by excessive production of nitric oxide-containing peroxides/free radical compounds which cause damage by nitration, nitrosation and nitrosylation.

The main chemical which produces these post transcriptional modifications is called peroxynitrite which is the anion of peroxynitrous acid (HOONO) or OONO-. This compound is produced by inflammatory cells mostly macrophages (M) although some occurs in neutrophils (N) (Figure 1).

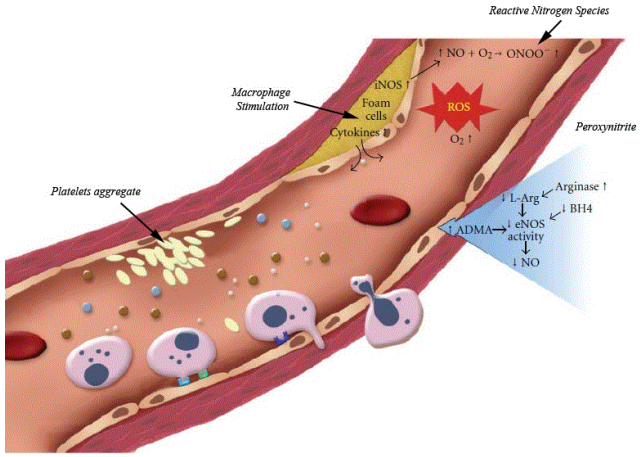

Figure 1: Vascular inflamation associated with diabetes.

When M and N cells become activated via the process of inflammation they can produce greatly increased amounts of peroxynitrite because the nitric oxide synthase 2 (NOS^{-2}) is highly inducible by inflammatory stimuli. This causes the reaction of L-arginine and oxygen to produce large amounts of the gas nitric oxide. In addition, these cells contain an NADPH oxidase oxidase complex in their membranes which converts oxygen into superoxide ($.O^{2-}$). When the nitric oxide and superoxide come together at diffusional speed (10^{-9} second), they produce peroxynitrite which can react by itself or as a derivative of itself with a variety of chemicals like phenols or double bonded molecules to cause nitration of these molecules or can react with sulfhydryl compounds to produce SNO-compounds. via nitrosylation. The third reaction of peroxynitrite is with amines which convert the NH_2 to N-N=O. and this is termed nitrosation.

What causes nitrosative stress in the body? The answer is related to the continual production of excessive production of nitric oxide and superoxide producing peroxynitrite (OONO-) and the deficiency of anti-nitrating compounds or nitration targets. The peroxynitrite can go on to react with carbon dioxide and produce a new carbon dioxide-peroxynitrite derivative and/or other nitrogen oxides which can cause excessive nitration of certain amino acids like tyrosine and tryptophan. In addition, these nitrating compounds can attack DNA, RNA, proteins and lipids.

Since L-tyrosines occur in active sites of insulin, insulin receptors and insulin-like compounds and key enzymes, nitration, nitrosylation or nitrosation can destroy the action of insulin by partially creating insulin resistance. This may not be the only mechanism of insulin resistance but it is likely a significant portion of it. Even glucagon which raises blood sugar has two tyrosines and a tryptophan which may be nitrated.

I have nitrated human insulin using tetranitromethane or peroxynitrite and if two of the four tyrosines are nitrated, insulin loses 50% of its sugar lowering capacity in the blood when injected into a diabetic animal. Therefore, nitrosative stress can actually produce major damage to the sugar controlling mechanisms [5]. Furthermore, nitration from peroxynitrite or a derivative can create loss of control of blood sugar, it can also cause toxicity to mitochondria thus causing loss off energy production and death of many cells. A disease which affects the basic core of metabolism and sugar control and energy production is likely to produce a shortening of life regardless of quality control of glucose metabolism.

Mitochondria of beta cells of the pancreas are particularly susceptible to excessive peroxynitrite causing death of the mitochondria and consequently the beta cell with the loss of production, storage and release of insulin. By the use of substances which can control the production of nitric oxide or activity of peroxynitrite, like carboxy-PTIO or targets of nitration like acetaminophen and quercetin have been shown to prevent diabetes and cataracts in both a streptozotocin-diabetic 1 and 2 models in rats by [6]. Therefore, the logical conclusion is that excessive nitric oxide, via peroxynitrite or one of its derivatives actually causes diabetes owing to nitrosative stress has been documented in several of our manuscripts and many manuscripts of those of others [7-10].

One could argue that the model we chose for our work does not mimic chronic diabetes and that is correct. It is also true that the first step in a long journey can be an important one, if it is linked to the final destination. Let us look at the ancillary pathology associated with diabetes. Stavniichuck has clearly implicated peroxynitrite and protein nitration in pathogenesis of diabetic peripheral neuropathy [11]. They used the peroxynitrite decomposition catalyst Fe (III) tetramethymesitylporphyrin octasulfonate (FeTMPS- and/or epicatechin gallate treatment after 28 weeks of hyperglycemia. Correction of motor nerve conduction post hyperglycemia and nerve fiber density was seen with FeTMPS only. Therefore, peroxynitrite decomposition catalysts such as FeTMPS may provide new and effective treatments for neuropathy if they are not excessively toxic.

Johns et al have used two different peroxynitrite decomposition catalysts SR-110 (2016-11) and SR-135 (2015-12) to protect beta cells improving glucose homeostasis, restoring beta cell morphology and insulin tolerance in mice fed a high fat diet [12]. Salvemini in her recent review has linked opiate antinocioceptive tolerance to effects caused by peroxynitrite and demonstrated the inhibitory effects of peroxynitrite decomposition catalysts.

Certainly, chronic pain is associated with pathological damage caused by diabetes. Inhibition of diabetic pain is actually indicating the cause of the causative agent of diabetic damage. Liang et al. have clearly demonstrated that peroxynitrite-induced nitration of proteins is responsible for renal mitochondrial damage in diabetic rats. Peroxynitrite is clearly implicated in diabetes types 1 or 2 in studies done by our group Van Dyke and associates but in particular cataract opacity formation in lenses of animals and likely humans caused by diabetes is clearly preventable by blocking the denaturing action of peroxynitrite on the clear crystallin protein using nitration targets or peroxynitrite destroyers. Since cataract surgery is the most common major surgery in the United States and it is very common around the world, it becomes likely that a similar treatment to ours, may be clearly possible to prevent blindness in humans and animals such an idea should be more studied. Pacher and Szabo detailed the role of peroxynitrite in pathogenesis of cardiovascular complications of diabetes [13]. Pacher et al. and Szabo et al. in separate articles indicated peroxynitrite, and nitric oxide's role in health and disease pathology and therapeutics [14,15].

One of the key pathological problems associated with diabetes is hypertension which is a major portion of the vascular complications which are known to cause morbidity and mortality in the diabetic population.

Diabetic clinical trials associated with complications of these diseases indicate a persistence of benefit from early and consistent intensive control of blood glucose levels which is often called metabolic memory. Since the control of gene action is now recognized as epigenetic, it is more than likely a major player in metabolic memory. In a recent article in May 9th issue 2016 of the Proceedings of the National Academy of Science (USA) by Chen et al. their study of epigenetic profiling reveals an association between the persistence of DNA methylation (DNA-me) and metabolic memory in the DCCT/EDIC type 1 diabetes cohort.

These results demonstrate that the DNA-me difference during the diabetes control and complication trial (DCCT) persist at certain loci associated with glycemia for several years post excellent glucose control seen during the epidemiology of Diabetes Control and Complications Trial (DCCT) which supports an epigenetic concept for metabolic memory. If nitrosative stress is controlled early and continuously in a person with diabetes using-peroxynitrite targets and destroyers and if glycemic memory is controlled-the complications from diabetes and diabetes itself could be either prevented or controlled. In type 2 diabetes, which is often attributed to insulin insensitivity or resistance, one simple method to control the disease is to decrease a person's weight to a normal range as well as exercise a proper amount. In many cases, these measures alone will control blood sugar to normal levels. Other methods are to have one of the surgeries which would have excess fat removed [16] or the use of bands to limit the amount of food the stomach can contain at one time [17]. These surgeries or modifications can reverse diabetes almost overnight or within a few days. It is clear that the removal of fat stores- removes a source of inflammation which likely delimits the continuous production of peroxynitrite from macrophages which engulf fat and become foamy macrophages. This likely activates nf-kappa b and starts and continues the acetylation of histones from inflammatory genes which keeps peroxynitrite levels high contributing to diabetic damage [18]. Discuss the use of insulin to control and/or inhibit oxidative/nitrosative stress.

Diabetes is well known to promote premature and accelerated atherosclerosis. The overall risk for cardiovascular disease for people with diabetes increases 3-5 fold in men and 3-5 folds in women. Approximately 50-70% of all people with diabetes of all types die from cardiovascular diseases [19]. The relationship of diabetes and premature vascular disease is well known. Long term glycemic control is a predictor of micro- and macro-vascular complications [20]. Both major type of diabetes are associated with premature and accelerated atherosclerosis with uncontrolled glucose levels.

Oxidative and nitrosative (O/N) stresses were significantly higher in diabetic patients in both serum and macrophages. There is a decrease in blood antioxidants with the increase in O/N stresses. Antioxidants like n-acetyl cysteine supplements to produce more reduced glutathione, and use of increased amounts of vitamins C and E and consumption of pomegranate juice decreases O/N stresses from diabetes if given multiple times per day or using sustained release supplements will help alleviate loss of antioxidants in patients with diabetes.

But, there are abnormalities in lipid metabolism affecting oxidized LDL and decreases in HDL in diabetics indicating increases in an oxidizing environment in patients with diabetes [21]. The cholesterol pathway is upregulated in diabetes and cholesterol increases to unacceptable levels considered for good health [22]. Insulin creates an atmosphere of efficient glucose utilization and provides protection against excessive lipid peroxidation. Diabetes causes oxidative/nitrosative stresses which decrease insulin production and Glut 4-glucose transporter increased expression is partly responsible for glucose uptake in important cell types and causes beta cell apoptosis delimits the amount of insulin available to regulate sugar levels to decrease O/N stress [23].

There is compelling evidence that insulin promotes protective anti-oxidation, reduces cholesterol and decreases atherosclerosis as well as lipid peroxidation and O/N stress toxicities.

Endothelial Dysfunction Caused by Diabetes: Angiogenesis, Vascular Remodeling and Wound Healing

Kolluru et al. reviewed endothelial cell (EC) dysfunction in diabetes creating marked changes in angiogenesis, vascular remodeling and wound healing [24]. Endothelial cells- line the blood vessels like arteries, arterioles, veins etc. and they perform a variety of important functions but a most important function is the control of vasodilation via (NO) production. Vasoconstriction via (angiotensin 2) causes increased blood pressure. So the balance of sufficient nitric oxide for vasodilation and delimiting angiotensin 2 vasoconstriction are major entities in maintaining normal blood pressure.

Normal blood pressure is regulated with a balance of nitric oxide/angiotensin 2 production in these endothelial cells which line the blood vessels. When endothelial cells become dysfunctional, they produce insufficient .NO and excessive angiotensin 2 which creates vasoconstriction and hypertension. Kolluru presented a clear diagram displaying 6 major diabetic vascular disease pathologies and the mediators involved. These include the following: diabetic associated diseases (Figures 1 and 2). Diagram presented is a simplified version from Kolluru et al.:

- Retinopathy blindness, blindness via cataracts
- Nephropathy
- Peripheral artery disease
- Heart disease and stroke
- Erectile dysfunction
- Neuropathy

Hyperglycemia over time creates a variety of pathological affects upon blood vessels including the following:

Atherosclerotic plaques initiated uptake of low density lipoproteins (LDL) into endothelial cells. Macrophages in the blood take up cholesterol and other lipids to become foam cells which release inflammatory cytokines and chemokines and other inflammatory mediators. This increases the production of superoxide and nitric oxide generating excessive peroxynitrite and other reactive oxygen and nitrogen species. White cells like neutrophils and monocytes adhere to the endothelial cells (leukocyte adhesion) migrate through cracks in the blood vessels called endothelial cell junctions and migrate into the tissues causing inflammation and damage. Excessive glucose leads to decreased L-arginine and tetrahydrobiopterin causing insufficient nitric oxide and concomitant hypertension [24]. Over time, this scenario occuring in major blood vessels causes atherosclerosis, enhanced or excessive peroxynitrite, chronic inflammation, heart disease and stroke which is one of the likely bases of cancer and heart diseases- the number one and two causes of early death in the United States and elsewhere.

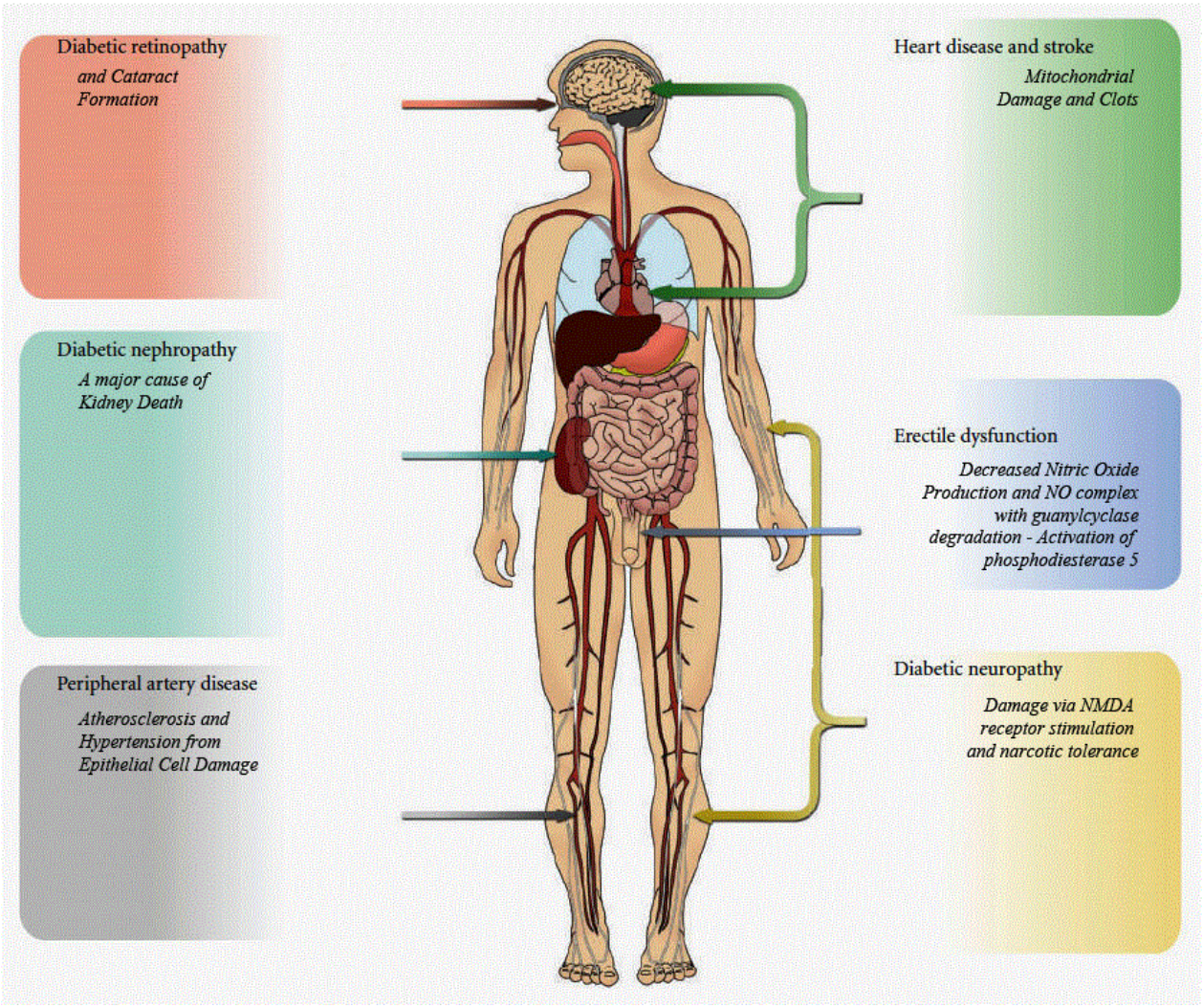

Figure 2: Pathology associated with diabetes.

Summary

The best treatment for both type1 and 2 diabetes is to discover these diseases early and prevent them being chronic. This can be accomplished by inhibiting excessive nitration which is responsible for both diseases. Type 1diabetes is more difficult to recognize because the damage to the insulin producing beta cells kills 80-90% of the insulin producing beta cells before blood sugar changes measurably. Type 2 diabetes can be generally controlled by weight loss and using a carbohydrate decreased diet.

In the case of type 1 diabetes if insulin becomes too low it must be replaced by one or two different insulins/day and many people have found in-dwelling insulin pumps effective. It has been found that a berberine hydrochloride capsule taken orally along with the insulin really is effective in controlling blood sugar.

In the case of type 2 diabetes there are many drugs which can be utilized to help control blood sugar, and metformin is probably the most utilized. But as a person ages, metformin can cause toxicity to the kidney. Berberine hydrochloride (400 milligrams) taken every eight hours is very helpful in controlling blood sugar and it is inexpensive without noticeable side effects, Literature suggests berberine hydrochloride actually stimulates production of insulin in the body but it likely works by multiple helpful mechanisms.

Another helpful treatment for all diabetics is to ingest 1-4 grams of sustained release L-arginine twice a day. This will produce extra nitric oxide which will control excessive production of peroxynitrite via distorting the nitric oxide superoxide ratio and produce more nitric oxide which is a major vasodilator in the body creating protection for blood vessels and organs like the kidney and liver and maintaining good health of the epithelial cells lining the blood vessels.

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