Diabetes Mellitus and Oxidative Stress in the Gastrointestinal Tract-Connecting the Dots

Subhankar Chakraborty M.D., Ph.D.

Diabetes mellitus is a global epidemic. In the United States alone, the National Diabetes Information Clearinghouse (NDCI), a joint service of the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Health estimates that 25.8 million people or about 8.3 percent of the population have the disease.[1] A worrisome statistic is that nearly 27% of these patients do not know that they have diabetes. While the detrimental effects of diabetes on the cardiovascular, neurologic and renal systems are well known, its effect on other organ systems including the gastrointestinal system are less well understood. Specifically, how diabetes induces inflammation of the intestinal mucosa and its effects on patients has been a source of intrigue. Population based studies suggest that patients with diabetes have certain gastrointestinal symptoms more commonly than healthy individuals. These include early satiety, bloating, post-prandial fullness, heartburn, dysphagia, anal blockage and urgency. In one study, fecal incontinence was the most common GI symptom in diabetics (adjusted odds ratio 2.74, 95% C.I. 1.4-5.4) followed by dysphagia (adjusted OR 2.71, 95% C.I. 1.7-4.4) and vomiting (adjusted OR 2.51, 95% C.I. 1.1-5.7).[2] Interestingly, the occurrence of certain symptoms showed a strong correlation with the degree of self-reported glycemic control in diabetics- e.g. nausea was the commonest symptom in those with poor glycemic control, followed by hard stools and fecal incontinence. Glycosylated hemoglobin (HbA1c) levels have been shown to independently predict the risk of occurrence of upper GI symptoms (gastroesophageal reflux and dyspepsia).[3] More recent studies have suggested that the relationship between diabetes and GI symptoms is not as straightforward as previously imagined. Quan and colleagues reported that the occurrence (loss or gain) of GI symptoms in diabetic patients was not significantly correlated with the tightness of glycemic control.[4] Instead, there was a positive association with depression.

Thus, gain of any GI symptoms (i.e. occurrence of a new symptom when at baseline there was none) was more common in diabetics than in non-diabetic controls (OR 2.62, 95% C.I. 1.02-6.7, p = 0.04).[5]

How are diet, inflammation and diabetes linked? Diabetes, particularly type 2 is associated with chronic low grade inflammation as evidenced by an increase in the level of inflammatory proteins like interleukins, tumor necrosis factor and lipopolysaccharide. Inflammatory cytokines in turn induce resistance to the hypoglycemic effects of insulin (termed insulin resistance). Data emerging in the last couple of years suggests that the microflora of the gut may have a pivotal role in weight gain, adiposity and possibly inflammation in diabetics. Studies in mice have revealed that feeding with a non-absorbable carbohydrate (i.e. dietary fiber) not only increased the number of beneficial *Bifidobacteria* in the gut but also decreased circulating levels of endotoxins induced by a high fat diet. Prebiotic fed mice also had higher sensitivity to insulin, gained less weight and had lesser accumulation of fat on a high fat diet compared to control mice. Prebiotics also decrease levels of pro-inflammatory cytokines like IL-1 (α,β) and IL-6.[6] Studies in human subjects have shown that an evening meal rich in non-digestible carbohydrates (e.g. barley kernels) reduces plasma glucose levels by nearly 29% in the morning, increases tissue uptake of glucose by 30% and associated with a lower post-prandial circulating IL-6 and TNF-α level.[7]

Diabetes is also associated with an increased expression of markers of oxidative stress. For instance patients with diabetes tend to have higher levels of lipid peroxidation than non-diabetics. The mechanisms underlying diabetes associated oxidative state include decrease in the body's reductive reserve (NADPH) due to increased conversion of glucose to sorbitol, formation of advanced glycation end products (AGEs) that activate intracellular ROS (through the cell surface RAGE receptors), and activation of the DAG-PKC (diacyl glycerol protein kinase C)

pathway that can among other things activates NADPH oxidase and thus enhance ROS production.[8]

Fillmann and co-workers in their article published in this issue of *Free Radicals and Antioxidants* have examined the efficacy of superoxide dismutase (SOD) in ameliorating the inflammatory changes in the bowel induced by streptozocin-mediated diabetes.[9] They noted that lipid peroxidation was increased by nearly 106% in streptozocin treated diabetic mice compared to control mice. Further, a 7-day once daily injection of copper-zinc superoxide dismutase (Cu/Zn SOD) produced a nearly 45% reduction in lipid peroxidation in the intestines of the diabetic mice. This reduction correlated with a significant decrease in histologic signs of inflammation in the intestines of the SOD treated mice. As noted above, GI symptoms including diarrhea were reported in previous studies of diabetics. Fillmann et al. also noted a significant reduction in anal sphincter pressure in diabetic mice compared to the non-diabetic controls.[9] Significantly, this reduction could be partly ameliorated by SOD treatment. The beneficial effect of SOD was further demonstrated by the observation that it significantly decreased DNA damage and showed no bone marrow toxicity both in non-diabetic and diabetic mice. However, there was no significant difference in its efficacy in diabetic vs. control mice.

SOD converts superoxide ions into hydrogen peroxide and water. Mammals possess three isoforms of SOD: SOD1 (Cu/Zn SOD), SOD2 (Mn SOD) and SOD3 (extracellular SOD). SOD1 or Cu/Zn SOD is a 32 kDa homodimer containing copper and zinc whose primary function is to reduce intracellular superoxide concentration. It is distributed in the cytoplasm, nucleus, peroxisomes and mitochondrial membrane.[10] The anti-lipid peroxidation effect of SOD observed by Fullmann and colleagues in their article is similar to that seen by Di Naso and workers in the liver of streptozocin induced diabetic rats.[10] Suys and co-workers observed that children with type 1 diabetes who had higher levels of Cu/Zn SOD had significantly higher flow-mediated dilation (FMD) in their carotid arteries.[11] FMD is a measure of normal endothelial function and a decrease in FMD secondary to deposition of foamy macrophages has been linked to atherosclerosis and narrowing of arteries in diabetes.

Thus, Cu/Zn SOD appears to be beneficial in countering the pro-oxidant effects of diabetes. It remains to be seen whether it can prevent or ameliorate other systemic complications of diabetes. Further, it will be interesting to investigate whether there are certain predictors of better response to Cu/Zn SOD to enable targeting of this potentially beneficial therapy to the most responsive patient cohorts.

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