Gut microflora for prevention and management of chronic metabolic diseases

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The major chronic metabolic diseases of national and global importance include obesity, Type II Diabetes Mellitus, cardiovascular disease, and cancer. According to the Center for Disease Control (CDC) and data from the National Health and Examination Survey (NHANES), approximately 33.8% of U.S. adults are obese and 17% of children and adolescents ages of 2 years to 19 years are also obese. Obesity arises as a consequence of how the body regulates energy intake (food intake), energy expenditure (exercise), and energy storage. This regulation of energy is known as "energy balance." Excessive energy intake and low energy expenditure, for example, can lead to a disproportionate energy balance and results in becoming overweight or obese. In addition, the American Diabetes Association reported 1.9 million new cases of diabetes diagnosed in people 20 years and older in 2010. In many cases, excessive eating and poor diet causes an excessive insulin release from the pancreas. Over-working the pancreas can result in β-cell exhaustion and decreased receptor function, leading to insulin resistance and thus, Type 2 Diabetes Mellitus. An emerging body of research is now directed toward the discovery of mechanisms and factors affecting the development of these metabolic diseases with growing global prevalence in children and adults.

Current research supports that nutrition, sedentary life-styles, environmental factors, and genetics are attributed to development of obesity, Type 2 Diabetes Mellitus, CVD, and cancer. Recent studies have been conducted to examine the role of gut microflora, consisting of microorganisms normally residing in the human gut, in the development of chronic inflammation that is a common process underlying these metabolic diseases. In one study performed at the Institute of Molecular Medicine in Toulouse, France, Cani et al. hypothesized that bacterial lipopolysaccharides (LPS), which are derived from gram-negative bacteria, may trigger inflammation. Cani et al. also found that a high-fat diet given to mice resulted in a significant increase of the dominant bacterial populations within the gut microflora. This response was associated with a considerable increase in plasma LPS, adipose tissue, body weight gain, liver hepatic triglyceride accumulation, inflammation, insulin resistance, and diabetes. In response to inflammation, the production of signaling molecules, such as cytokines, amplify the inflammatory response. The Cani et al. study also evidenced that LPS is an effective stimulator of cytokines, which can also be key inducers of insulin resistance.

Barbier de La Serre et al., at the University of California Davis, also determined that the development of intestinal epithelial inflammation was a result of a high-fat diet in rat studies. Their data also suggested that high-fat diets are a possible triggering mechanism in the appearance of hyperphagia, or chronic over-eating, and obesity. Another inflammatory response is metabolic endotoxemia, which is the presence of endotoxins in the blood from the breakdown of the LPS layer in gram negative bacteria. These endotoxins mediate low-grade systemic inflammation. Continuous consuming a high-fat diet will likely maintain elevated LPS plasma levels, which will result in a chronic systemic inflammation.

In another study at the University of North Carolina at Chapel Hill, Ding et al.'s study revealed that high-fat diets in mice induced two inflammatory biomarkers in the intestine, tumor necrosis factor (TNF-α) mRNA and nuclear factor kappa-light-necrosis factor (NF-κB) activation. Macrophages can over-produce TNF-α in adipose tissue, and this may contribute to the development of insulin resistance, by limiting insulin receptor signaling. In addition, TNF-α activates inflammatory pathways such as NF-κB, which are involved in the etiology of insulin resistance and Type 2 Diabetes Mellitus. Ding et al. also concluded that high-fat diet induced inflammatory changes in the intestine occur prior to the development of weight gain and insulin resistance, and involve and enteric bacteria working together. The data from these studies suggest that high-fat diets induce intestinal inflammation and that biomarkers such as LPS levels, TNF-α mRNA, and NF-κB activation merit further investigation as clinical indicators for assessment of obese or obese-prone patients.

Long-term changes in one's lifestyle, including increased consumption of healthy foods and physical activity, are promising strategies for managing and possibly reversing or preventing obesity, Type 2 Diabetes Mellitus, CVD, and cancer. DiBaise et al. discusses that modulation and manipulation of gut flora through the use of probiotics, prebiotics, and antibiotics, may be effective in reversing obesity. Prebiotics are valuable for increasing the growth of beneficial bacteria in the gut. In rats, Brugman et al.'s data revealed that antibiotic use decreased the incidence of diabetes in the diabetes-prone model. The onset of diabetes was also delayed in rats that displayed symptoms of the disease. Probiotics are live microorganisms that provide health benefits to the host when ingested. Lactobacillus rhamnosus is one of these probiotic bacteriums that produces linoelic acid. Lee et al. investigated this bacterium in diet-induced mice and found that the mice lost weight while maintaining their energy intake. These findings suggest that probiotics may play an important role during weight loss.

Obesity, Type II Diabetes Mellitus, CVD and some cancers share alterations in inflammation and overall metabolism. This relationship has motivated additional research examining gut microflora, specific diets, and the development of CVD and cancer. Ryan et al. determined that rice bran components when fermented with a yeast probiotic have enhanced bioactivity against cancer cells. Currently, the Bean/Bran Enriching Nutritional Eating for Intestinal Health Trial (BENEFIT) trial is being conducted as part of an academic-community partnership in Northern Colorado. The Colorado State University Animal Cancer Center has combined efforts with the Kendall Anderson Nutrition Center and Poudre Valley Health (PVH) Cancer Network to investigate how increased dietary consumption of cancer fighting foods modulate gut microflora. BENEFIT is a human clinical research study designed to examine the disease prevention properties of dry beans (e.g. navy, black, pinto) and rice bran (polished from brown rice) for cancer control and maintenance. Dr. Elizabeth Ryan and her research team are assessing changes in the gut microflora and metabolome using high throughput research tools. They hypothesize that these foods have multiple mechanisms for inhibiting tumor development and advocate that more human research is needed to support the evidence from animal studies with rice bran and beans. Beans and whole grain rice contain a number of substrates for microflora. The data generated from the highly collaborative BENEFIT study has strong potential to provide valu-
able information for developing public health strategies to prevent and manage cancer in diverse populations.

Continued research on modulation of the gut microbiota by environmental factors such as diet and physical activity, and thus its role in the development of obesity, Type 2 Diabetes Mellitus, CVD, and cancer may prove to be beneficial for reducing the prevalence of chronic metabolic diseases affecting much of the population.

References