Intermittent Fasting and Prevention of Diabetic Retinopathy: Where Do We Go From Here?

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Diabetes 2018;67:1745–1747 | https://doi.org/10.2337/dbi18-0022

Type 2 diabetes represents one of the most significant global health threats of the 21st century owing to its constantly increasing prevalence and long-term debilitating complications (1). In addition to accelerated macrovascular disease in poorly controlled diabetes that is responsible for increased cardiovascular morbidity and mortality, microvascular complications, such as diabetic nephropathy, neuropathy, and retinopathy, cause a significant burden and may markedly impair not only life expectancy but also quality of life of patients with diabetes (2). Diabetic retinopathy is the most common cause of blindness in developed countries and one of the most feared diabetes complications (3).

Significant progress has been made in our understanding of the etiopathogenesis of type 2 diabetes with numerous novel contributing mechanisms identified in the past couple of years (4). Both experimental and clinical studies have demonstrated that gut represents a vital organ with respect to regulation of glucose metabolism and modulation of the risk of type 2 diabetes development (5). Multiple facets of the gut–glucose metabolism interconnection have been uncovered in particular by studying the changes induced by weight loss associated with bariatric surgery or endoscopic methods mimicking bariatric surgery. The possible mechanisms of gut-driven improvements in glucose metabolism after surgical or endoscopic interventions include restriction of food amount, enhanced passage of chymus into distal parts of small intestine with subsequent modification of gastrointestinal hormones and bile acid secretion, neural mechanisms, changes in gut microbiota, and many others (6). Studies have shown that type 2 diabetes is accompanied by impaired microbiota composition and its decreased diversity, with subsequent modulations of energy yield from intestinal content, metabolization of bile acids, intestinal permeability, and other characteristics of the gut (7).

Energy restriction is an important therapeutic approach leading to improvement of glucose control in patients with type 2 diabetes. Nevertheless, the compliance of patients to long-term hypocaloric diet is limited, and other approaches more acceptable from the patient perspective are needed. Intermittent fasting represents an alternative and more physiological way to prevent deleterious effects of chronic excess of food intake. This approach enables the combination of energy-restricted and unrestricted days, which is better accepted by the majority of patients. In both experimental and clinical studies, intermittent fasting has been shown to improve insulin sensitivity and glucose control along with modest decreases in body weight (8). The long-term effects of intermittent fasting on glucose control and diabetes complications are largely unknown.

In this issue of *Diabetes*, Beli et al. (9) bring an important body of evidence to the puzzle of possible effects of intermittent fasting on the reduction of microvascular diabetes complications. They used the genetic model of severe type 2 diabetes leptin receptor–deficient *db/db* mice to study the effects of intermittent fasting versus ad libitum feeding on long-term survival, metabolic parameters, and diabetic retinopathy. They found that, despite no significant effects of intermittent fasting on body weight or glucose control, this regimen resulted in longer survival and reduction of diabetic retinopathy end points, including acellular capillaries and leukocyte infiltration, in *db/db* mice. They further demonstrated that intermittent fasting markedly altered gut microbiota composition with increased levels of Firmicutes and decreased Bacteroidetes and Verrucomicrobia along with improvement in gut structure, including increased gut mucin, goblet cell number, and villi length and reduced peptidoglycan, suggesting improved gut barrier. Most importantly, intermittent fasting increased concentrations

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See accompanying article, p. 1867.

COMMENTARY

of tauroursodeoxycholate (TUDCA), a secondary bile acid with neuroprotective properties (10). The authors have demonstrated the presence of TUDCA TGR5 receptors in neural cells of the retina, and pharmacological activation of TGR5 by potent semisynthetic bile acid derivative INT-767 (11) prevented diabetic retinopathy in another diabetic mouse model. This led the authors to the conclusion that intermittent fasting modified the gut microbiota toward species that produce TUDCA, which subsequently prevented retinopathy by TGR5 activation in retinal neural cells. The hypothetic mechanism of action of intermittent fasting on diabetic retinopathy is depicted in Fig. 1.

Overall, the study brings a very interesting concept that is well supported by provided data. Yet as with any good research, although some of the questions were answered, several more emerged. As the authors focused mostly on microbiota and changes in secondary bile acids as possible mechanisms of retinopathy improvements, it is not clear if other changes induced by intermittent fasting also contributed to the favorable outcomes. Previous studies have shown that intermittent fasting can improve autophagy, reduce oxidative stress and advanced glycation end products, modulate endocrine function of adipose tissue toward increased production of adiponectin and other "healthy" adipokines, and have multiple other beneficial effects (12). Further studies are necessary to dissect the possible contribution of these other potentially beneficial mechanisms.

As the TUDCA TGR5 receptors are present in neural cells, it is tempting to speculate that intermittent fasting could also have the potential to improve other diabetic microvascular complications, in particular diabetic neuropathy. The most important question, however, is whether and to what degree could such a concept be extrapolated to humans. Although changes in gut microbiota have been studied in numerous clinical situations, it is currently not known if intermittent fasting alters gut microbiota composition and/or circulating bile acid levels in humans. It is also quite difficult to predict whether intermittent fasting could be successfully applied in long-term clinical studies or, optimally, in routine clinical practice. Another interesting possibility could be to ameliorate diabetic retinopathy by administration of TUDCA or its synthetic agonists.

In summary, the study by Beli et al. (9) offers a completely new potential mechanism of improving diabetic retinopathy with dietary modifications without significant changes in glucose control or body weight. Such concepts may apply not only to dietary approaches but also to changes in gut microbiota composition induced by bariatric surgery or endoscopic methods for diabetes treatment. Finally, it is tempting to speculate that differences in gut microbiota may explain why some of the patients with diabetes are more prone to developing diabetic retinopathy as compared with others while having the same control of diabetes and other risk factors. These data open up new avenues for clinical research aimed at delaying or

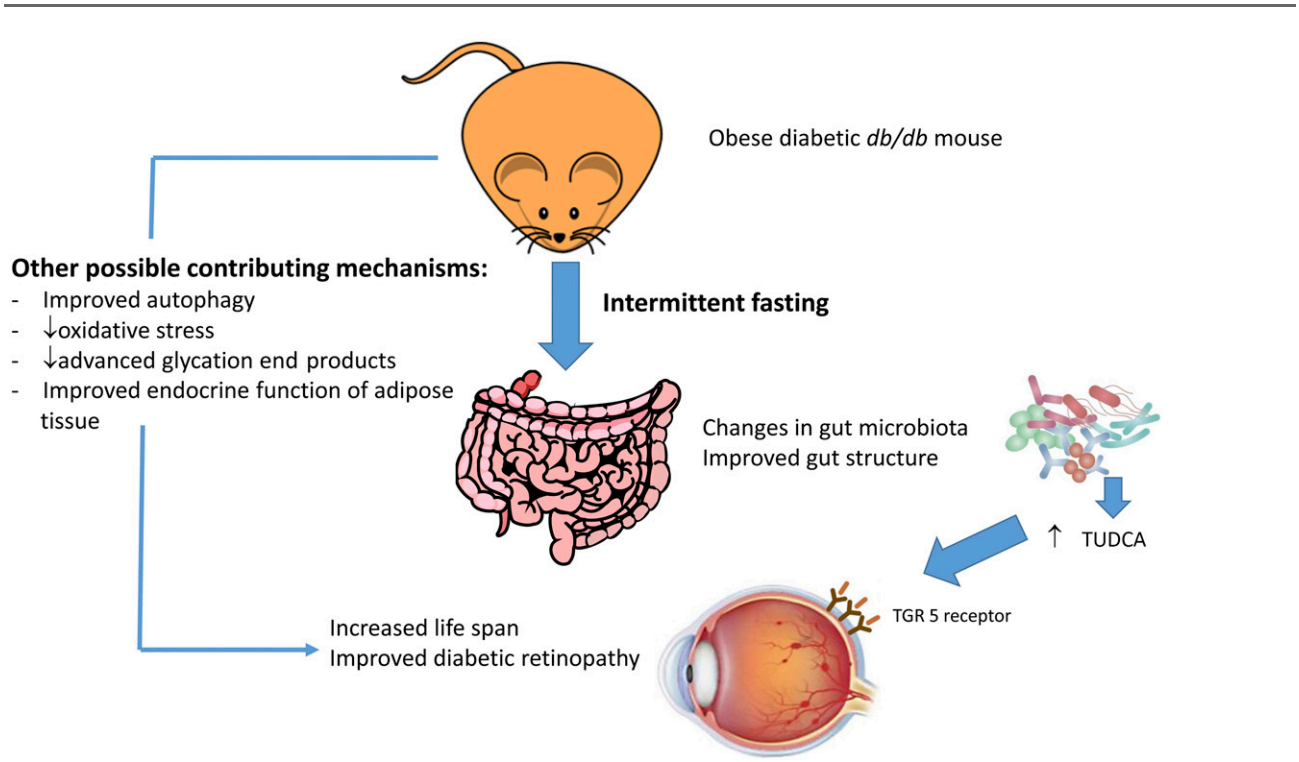

Figure 1—Potential mechanisms of diabetic retinopathy improvement by intermittent fasting.

preventing diabetic retinopathy that could markedly alter the fate of many patients with diabetes.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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