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Does Hepatic Dysfunction Worsen Glucose Homeostasis by Impairing Vitamin D Metabolism?

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The Management of diabetes mellitus (DM) remains an enigma even though the symptoms of the disease had been described more than 3000 years ago. This is because the central therapeutic goal of DM therapy, euglycemia, is influenced by complex physiologic and pathologic processes, some of which are clearly understood, while others are less clear. Suboptimal glycemic control is a recognized risk factor for acute and chronic complications of diabetes including microvascular and macrovascular diseases [1-3]. The central question for this editorial is whether mild hepatic dysfunction could impair vitamin D metabolism and secondarily lead to sub-optimal glycemic control.

Poor glycemic control is a growing problem in patients with type 1 (T1DM) or type 2 diabetes (T2DM) [4] despite improvements in insulin formulation, delivery and adjunctive therapies [5]. A high proportion of youth with diabetes had elevated hemoglobin A1c (HbA1c) values, with 17% with TIDM, and 27% of those with T2DM showing poor control, defined as HbA1c ≥ 9.5% [4].

Nonalcoholic fatty liver disease (NAFLD) is the most common form of liver dysfunction in children [6]. Even though its prevalence is rising in parallel with the prevalence of childhood obesity [7], its role in poor glycemic control in diabetes is unknown. NAFLD represents a spectrum of conditions characterized by macrovesicular hepatic steatosis and little or no exposure to alcohol [7]. The hepatic pathology encompasses a range from isolated fatty infiltration to steatohepatitis, advanced fibrosis, and cirrhosis [6]. NAFLD is the leading cause of elevated liver enzymes in obese youth [8]. Several studies have reported an association between liver dysfunction and low vitamin D levels [9,10], as well as liver dysfunction and poor glycemic control [11], but not all three disorders acting in concert.

A crucial step in the metabolism of vitamin D, the hydroxylation of pre-vitamin D at the 25 position, occurs in the liver. The role of NAFLD on this critical step in vitamin D metabolism in children and adolescents with diabetes has not been fully studied. Equally, the effects of the resultant vitamin D deficiency on glycemic control in these patients have also not been well described.

The role of vitamin D on glycemic control has not been fully studied. A study in healthy adults with normal glucose tolerance using the hyperglycemic clamp technique showed a positive correlation of 25-hydroxyvitamin D (25OHD) level with insulin sensitivity [12]. Extrapolation of the data suggested that increasing the serum concentrations of 25OHD from 25-80 nmol/L would increase insulin sensitivity by 60% [12], indicating that perhaps vitamin D supplementation offers promise as an adjunctive therapy for those with DM [13]. Mitri et al. [14] reported improved pancreatic β cell function as well as a trend toward attenuation of the rise in HbA1c levels in adults at high risk of T2DM who received 2000 IU of vitamin D daily for 16 weeks. A study in children and adolescents showed that low levels of 25OHD are associated with increasing insulin resistance in patients at risk for diabetes [15]. Another study reported that an increase in vitamin D levels decreased systemic inflammatory markers in patients with T2DM [16]. However, a recent report by the Institute of Medicine did not provide support for these extra-skeletal actions of vitamin D [17]. Equally, a recent study failed to show any strong associations of 25OHD with either myocardial structure or function [18].

There is a high prevalence of vitamin D deficiency in patients with TIDM and T2DM [19,20]. This vitamin D deficiency is often attributed to sequestration in fat depots, lack of sun exposure, and insufficient intake of vitamin D containing foods. However, the effect of hepatic dysfunction on the critical step of hydroxylation of pre-vitamin D at the 25 position has not been adequately described in those with DM.

Therefore, to achieve the goal of glycemic control in diabetes, euglycemia, it will be necessary to investigate beyond the conventional modalities of diabetes management. It will be necessary to conduct studies examining the roles of hepatic dysfunction and associated vitamin D deficiency on glycemic control in patients with diabetes mellitus. My colleagues and I have embarked on this mission.

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