

Bilirubin as a New Biomarker of Diabetes and its Microvascular Complications

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Commentary

Hyperglycemia is the hallmark of diabetes mellitus [DM]; it activates certain biochemical pathways leading to micro- and macrovascular complications in diabetic patients [1]. Moreover, hyperglycemia generates oxidative stress and causes free radical-mediated lipid peroxidation [2,3]. In turn, the oxidative stress causes endothelial dysfunction, and has been suggested as one of the important mechanisms underlying the onset and progression of diabetic vascular complications [4].

Bilirubin, the end product of heme catabolism, is known to exhibit strong anti-oxidant and anti-inflammatory properties on the vasculature [5,6]. It has been reported that the prevalence of vascular complications in diabetic patients with Gilbert syndrome, a congenital hyperbilirubinemia, is lower compared with in those without this syndrome [7]. Further, bilirubin has been shown to reduce the oxidant levels in wounds and to accelerate wound healing in diabetic rats [8]. In accordance with the results of this previous animal study, several literatures have reported the association between diabetic microvascular complications and bilirubin by comparing serum bilirubin concentrations in diabetic patients with and without microvascular complications such as neuropathy [9], nephropathy [10], and retinopathy [11,12]. However, out of these three microvascular complications, prospective findings have only been acquired for nephropathy [13,14]. Recent prospective cohort studies have demonstrated that a low serum bilirubin concentration is a novel risk factor for the development of albuminuria in type 2 DM patients [13,14]. In other words, with regards to neuropathy and retinopathy, no causal relationships with bilirubin have yet been determined, owing to the cross-sectional and retrospective natures of the studies on the topic. Interestingly, elevated bilirubin levels have been shown to be a protective determinant for the incidence of type 2 DM per se [15].

Recently, we reported that type 1 DM patients with retinopathy and nephropathy showed a lower serum total bilirubin concentration than those without these complications [16,17]. We also reported that indirect bilirubin showed a stronger association with nephropathy than total bilirubin in type 1 diabetics [16]. However, other than our observations, reports about the relationships between bilirubin and diabetic complications have been restricted to type 2 diabetics so far. Concerning the types of bilirubin [total, direct, or indirect], the concentrations of all three types have been shown to be lower when retinopathy is present in type 2 DM patients [18], whereas no reports other than ours are available on type 1 DM patients. Whether bilirubin plays important roles in the onset and progression of vascular complications and what type of bilirubin is important in type 1 DM patients are exciting and important clinical questions. In order to

elucidate the pathophysiological role of bilirubin in type 1 DM, our results should be verified in large-scale, prospective studies.

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