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COMMENTARY

Bilirubin as an important physiological modulator of oxidative stress and chronic inflammation in metabolic syndrome and diabetes: a new aspect on old molecule

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Bilirubin belongs to the superfamily of tetrapyrrolic compounds, which is one of the most highly conserved groups of molecules. These compounds have evoked to have pluripotent roles, starting from the role as light harvesting and energy generating pigments in a photosynthetic process in algae and plants. For decades bilirubin has been believed to be a toxic waste product of heme catabolism in human, while in recent years accumulating evidence has shown that bilirubin has beneficial effects upon various oxidative stress-associated diseases. In this commentary, we show that serum bilirubin may be an important biomarker and a potential therapeutic target in diabetes and metabolic syndrome.

Bilirubin is formed by the ubiquitously expressed heme oxygenase (HO), the rate-limiting enzyme involved in heme catabolism. HO participates in heme breakdown to generate biliverdin, free ferrous iron and carbon monoxide. Bilverdin is rapidly converted to bilirubin by biliverdin reductase. Bilirubin is further processed in the liver, where it is conjugated with glucuronic acid by uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) to a water-soluble form for elimination. Recently, clinical and experimental evidence has increasingly shown that HO and its reaction product bilirubin may serve as an important endogenous agent with cytoprotective activity against oxidative stress-induced injury. We found for the first time that diabetic patients with Gilbert syndrome, who have a genetic variant in UGT1A1 and moderately elevated levels of serum bilirubin levels, had a lower prevalence of vascular complications including retinopathy, nephropathy and cardiovascular disease, comparing to the patients without the syndrome, along with reduced markers of oxidative stress and inflammation [1]. This evidence strongly suggested that sustained moderate hyperbilirubinemia may inhibit oxidative stress and prevent the diabetic vascular complications. Such protective effects of bilirubin have been supported by increasing number of studies on both clinical and laboratory outcomes of diabetic patients. Serum bilirubin concentrations were demonstrated to be negatively associated with albuminuria in patients with type 2 diabetes [2]. The Hisayama Study group reported that comparing to the lowest bilirubin quartile, those with the highest bilirubin levels had a four times lower prevalence of diabetic retinopathy [3]. In a large Korean cross-sectional study on 94,000 subjects, high serum bilirubin was found to be associated with the reduced risk of both diabetes mellitus and diabetic nephropathy [4]. Recent report showed a significant and graded inverse association between baseline serum bilirubin levels and the progression of diabetic nephropathy in a post hoc analysis in the RENNAL trial [5]. Data from this study were independently verified using the IDNT [5]. In a both trail, the renal endpoint was examined over 2.5-year follow-up period and defined as doubling of serum creatinine or endo-stage renal disease requiring dialysis or transplantation.

We also found the inverse associations of serum bilirubin with high sensitivity C-reactive protein, HbA1c and the prevalence of type 2 diabetes in approximately 12,500 middle-aged and elderly Japanese subjects [6], suggesting that bilirubin may prevent the development of

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type 2 diabetes. Consistent with this data, higher serum bilirubin levels were reported to protect from diabetes mellitus in the US National Health and Nutrition Examination Survey (NHANES) on almost 16,000 subjects [7]. Importantly, recent report showed that genetically elevated bilirubin levels are causally protective against the development of type 2 diabetes using Mendelian randomization in a cohort study [8].

In diabetes, the protective properties of bilirubin are likely due to its potent antioxidant properties [9]. Bilirubin has been shown to be more effective at protecting lipids from oxidation than water-soluble antioxidant glutathione, and almost 30 times more potent toward the prevention of LDL oxidation compared to a lipid-soluble vitamin E analog. Moreover, serum bilirubin has been shown to be a major contributor to the total antioxidant capacity in blood. In addition, bilirubin was reported to inhibit NAD(P)H oxidase, which is a major source for reactive oxygen species (ROS) production in various tissues including vascular tissues and phagocytes. In rodents, we reported that bilirubin and biliverdin inhibited albuminuria and the progression of renal mesangial expansion in diabetes, as well as normalization of oxidative stress and the expression of NAD(P)H oxidase subunits in the kidney [10]. In addition, we also reported that biliverdin treatment partially prevented a worsening of glucose tolerance in db/db mice via inhibition of oxidative stress-induced pancreatic β cell damage, accompanied by normalization of the expression of NAD(P)H oxidase subunits in β cells [11]. Notably, more recent studies have shown that bilirubin has anti-inflammatory properties, and also has the potential properties in activation of Akt and eNOS and synthesis of NO [12], which improves endothelial cell function and insulin resistance as well. In recent years, chronic inflammation is considered to play an important role in multiple organ damage in obesity, metabolic syndrome, and

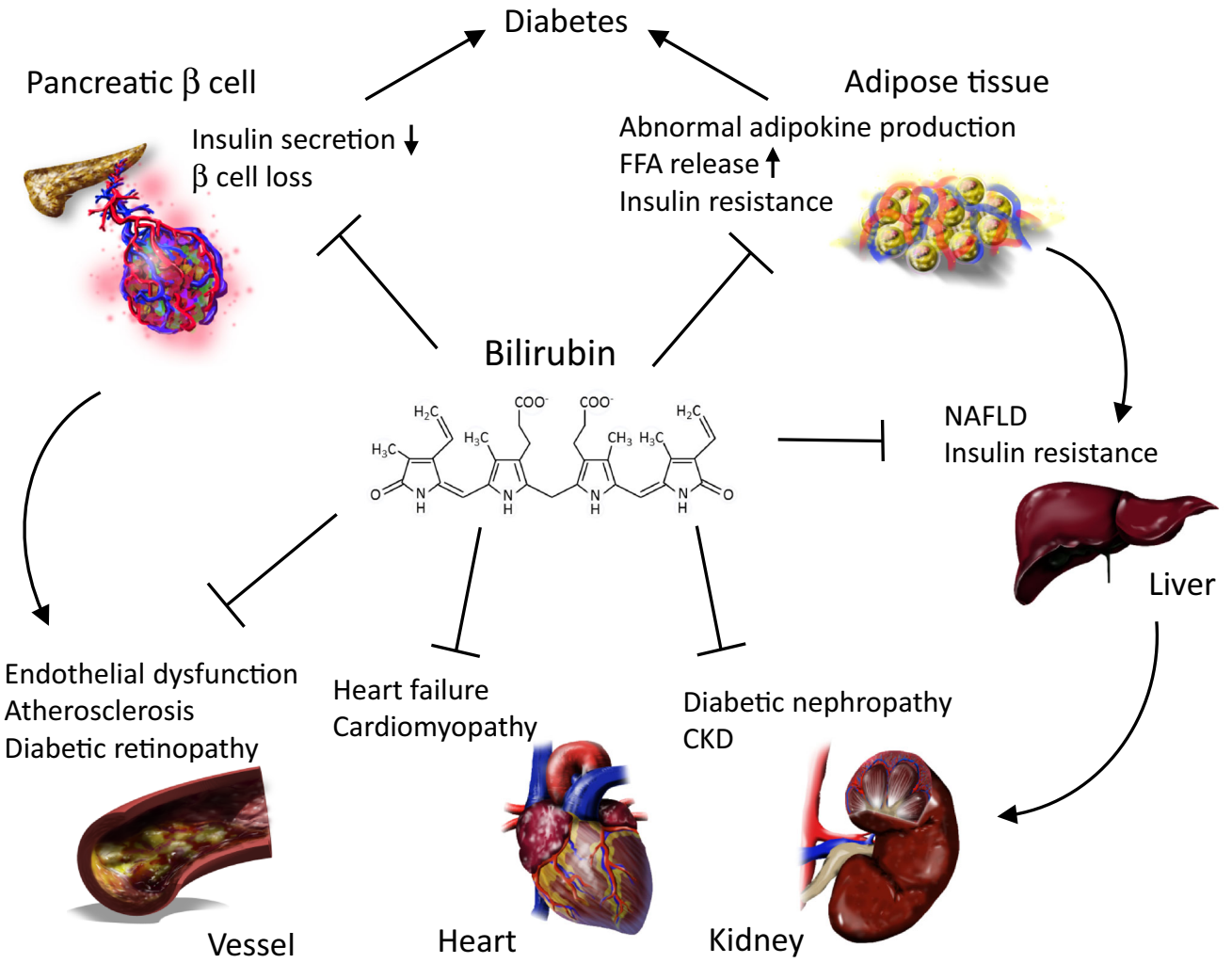

Fig. 1 The possible protective role of bilirubin on oxidative stress- and chronic inflammation-associated multiple organ dysfunction in metabolic syndrome and diabetes. *FFA* free fatty acid, *NAFLD* non-alcoholic fatty liver disease, *CKD* chronic kidney disease

diabetes. These organs include adipose tissue, liver, aorta, heart, kidney, and pancreatic islets. It is very likely that ant-inflammatory effect as well as anti-oxidative effect may contribute to the protective effect of bilirubin on vascular damage. Of interest, HO-1 induction was reported to reduce visceral and subcutaneous obesity in diabetic and obese mice through mechanism involving the attenuation of the inflammation process, as well as modulation of PPAR γ signaling [13]. Bilirubin was also reported to increases insulin sensitivity in leptin-receptor deficient and diet-induced obese mice through suppression of ER stress and chronic inflammation in adipose tissues and liver [14]. Collectively, serum bilirubin may serve as an important physiological modulator of oxidative stress and chronic inflammation in metabolic syndrome and diabetes (Fig. 1).

Given the increasing understanding of the protective properties of bilirubin and its profound association with diabetes and its complications, it is strongly suggested that serum bilirubin may be an important biomarker for the development of diabetes and its complications. Further studies should be done to clearly define how we should use serum bilirubin levels in estimating the disease state for the purpose of treatment planning. More importantly, it is also suggested that elevating serum bilirubin levels may be a feasible therapeutic strategy. This may include administration of HO-1 inducers, supplementation with bilirubin or biliverdin, and administration of drugs which decrease UGT1A1 activity. HO-1 can be upregulated by many common drugs including non-steroidal anti-inflammatory drugs and PPAR α agonists, and also by natural inducers originating from plants such as polyphenols, curcumin and silymarin. However, there has been no established evidence yet showing the beneficial effect of these drugs and natural inducers. We reported that supplementation of phycocyanobilin extracted from Spirulina platensis a blue-green algae prevented the progression of diabetes nephropathy in db/db mice by inhibiting oxidative stress [15]. Notably, the feasibility of targeting UGT1A1 is supported by a report that atazanavir, which has an inhibitory effect of UGT1A1, elevated serum unconjugated bilirubin levels and improved endothelial function in patients with diabetes [16]. This suggests that UGT1A1 inhibitor could be used to induce an "iatrogenic Gilbert syndrome" [17] to prevent the development of diabetes and its complications. This concept may be favored by findings that subjects with Gilbert syndrome or relatively higher serum bilirubin levels in normal range might have lower mortality from any cause in a large scale population-based cohort study [18, 19].

In conclusion, bilirubin is an old molecule, but accumulating evidence suggests that bilirubin may be important physiological modulator of oxidative stress and chronic inflammation in metabolic syndrome and diabetes. Studies should be done to further explore the potential of bilirubin as a new biomarker and a therapeutic target.

Compliance with ethical standards

Human rights statement and informed consent This article does not report any original studies with human or animal subjects that were performed by any of the authors.

Conflict of interest T. Inoguchi received speaker honoraria from Boehringer Ingelheim GmbH, Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Sanofi K.K., Astellas Pharma Inc., Kowa Pharmaceutical Co. Ltd., Novartis Pharma K.K., AstraZeneca K.K., Ono Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Eli Lilly Co. Ltd., Kissei Pharmaceutical Co. Ltd., Dainippon Pharmaceutical Co. Ltd. N. Sonoda received speaker honoraria from Takeda Pharmaceutical Co. Ltd., AstraZeneca K.K., Mitsubishi Tanabe Pharma Corporation. T. Inoguchi received scholarship grants from Dainippon Sumitomo Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, Astellas Pharma Inc., Ono Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Taisho Toyama Pharmaceutical Co. Ltd., Novo Nordisk Pharma Ltd., Eli Lilly Co. Ltd. Y. Maeda has no conflict of interest.

References

1. Inoguchi T, Sasaki S, Kobayashi K, et al. Relationship between Gilbert syndrome and prevalence of vascular complications in patients with diabetes. JAMA. 2007;298:1398–400.
2. Fukui M, Tanaka M, Shiraishi E, et al. Relationship between serum bilirubin and albuminuria in patients with type 2 diabetes. Kidney Int. 2008;74(1197–20):1.
3. Yasuda M, Kiyohara Y, Wang JJ, et al. High serum bilirubin levels and diabetic retinopathy: the Hisayama Study. Opthalmology. 2011;118:1423–8.
4. Han SS, Na KY, Chin HJ, et al. High serum bilirubin is associated wuth the reduced risk of diabetes mellitus and diabetic nephropathy. Tohoku J Exp Med. 2010;221:133–40.
5. Riphagen IJ, Deetman PE, Bakker SJL, et al. Bilirubin and progression of nephropathy in type 2 diabetes: a post hoc analysis of RENNAL with independent replication in IDNT. Diabetes. 2014;63:2845–53.
6. Ohnaka K, Kono S, Inoguchi T, et al. Inverse association of serum bilirubin with high sensitivity C-reactive protein, glycated hemoglobin, and prevalence of type 2 diabetes in middle-aged and elderly Japanese men and women. Diabetes Res Clin Pract. 2010;88:103–10.
7. Cheriyath P, Gorrepati VS, Peters I, et al. High total bilirubin as a protective factor for diabetes mellitus: an analysis of NHANES data from 1996–2006. J Clin Med Res. 2010;2:201–6.
8. Abbasi A, Deetman PE, Corpeleijin EVA, et al. Bilirubin as a potential causal factor in type 2 diabetes risk: a Mendelian randomization study. Diabetes. 2015;64:1459–69.
9. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235:1043–6.
10. Fujii M, Inoguchi T, Sasaki S, et al. Bilirubin and biliverdin protect rodents against diabetic nephropathy by downregulating NAD(P)H oxidase. Kidney Int. 2010;78:905–19.
11. Liu J, Wang L, Tian XY, et al. Unconjugated bilirubin mediates heme oxygenase-1-induced vascular benefits in diabetic mice. Diabetes. 2015;64:1564–75.

12. Ikeda N, Inoguchi T, Sonoda N, et al. Biliverdin protects against the deterioration of glucose tolerance in db/db mice. Diabetologia. 2011;54:2183–91.
13. Li M, Kim DH, Tsenovoy PL, Peterson SJ, et al. Treatment of obese diabetic mice with a heme oxygenase inducer reduces visceral and subcutaneous adiposity, increases adiponectin levels, and improves insulin sensitivity and glucose tolerance. Diabetes. 2008;57:1526–35.
14. Dong H, Huang H, Yun X, et al. Bilirubin increases insulin sensitivity in leptin receptor deficient and diet-induced obese mice through suppression of ER stress and chronic inflammation. Endocrinol. 2014;155:818–28.
15. Zheng J, Inoguchi T, Sasaki S, et al. Phycocyanin and phycocyanobilin from Spirulina platensis protect against diabetic nephropathy by inhibiting oxidative stress. Am J Physiol Regul Integr Comp Physiol. 2013;304:110–20.
16. Dekker D, Dorresteijn MJ, Pijnenburg M, Heemskerk S, et al. The bilirubin-increasing drug atazanvir improves endothelial function in patients with type 2 diabetes mellitus. Arterioscler Thromb Vasc Biol. 2011;31:458–63.
17. McCarty MF. "Iatrogenic Gilbert syndrome"—A strategy for reducing vascular and cancer risk by increasing plasma unconjugated bilirubin. Med Hypotheses. 2007;69:974–94.
18. Horsfall LJ, Nazareth I, Pereira SP, et al. Gilbert's syndrome and the risk of death: a population-based cohort study. J Gastroenterol Hepatol. 2013;28:1643–7.
19. Horsfall LJ, Rait G, Walters K, et al. Serum bilirubin and risk of respiratory disease and death. JAMA. 2011;305(7):691–7.