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Serum bilirubin as a biomarker of oxidative stress in children with type 1 diabetes mellitus

An observational study

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Abstract

This study aims to explore whether bilirubin can act as a biomarker of oxidative stress in type 1 diabetes mellitus (T1DM) by analyzing the serum bilirubin levels and possible influencing factors in different disease states and durations in children with T1DM. This is a retrospective study. The medical records of 1652 inpatients with T1DM and 101 healthy children in Shanxi Provincial Children's Hospital from 2014 to 2023 were collected and divided into different subgroups. The relevant indices in different disease states and durations in the T1DM group were statistically analyzed, particularly the serum bilirubin levels and possible influencing factors. Compared to children without diabetic ketoacidosis (DKA)/diabetic ketosis (DK), children with DKA/DK exhibited higher random blood glucose (RBG), HbA1C, total bilirubin (TBil), and indirect bilirubin (IBil) ($P < .05$). Compared to the control group, the levels of TBil and IBil in the newly-diagnosed and established T1DM children were statistically significantly higher ($P < .05$). Compared to newly-diagnosed T1DM children, serum TBil and IBil levels were statistically significantly lower in the established T1DM group and subgroups with different disease durations ($P < .05$). TBil and IBil were correlated with the status of blood glucose control and can be reflected by RBG, HbA1C, and DKA/DK ($P < .05$), but had no correlation was observed with disease duration ($P > .05$). Serum bilirubin possesses the potential to be a biomarker of oxidative stress in T1DM children.

Abbreviations: ADA = American Diabetes Association, DBil = direct bilirubin, DK = diabetic ketosis, DKA = diabetic ketoacidosis, GSH = glutathione, HbA1C = glycated hemoglobin A1C, HO-1 = heme oxygenase-1, IBil = indirect bilirubin, Nrf2 = nuclear factor erythroid 2-related factor 2, RBG = random blood glucose, ROS = reactive oxygen species, SOD = superoxide dismutase, T1DM = type 1 diabetes mellitus, TBil = total bilirubin, WHO = World Health Organization.

Keywords: bilirubin, blood glucose, children, oxidative stress, type 1 diabetes mellitus

1. Introduction

Type 1 diabetes mellitus (T1DM) is a common chronic endocrine disease accounting for approximately 90% of the total amount of diabetes in children and adolescents.[1] The global incidence of T1DM has steadily increased with an average annual increase of 3% to 4% over the past 3 decades, and the onset of T1DM has exhibited an increasing trend at younger age.[2] Its pathogenesis is complex and involves genetic, environmental and immunologic factors that destroy pancreatic islet β cells and lead to insulin deficiency.[3] Additionally, the role of oxidative stress in the development of T1DM has attracted increasing attention. Studies have determined that children with T1DM at different disease stages experience oxidative stress that is activated by blood glucose fluctuation and can cause oxidative damage to various organ cells throughout the body, affect the balance of the immune system, and promote the occurrence and development of autoimmune inflammatory response and its complications.[4–6] Preventing and reducing oxidative stress damage in patients with T1DM has become the focus of scientific research and medical staff.

Bilirubin, of which indirect (unconjugated) bilirubin is the main form in the body, is one of the products of heme catabolism in mammals. Not only is it an endogenous strong antioxidant, but it also exerts anti-inflammatory and immunomodulatory effects. The antioxidant mechanism of bilirubin has not been fully elucidated and may be linked to 3 paths: its tetrapyrrole structure that can donate a hydrogen atom to scavenge reactive oxygen species (ROS); the bilirubin-biliverdin redox amplification cycle; the active of intranuclear regulation of transcription

JW and JW contributed to this article equally.

This study was approved by the Human Research Ethics Committee of the Shanxi Medical University (ethics approval number: 2020sll003-3), which exempted the informed consent of survey subjects, as this was a retrospective study and there was not any intervention, personal information, or privacy involved.

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The datasets generated during and/or analyzed during the current study are publicly available.

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factor nuclear factor erythroid 2-related factor 2 (Nrf2) that can induce numerous antioxidant defense mechanisms, including heme oxygenase-1 (HO-1), glutathione (GSH), superoxide dismutase (SOD) and others.[7] Mild elevations in systemic or localized bilirubin levels can yield substantial benefits, significantly reducing oxidative injury and the risk of oxidative stress-related diseases such as autoimmune diseases and type 2 diabetes mellitus and their complications such as diabetic nephropathy, retinopathy, and neuropathy.[8–11] However, there are few studies focused on bilirubin levels in children with T1DM.

This study collected and analyzed the serum bilirubin levels in T1DM children in different disease states and durations, explored possible influencing factors, and discussed its clinical significance to provide new ideas for the prevention and treatment of T1DM and its complications.

2. Methods

2.1. Subjects

This is a retrospective study. A total of 1652 inpatients with T1DM from the Department of Endocrinology, Genetics and Metabolism of Shanxi Children's Hospital from 2014 to 2023 were collected as the T1DM group, and 101 healthy children with outpatient physical examination from 2018 to 2019 were enrolled as the control group. This study has been approved by the Ethics Committee of Shanxi Medical University (2020sll003-3), and the informed consent of survey subjects was exempted, as there was not any intervention, personal information, or privacy involved.

The inclusion criteria: the inpatients <18 years old who meet diagnostic criteria for T1DM were included. Children with liver disease or abnormal liver function, hemolytic diseases, and using hepatotoxic drugs were excluded. The diagnostic criteria for T1DM in children referred to the 1999 World Health Organization T1DM diagnostic scale,[12] and the diagnosis of DKA and DK referred to the 2014 American Diabetes Association diagnostic criteria for DKA and DK.[13]

According to the onset of diabetes and the presence of diabetic ketoacidosis (DKA) or ketosis (DK), children in the T1DM group were divided into the newly-diagnosed group and the established diabetes group. These children were divided into 4 subgroups with different disease states, including newly-diagnosed without DKA/DK, newly-diagnosed with DKA/DK, established without DKA/DK, and established with DKA/DK, according to whether they experienced diabetic ketoacidosis (DKA) or diabetic ketosis (DK). The established T1DM patients were also divided into 3 subgroups according to the disease duration that included < 1 year, 1 to 5 years (≥1 year and < 5 years) and ≥ 5 years.[6]

The collected data of T1DM inpatients included age, gender, admission diagnosis, disease duration, random blood glucose (RBG), glycated hemoglobin A1C (HbA1C), pH value, triglycerides, cholesterol, serum total bilirubin (TBil), direct bilirubin (DBil), and indirect bilirubin (IBil), and the collected data of the control group primarily included age, gender, TBil, DBil, IBil. The biochemical method of measuring bilirubin was the diazonium salt method. Because all these indices were collected from the medical records of patients, we didn't describe the relative detection methods in detail, which was not the focus of this study. The changes of related indices, particularly bilirubin levels in different disease states and disease durations in T1DM group, and the correlation between bilirubin and other indices including RBG, HbA1C, pH, triglycerides, cholesterol, and disease duration, and the possible influencing factors were analyzed.

2.2. Statistical methods

The data were statistically analyzed using the GraphPad Prism statistical software (Version 5.0, Graphpad Software Inc, San Diego). The quantitative data are presented as mean ± standard deviation if conforming to the normal distribution or approximate normal distribution or as median [interquartile range] if skewed distribution, and they were then analyzed using Welch *t*-test or Mann–Whitney test to analyze the difference between 2 groups or 1-way ANOVA followed by Newman–Keuls test or Kruskal–Wallis followed by Dunns test to analyze the difference between multiple groups according to homogeneity test results of variance. The qualitative data were presented in terms of number of people and composition ratio (%) that was tested by Chi-Square test to confirm whether the difference between groups was statistically significant. The correlations between bilirubin and RBG, HbA1C, pH value, triglycerides, cholesterol, and disease duration in the T1DM group were analyzed using Pearson linear correlation analysis or Spearman correlation, and multiple linear regression analysis was performed to screen for possible influencing factors of bilirubin. $P < .05$ indicated that the difference was statistically significant.

3. Results

3.1. Comparison of demographic and clinical data of children in different groups

It was demonstrated that the numbers of male and female children with newly-diagnosed T1DM were 291 and 339 respectively, and the peak age of newly-diagnosed T1DM children was 8.0 [5.0, 11.0] years old. The overall proportion of T1DM inpatients with DKA/DK was 867/1652 (52.5%). The proportions of newly-diagnosed T1DM inpatients with DKA/DK and established T1DM inpatients with DKA/DK were 532/630 (84.4%) and 335/1022 (32.8%), respectively. There was a significant difference in the composition ratio of children with DKA/DK between established and newly-diagnosed group ($P < .0001$) (Table 1).

Table 1

General information of children in different groups.

Groups	N	M/F (N)	Age (yrs)	<5 yr (N)	5 to 10 yr (N)	≥10 yr (N)
Control group	101	61/40	8.0 (5.0–11.0)	17	51	33
T1DM group	1652	677/975	10.0 (6.9–12.0)	230	549	873
Established group	1022	386/636	11.0 (8.0–13.0)	75	309	638
1 Established without DKA/DK	687	268/419	10.4 (8.0–13.0)	63	219	405
2 Established with DKA/DK	335	118/217	11.0 (9.0–13.0)	12	90	233
Newly diagnosed group	630	291/339	8.0 (5.0–11.0)	155	240	235
3 Newly diagnosed without DKA + DK	98	50/48	9.0 (5.0–11.5)	16	36	46
4 Newly diagnosed with DKA/DK	532*	241/291	7.3 (4.0–11.0)	139	204	189

DKA = diabetic ketoacidosis, DK = diabetic ketosis, F = female, M = male, N = number, T1DM = type 1 diabetes mellitus.

*Compared the difference in the composition ratio of children with or without DKA/DK between established group and newly-diagnosed group, $P < .0001$.

3.2. Bilirubin levels in children with DKA/DK were higher than in those without DKA/DK

Except for HbA1C, other indices of the established T1DM and the newly-diagnosed T1DM inpatients without DKA/DK were in the normal range. Compared to children without DKA/DK, RBG, HbA1C, triglycerides, cholesterol, and pH value were statistically significantly higher in children with DKA/DK whether in the newly-diagnosed or established group ($P < .05$, Table 2), and this was consistent with the metabolic disorder of DKA/DK.

As presented in Tables 2 and 3, compared to the control group, the levels of TBil and IBil in the newly-diagnosed and established T1DM children and in subgroups with disease duration ≥ 1 years were statistically significantly higher ($P < .05$). The serum TBil and IBil levels in T1DM inpatients with DKA/DK, whether newly-diagnosed or not, were statistically significantly higher than those without DKA/DK ($P < .05$). Compared to newly-diagnosed T1DM children, serum TBil and IBil levels were statistically significantly lower in established T1DM group and subgroups with different disease durations ($P < .05$).

There was a significant difference in the composition ratio of TBil at different levels among the control group, newly-diagnosed group, and established subgroups ($P < .05$), and the proportions of TBil levels > 25.14 μmol/L in the established subgroups increased with the extension of the disease duration. Additionally, most of the levels of RBG and HbA1C in the established group and subgroups with different disease duration were statistically significantly lower than they were in the newly-diagnosed group, but they were higher than the normal level, indicating poor control of blood glucose (see Table 3).

3.3. The status of blood glucose control is the most significant factor influencing bilirubin levels rather than disease duration

The correlation analysis demonstrated that serum TBil and IBil were positively correlated with RBG and HbA1C ($P < .0001$, Table 4), and the multiple linear regression analysis indicated that serum TBil and IBil were correlated with DKA/DK ($P < .001$, Table 5). Although the levels of TBil and IBil in 3 subgroups with different disease durations in the established T1DM group appeared to increase with the prolongation of the disease duration, and the differences were statistically significant when comparing the bilirubin levels of patients whose disease durations were 1 to 5 years and ≥ 5 years with those < 1 year as presented in Table 3 ($P < .05$). However, there were no correlations between serum bilirubin and disease duration ($P > .05$) as presented in Table 4. It is worth noting that the levels of RBG and HbA1C and the proportions of patients with DKA/DK in 3 different subgroups also increased with the extension of the disease duration ($P < .05$, see Table 3). Additionally, serum bilirubin levels were also correlated with pH value, which can reflect the status of DKA. The above results demonstrate that the status of blood glucose control, which can be reflected by certain indicators such as RBG, HbA1C and with/without DKA/DK, was the most significant factor influencing bilirubin levels rather than disease duration.

4. Discussion

T1DM is an autoimmune disease characterized by hyperglycemia, and approximately 40% to 60% of T1DM children at the onset were accompanied by DKA or DK that can be life-threatening if not treated in a timely manner.[2] In this study, the proportion of T1DM children with DKA/DK in all included inpatients was 52.5%, while it was 84.4% in the newly-diagnosed and 32.8% in the established group,

Table 2

Comparison of bilirubin and related indicators in children with T1DM in different states.

Groups	RBG (mmol/L)	HbA1C (%)	pH	TBil (μmol/L)	IBil (μmol/L)	DBil (μmol/L)	Triglycerides (mmol/L)	Cholesterol (mmol/L)
Normal range	<11.1	4 to 5.6	7.35 to 7.45	1.7 to 20.5	1.7 to 13.7	1.7 to 7.0	0.56 to 1.7	2.8 to 5.2
Control group	–	–	–	10.22 ± 3.34	8.45 ± 2.94	1.78 ± 0.65	–	–
T1DM group	14.85 (8.52–23.33)	10.75 (8.30–12.90)	7.29 (7.16, 7.38)	12.60 (8.70–18.40)†	10.40 (7.00–15.70)†	2.00 (1.50–2.80)†	1.28 (0.74–2.73)	4.38 (3.75–5.30)
Established group	12.25 (7.07–19.31)*	9.00 (7.60–11.25)*	7.30 (7.17–7.38)	11.50 (8.48–16.70)*,†	9.40 (6.80–14.05)*,†	2.10 (1.50–2.80)*,†	0.91 (0.65–1.70)*	4.20 (3.664.99)*
1 Established without DKA/DK	9.16 (6.03–13.94)	8.40 (7.20–9.90)	7.40 (7.37–7.43)	10.60 (8.20–14.10)	8.60 (6.50–11.70)	2.00 (1.60–2.70)†	0.78 (0.61–1.07)	4.01 (3.57–4.68)
2 Established with DKA/DK	19.83 (12.90–28.31)‡	11.10 (9.00–13.20)‡	7.25 (7.15–7.34)‡	15.70 (9.80–22.80)†,‡	13.70 (8.10–20.10)†,‡	2.20 (1.50–3.10)†,‡	2.03 (1.09–3.30)‡	4.69 (3.96–5.71)‡
Newly diagnosed group	19.95 (12.48–27.17)	12.50 (11.30–13.90)	7.28 (7.16–7.38)	14.75 (9.30–19.73)†	12.55 (7.80–17.33)†	1.90 (1.40–2.80)†	2.29 (1.23–4.44)	4.72 (3.97–5.78)
3 Newly diagnosed without DKA + DK	9.57 (6.01–13.54)	11.21±0.04§	7.40 ± 0.05	10.80 (7.88–14.98)	8.90 (6.60–12.25)	1.95 (1.38–2.80)	1.03 (0.75–1.82)§	4.19 (3.64–4.71)
4 Newly diagnosed with DKA/DK	21.62 (15.24–28.17)‖	12.70 (11.50–14.03)‖,¶	7.27 (7.15–7.33)‖	15.40 (9.90–19.90)†,‖	13.25 (8.30–17.90)†,‖	1.90 (1.40–2.80)†,¶	2.69 (1.50–5.13)‖,¶	4.87 (4.07–5.98)‖

DBil = direct bilirubin, DK = diabetic ketosis, DKA = diabetic ketoacidosis, HbA1C = glycated hemoglobin A1C, IBil = indirect bilirubin, RBG = random blood glucose, T1DM = type 1 diabetes mellitus, TBil = total bilirubin.

*Compared with newly-diagnosed group, $P < .05$.

†Compared with control group, $P < .05$.

‡Comparision of subgroup 2 and 1, $P < .05$.

§Comparision of subgroup 3 and 1, $P < .05$.

‖Comparision of subgroup 4 and 3, $P < .05$.

¶Comparision of subgroup 4 and 2, $P < .05$.

Table 3

Comparison of bilirubin and related indicators in children with T1DM in different disease stages.

Groups	N	TBIL (μmol/L)	IBIL (μmol/L)	N(%) of TBil between 13.68 and 25.14 (μmol/L)	N(%) of TBil > 25.14 (μmol/L)	RBG (mmol/L)	HbA1C (%)	N(%) of patients with DKA/DK
Control group	101	10.22 ± 3.34	8.45 ± 2.94	16 (15.8)	0 (0)	–	–	–
Newly-diagnosed group	630	14.75 (9.30–19.73)*	12.55 (7.80–17.33)*	274 (43.5)	41 (6.5)	19.95 (12.48–27.17)	12.50 (11.30–13.90)	532 (84.4)
Established group	1022	11.50 (8.48–16.70)*,†	9.40 (6.80–14.05)*,†	310 (30.3)	86 (8.4)	12.25 (7.07–19.31)†	9.00 (7.60–11.25)†	335 (32.8)
<1 yr	177	10.30 (7.30–14.00)‡	8.40 (6.03–11.88)‡	42 (23.7)	6 (3.4)	8.06 (5.77–13.89)‡	7.80 (6.70–9.43)‡	42 (23.7)
1 to 5 yr	563	11.60 (8.50–17.10)*,‡,§	9.50 (6.90–14.60)*,‡,§	181 (32.1)	49 (8.7)	12.69 (7.15–19.83)‡,§	9.10 (7.50–11.10)‡,§	190 (33.7)
≥5 yr	282	12.25 (9.20–18.00)*,‡,§	10.05 (7.50–14.65)*,‡,§	87 (30.9)‖	31 (11.0)‖	13.51 (9.03–21.55)‡,§	9.85 (8.40–11.90)‡,§	103 (36.5)¶

DKA = diabetic ketoacidosis, DK = diabetic ketosis, HbA1C = glycated hemoglobin A1C, IBil = indirect bilirubin, N = number, RBG = random blood glucose, TBil = total bilirubin.

*Compared with control group, $P < .05$.

†Comparison of newly-diagnosed group and established group, $P < .05$.

‡Comparison of each established T1DM subgroup with different disease duration and newly-diagnosed group, $P < .05$.

§Compared with subgroup with disease duration < 1 yr, $P < .05$.

‖Chi-square test of newly-diagnosed T1DM group, established T1DM subgroups and control group: $P < .001$.

¶Chi-square test of established T1DM subgroups.

respectively, manifested by higher RBG, HbA1C, triglycerides, cholesterol, TBil, IBil and lower pH that indicate the existence of metabolic disorders. Compared to newly-diagnosed T1DM children, the levels of RBG, HbA1C, TBil, and IBil were lower in children with different disease durations in the established T1DM group. Although the RBG, TBil, and IBil levels of 3 subgroups with different disease durations in the established T1DM group exhibited an increasing trend with the extension of the disease duration, further correlation and multiple linear regression analysis indicated that serum TBil and IBil levels were positively correlated with RBG, HbA1C, and DKA/DK and exhibited no correlation with the disease duration, suggesting that the bilirubin level may be more affected by the control status of blood glucose.

RBG and HbA1C can respectively reflect the immediate blood glucose and blood glucose control in the most recent 2 to 3 months. Oxidative stress is believed to be the pathogenesis of diabetes itself, leading to insulin resistance, dyslipidemia, β-cell dysfunction, and impaired glucose tolerance.[14] Studies have determined that persistent chronic hyperglycemia and glycemic fluctuations can trigger oxidative stress responses, and glycemic fluctuations may exert stronger pro-oxidative effects.[3,4] It was also observed that blood glucose fluctuations in new cases in the acute metabolic disorder phase and T1DM children in the honeymoon and permanent phases were positively correlated with oxidative stress, and the levels of oxidative stress in patients with acute DKA were significantly higher than those in patients with simple diabetes and chronic diabetes complications.[4,15–17] The results of this study indicated that the mean HbA1C values in all T1DM groups and subgroups were higher than normal, and the average RBG was also higher than normal except for the children without DKA/DK, indicating that recent blood glucose control of hospitalized children was not satisfactory and that the children may experience oxidative stress. Bilirubin is a metabolite of HO-1 that degrades heme. HO-1 can be induced by a variety of stimulants such as substrate heme, oxidative stress, ultraviolet radiation, heat shock, ischemia-reperfusion injury, heavy metals, infection, and others.[18] Studies have reported that oxidative stress can upregulate heme oxygenase activity to increase the production of bilirubin and antioxidant capacity of body to reduce oxidative damage.[19,20] As an endogenous strong antioxidant, whether bilirubin can be used as a biological indicator to reflect the redox homeostasis and antioxidant capacity in children with T1DM was also the focus of this study.

The results of this study determined that RBG, HbA1C, TBil, and IBil levels in children with T1DM, particularly those with DKA/DK, were higher than the normal range or control group, suggesting that hyperglycemia and blood glucose fluctuations in the acute metabolic disorder period were more likely to cause oxidative stress and mobilize the antioxidant system in the body to increase bilirubin production and reduce oxidative stress damage. The levels of RBG, HbA1C, TBil, and IBil in newly-diagnosed T1DM children were higher than those in the subgroups of established T1DM children with different disease durations, and this may be related to the significantly increased proportion of new patients with DKA/DK who are more prone to blood glucose fluctuations and hyperglycemia, suggesting that there are also differences in oxidative stress between newly-diagnosed and established T1DM children. The levels of RBG, HbA1C, TBil, and IBil and the proportion of TBil levels > 25.14 μmol/L in the subgroups of established T1DM children with different duration appeared to increase with the prolongation of the disease duration, and this may be associated with poor control of blood glucose and persistant oxidative stress that can lead to heme oxygenase activity and bilirubin level remaining at a higher level. Combined with the results of the correlation and multiple linear regression analysis, it was observed that bilirubin levels were related to glycaemic control status and not to the disease duration. The results of this study are less consistent with previously published results,[21] and this

Table 4

Correlation analysis of bilirubin with other indices in T1DM group.

	Correlation analysis	RBG (mmol/L)	HbA1C (%)	Triglycerides (mmol/L)	Cholesterol (mmol/L)	pH	Disease duration (yrs)
TBil (μmol/L)	*r*	0.2340	0.1869	0.0274	0.0207	0.0574	0.0026
	P	*<.0001*	*<.0001*	.2834	.4149	.0812	.9169
IBil (μmol/L)	*r*	0.2578	0.2175	0.0602	0.0619	0.0439	−0.0112
	P	*<.0001*	*<.0001*	.0182	.0148	.1823	.6485

Italics denote statistically significant values.

HbA1C = glycated hemoglobin A1C, IBil = indirect bilirubin, RBG = random blood glucose, TBil = total bilirubin.

Table 5

Multiple linear regression analysis of influencing factors of bilirubin in T1DM patients.

TBil	*b*	*P*	IBil	*b*	*P*
(Intercept)	−50.84821	.019	(Intercept)	−65.05524	.001
DKA/DK	4.12818	.001	DKA/DK	4.14055	<.001
pH	8.57934	.003	pH	10.16634	<.001
Age	0.31647	.004	Age	0.27239	.006
Triglycerides	−0.22862	.038			

DK = diabetic ketosis, DKA = diabetic ketoacidosis, IBil = indirect bilirubin, TBil = total bilirubin.

and may be related to the previous small sample size and coarser classification of the disease duration. It can be observed that combined with blood glucose indicators, serum bilirubin can help determine oxidative stress status in children with T1DM, and regularly monitoring the level of bilirubin in the body can provide a reference for clinicians for blood glucose management and antioxidant therapy.

In recent years, the incidence of T1DM in children has increased year by year and has exhibited a trend of younger age, suggesting that the survival time of children with the disease is prolonged.[1] It is well known that chronic complications of diabetes, including microvascular and macrovascular complications, are the leading causes of death and disability in diabetic patients,[22] Increased production of ROS and decreased activity of antioxidant defence system caused by hyperglycemia are considered to be the main causes of diabetes complications. In hyperglycemic environment, ROS are a factor that regulates the transition from apoptosis to necrotic apoptosis.[14,23] So it is important to prevent or delay the occurrence and development of these complications. Due to the role of oxidative stress in the occurrence and development of diabetic complications, determining how to manage blood glucose well to avoid blood glucose fluctuations and the occurrence of oxidative stress damage and complications is important for diabetic patients and also presents an emerging challenge for doctors. Studies have reported that when the serum bilirubin maintains at a high level within the normal physiological range (13.68–25.14 μmol/L), the protective effect on the body is strong,[24,25] and the serum total bilirubin level of diabetic patient is negatively correlated with the severity of cardiovascular and cerebrovascular lesions, neuropathy, retinopathy, and nephropathy.[6,8–10,26] Based on this, bilirubin level may be used as a biological marker and potential intervention target for the diagnosis and treatment of diabetes and its vascular complications. It is important to note that serum bilirubin of >25.14 μmol/L can induce pro-oxidative and toxic effects, with higher levels being more toxic.[27] In this study, with the prolongation of the disease duration, the proportion of bilirubin >25.14 μmol/L increased, and most of these children exhibited poor blood glucose control. Additionally, high levels of bilirubin and blood glucose fluctuations may have double adverse effects on the body, and this requires attention. As it is difficult to follow-up bilirubin levels in outpatient clinics of diabetic children with good blood sugar control, the disease duration is still short, and there are no chronic complications. The future follow-up of blood glucose control, bilirubin level changes, complications, and the relationship between the 3 needs to be supported by multi-center large sample data, and even high-quality prospective studies are necessary to further clarify the role and impact of bilirubin levels on children with diabetes.

The many protective effects of bilirubin in diseases and health are increasingly being recognized, particularly the antioxidant and immunomodulatory effects.[24,27,28] In recent years, the role of bilirubin in the development of diabetes and its complications has also received greater attention.[8–10,21,26,29] It is exciting that certain approaches can be used to mildly elevate the bilirubin level above the optimal threshold (>10 μmol/L), such as healthy diet and lifestyle, nutraceutical, and pharmacological applications that can modulate the activities of HO-1/UDP-glucuronosyltransferase as well as the functions of liver to transport bilirubin.[28] Bilirubin and these approaches may serve as new therapeutics for diabetes in the future. However, until now, most studies were retrospective studies and animal experiments, and there is a lack of prospective clinical studies, particularly with the intervention of bilirubin as the antioxidant or other approaches to elevate bilirubin level.

Islet transplantation is considered the most promising treatment option for patients with T1DM. However, islets are susceptible to oxidative stress and nonspecific inflammatory damage in the early stage of transplantation, and this is the main cause of islet transplantation failure. Teams at home and abroad[11,30] have developed new bilirubin nanoparticles or supramolecular carriers for islet transplantation in animal experiments and determined that the new-type bilirubin possesses the characteristics of long local action time, stronger antioxidant, and anti-inflammatory ability, overcoming the shortcomings of traditional bilirubin such as water insolubility, fast metabolism, systemic action, and low toxicity, protecting the transplanted islets from oxidative stress damage and inhibiting the production of inflammatory cytokines, prolongs the life and the function of regulating blood sugar of islet cells. Therefore, in the future, this approach possesses good research prospects and socio-economic significance to improve blood glucose control, reduce oxidative stress damage, and delay the loss of islet function and the occurrence and development of complications by targeted control of bilirubin metabolism and level.

Certain limitations exist in this study. First, we just speculated the oxidative stress was present in T1DM patients according to other research results, and we did not directly assess the redox homeostasis of the body and analyze the associations of some oxidative stress indicators and bilirubin levels. Second, we did not monitor the changes of bilirubin levels in different disease states and disease durations in the same patient. Third, we did not investigate the effect of administration of exogenous bilirubin as an antioxidant to T1DM patients.

5. Conclusions

In summary, serum bilirubin level may be associated with the status of blood glucose control and oxidative stress, and it possesses the potential to be a biomarker of oxidative stress in children with diabetes. However, long-term follow-up, multi-center large sample data support and in-depth research focused on children with diabetes are still required.

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Author contributions

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