International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2019): 7.583

Role of Bilirubin in the Development and Progression of Diabetes Mellitus Type (2) and its Complications

Hadeer M. Baker[1], Soher A.Mohamed Ismail[2], Ahmed M. Sayed Nasr[3], Iman A. Fahmy[4], Safyea Mohamed Abo. El-Makarem[5], Mamdouh A.Taha[6]

[1, 3. 6]Chemistry Department, Faculty of Science, Fayoum University

[2]Medical Biochemistry Department, Research Institute of Ophthalmology

[4]Ophthalmic Medicine and Surgery Department, Research Institute of Ophthalmology

[5]Clinical Pathology Department, Research Institute of Ophthalmology

Abstract: ***Diabetes mellitus (DM) is defined as a metabolic disorder that is characterized by hyperglycemia and disturbance in the metabolism of macromolecules. Complications of DM include micro-vascular diabetic complications such as nephropathy and retinopathy. Bilirubin is a waste toxic product, however, its role as an endogenous anti-oxidant was studied. The study aims to investigate the role of bilirubin in the progression of nephropathy and retinopathy in type (2) diabetes patients. This was conducted on 4 groups, healthy controls, diabetics without complications, diabetics with retinopathy and diabetics with nephropathy. Laboratory investigations were performed for participants including; urine albumin/creatinine ratio, glycosylated hemoglobin (HBA_{1C}), serum total and direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, cholesterol, triglycerides, high-density lipoprotein –cholesterol (HDL) and fasting blood glucose (FBG).There was a significant increase in serum total bilirubin, direct bilirubin, ALT, AST, urea, creatinine, total cholesterol and HBA_{1C} between the control group and all groups of patients. Also, there was a significant difference in urine albumin /creatinine ratio in all groups of patients compared to controls. Serum direct bilirubin was significantly higher in the diabetic nephropathy group when compared to the diabetics without complications and retinopathy groups. Serum total bilirubin was lower in diabetics with retinopathy when compared to diabetics without complications. These results mean that increased serum level of both direct and total bilirubin has a protective effect in diabetic nephropathy and retinopathy.***

Keywords: T2D, Bilirubin, Nephropathy, Retinopathy

1. Introduction

DM was defined by American Diabetes Association (**ADA)** and World Health Organization (**WHO)** as the metabolic disease that generates from multiple etiologies, characterized by hyperglycemia and disturbance in the metabolism of carbohydrates, proteins, and fats resulting from defects in insulin action or secretion or even both. DM incidence is growing globally (**Boulton et al., 2005)** and it is expected to grow to a population of 366 million by 2030 (**Wild et al., 2004).**

The burden of DM is taking place in developing countries and 80% of diabetic cases are living in developing countries (**Shaw et al., 2010).** It was found that diabetes was prevalent in 20% of the Egyptian rural population **(Bos et al., 2013).** It was stated that diabetes prevalence was around 15.56% among Egyptian adults between 20 and 79 years (**Hegazi et al., 2015).**

Diagnosis of DM characterized by the presence of hyperglycemia symptoms and plasma glucose concentration ≥7 mmol/L. There are two types of diabetes, type (1) and type (2). Type (2) develops in adults and it is correlated to an unhealthy diet, lack of physical activity, hereditary risk factors and obesity (**Al Bahnasy et al., 2017).**

HbA_{1C}recommended by **ADA., 2010 & WHO., 2011**as a measurement for the average glycaemia over previous 2-4 months (**Nathan et al., 2007).**

Complications of DM include micro-vascular diabetic complications which are associated with vascular permeability impairment that has an effect on different organs and tissues such as neurons, kidneys, and retina **(Mokini and chiarelli., 2006).** Hyperglycemia stimulates protein kinase-C (PKC) which in turn induces diabetic retinopathy (**Lotfy et al., 2017).**

The elevation of blood glucose in retinal cells of diabetic patients may lead to increased risk of both retinopathy and accompanied blindness (**Ola et al., 2006 &Mohamed et al., 2007).** As retina is susceptible to oxidative damage (**Kumari et al., 2008)**, oxidative stress acts as a key factor in the pathogenesis of diabetic retinopathy (**Madsen-Bouterse and Kowluru., 2008).**

Diabetic nephropathy is another complication of DM and it results in protein filtration elevation in urine (**Susztak and Bottinger., 2006).** The increased urinary albumin excretion is an early indicator of diabetic nephropathy (**Dronavalli et al., 2008).**

Both of pathogenesis and etiology of diabetic nephropathy aren't clear, however, oxidative stress was associated with diabetic nephropathy progression and it was suggested that

inhibition of kidney dysfunction may occur by antioxidants (**Zhang et al., 2017)**

Bilirubin was considered a waste toxic product for a long time, however, it was recognized that it has a potential endogenous anti-oxidant role under physiological conditions (**Stocker et al., 1987).** Therefore, in the present study, we aimed to investigate the effect of bilirubin on the progression and development of nephropathy and retinopathy in diabetic patients.

2. Subjects and methods

2.1 Subjects and study design:

This study included 60 individuals who were divided into 4 groups, healthy controls, diabetics without complications, diabetic retinopathy and diabetic nephropathy groups. Each group involved 15 individuals. The participants were outpatients of the Research Institute of Ophthalmology referred to subspecialty clinics (medical and biochemical clinics). Age of subjects ranged from 40 to 60 years. All subjects have been investigated clinically and ophthalmologically to diagnose diabetes, diabetic nephropathy, and diabetic retinopathy. The exclusion criteria were: smokers, diabetic neuropathy, heart disease and other eye diseases except for retinopathy.

2.2 Laboratory Investigations

Whole blood samples were collected on EDTA to investigate HBA_{1c}, urine samples were collected to investigate albumin/creatinine ratio, while serum samples were collected to investigate total and direct bilirubin, ALT, AST, serum urea, serum creatinine, serum cholesterol, serum triglyceride, serum HDL and fasting blood glucose. All parameters were measured by using usual commercial kits except HBA1C which was measured by using libona system (**ADA., 2010)**.

2.3 Statistical Analysis

The statistical package for social science (SPSS version 21) was used for data analysis. Mean and the standard deviation were used to describe quantitative data. The bivariate relationship was displayed in cross tabulations. P-value was significant at (≤0.05) level. Sensitivity and specificity were determined using Roc curve.

3. Results

The present study included 60 participants who were classified into four groups, healthy individuals as controls, patients with type (2) diabetes as diabetics without complications, patients as diabetics with nephropathy and patients as diabetics with retinopathy (15 of each).

Table 1: Laboratory Mean level Values of the Studied Groups

Lab investigations	Control group Mean ±SD	Diabetic without complications group Mean ±SD	Diabetic Retinopathy group Mean ±SD	Diabetic Nephropathy group Mean ±SD	P-value
S. Total bilirubin (ng/ml)	1.13±0.13	0.83±0.10	0.49±0.08	0.79±0.24	<0.001*
S. Direct bilirubin (mg/dl)	0.32±0.12	0.28±0.09	0.24±0.06	0.39±0.16	0.004*
S. AST (IU/L)	13.5±3.4	25.7±9.5	37.3±18.0	22.0±6.8	<0.001*
S. ALT (IU/L)	15.9±5.5	28.3±9.9	35.2±13.0	27.2±9.5	<0.001*
Creatinine (mg/dl)	0.96±0.22	0.87±0.23	0.86±0.22	2.54±1.32	<0.001*
S. Urea (mg/dl)	29.1±8.1	31.3±14.8	25.9±9.1	83.2±38.4	<0.001*
S. Cholesterol (mg/dl)	128.0±40.9	178.9±37.5	162.3±44.2	196.5±70.0	0.003*
S. Triglycerides (mg/dl)	93.5±20.5	168.4±50.7	171.5±115.8	189.4±105.1	0.013*
S. HDL (mg/dl)	55.5±14.7	37.3±4.0	41.6±7.6	37.0±3.3	<0.001*
S. Albumin/creatinine ratio	13.0±6.0	22.4±4.7	33.7±6.8	35.2±6.0	<0.001*
S. FBG (gm/ml)	84.7±12.5	113.1±28.4	166.9±57.5	158.1±38.3	<0.001*
S. HbA_{1C}	6.3±0.2	6.8±0.9	9.1±1.5	9.6±1.8	<0.001*

(HBA_{1C}) Glycosylated hemoglobin. **(ALT)** Alanine aminotransferase. **(AST)** Aspartate aminotransferase. **(HDL)** High density lipoprotein. **(FBG)** Fasting blood glucose.

Mean levels of measured parameters for all studied groups shown in the table (1).

Total and direct bilirubin were significantly different in all groups and exhibit the lowest mean levels in diabetic retinopathy group (P-value<0.001, 0.004) respectively. In contrast to AST, ALT, HDL, and FBG which exhibit highest mean levels (P-value<0.001) for each on retinopathy group.

Other parameters; creatinine, urea, cholesterol, triglycerides, albumin /creatinine ratio and HbA_{1c} recorded the highest mean levels in the nephropathy group (P-value<0.001, <0.001, 0.003, 0.013,<0.001,<0.001) respectively.

Table 2: Laboratory findings in DM with Nephropathy and Retinopathy

Lab investigation	Diabetic retinopathy		Diabetic nephropathy	
	P-value	95% CI	P-value	95% CI
Total bilirubin	**<0.001***	1.000–1.000	0.431	0.362–0.807
Direct bilirubin	0.340	0.397–0.808	**0.046***	0.528–0.899
S.AST	**0.046***	0.520–0.907	0.633	0.336–0.766
S.ALT	0.254	0.408–0.836	0.901	0.297–0.730
Creatinine	0.983	0.289–0.715	**<0.001***	0.000–1.000
Urea	0.184	0.434–0.850	**<0.001***	0.000–1.000
Cholesterol	0.130	0.452–0.872	0.290	0.400–0.827
Triglycerides	0.648	0.333–0.765	0.663	0.334–0.759
HDL	0.062	0.501–0.899	0.917	0.299–0.723
Albumin/ creatinine	**<0.001***	0.000–1.000	**<0.001***	0.000–1.000
FBG	**0.002***	0.674–0.979	**<0.001***	0.000–1.000
HbA1c	**<0.001***	0.000–1.000	0.000	0.000–1.000

(HBA_{1C}) Glycosylated hemoglobin
(ALT) Alanine aminotransferase
(AST) Aspartate aminotransferase
(HDL) High density lipoprotein
(FBG) Fasting blood glucose

Direct bilirubin had higher mean level in nephropathy group than diabetics without complications (P-value=0.046).Also, creatinine, urea, albumin/creatinine ratio and FBG had higher mean level in nephropathy group than diabetics without complications (P-value<0.001).

Retinopathy group had higher mean levels as regards ofAST (P-value=0.046), total bilirubin, albumin/creatinine ratio, HbA_{1c} (P-value<0.001) and FBG (P-value=0.002).

Table3: Correlations of Different Laboratory Values in both of FBG and HbA_{1c}

Lab investigation		Fasting blood glucose			
		Control group	Diabetic group	Nephropathy group	Retinopathy group
HbA1c	**r**	0.247	-0.086	-0.237	0.558
	p	0.374	0.761	0.394	**0.031***
ALT	**r**	0.065	0.532	0.346	0.177
	p	0.819	**0.041***	0.207	0.528
Albumin/ creatinine ratio	**r**	0.132	-0.086	-0.111	0.612
	p	0.640	0.761	0.693	**0.015***
Total bilirubin	**r**	-0.290	-0.393	0.380	-0.353
	p	0.295	0.148	0.162	0.196
Direct bilirubin	**r**	0.197	-0.322	0.322	-0.199
	p	0.481	0.241	0.241	0.476
	HbA_{1c}				
Creatinine	**r**	0.260	0.110	0.953	0.094
	p	0.349	0.697	**<0.001***	0.738
Urea	**r**	-0.245	-0.562	0.928	0.175
	p	0.378	0.029	**<0.001***	0.533
Triglycerides	**r**	-0.296	-0.462	0.619	0.294
	p	0.284	0.083	**0.014***	0.287
Albumin/ creatinine ratio	**r**	-0.098	-0.096	0.884	0.069
	p	0.728	0.734	**<0.001***	0.807
Total bilirubin	**r**	0.032	0.078	-0.234	-0.007
	p	0.911	0.783	0.402	0.981
Direct bilirubin	**r**	0.206	-0.026	0.062	-0.191
	p	0.462	0.927	0.825	0.495

Glycosylated hemoglobin (HBA_{1C}), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), High density lipoprotein (HDL), Fasting blood glucose (FBG)

Correlation between different laboratory parameters against FBGand HbA_{1c} in the four groups were assessed in (Table3).

FBG positive correlation detected with HbA_{1c} (P-value=0.031, r=0.558) and with albumin/creatinine ratio (P-value=0.015, r=0.612) in the diabetic retinopathy group, while correlated positively with ALT (P-value=0.041, r=0.532) in diabetics without complications.

$HbA_{1c,}$ positive correlation detected with each of creatinine (P-value<0.001, r=0.953), urea (P-value<0.001, r=0.928), triglycerides (P-value=0.014, r=0.619) and albumin/creatinine ratio with (P-value<0.001, r=0.884) in the nephropathy group.

4. Discussion

Diabetic nephropathy and diabetic retinopathy are the main complications of diabetes.Therefore, comparison of mean levels of the studied parameters in diabetics without complications and diabetics with nephropathy or retinopathy and their effect on the progression of diabetic complications was studied

Four groups were investigated to detect the effect of bilirubin on the progression of both diabetic retinopathy and diabetic nephropathy through measurement of total and direct bilirubin, liver enzymes (AST, ALT), lipid profile (cholesterol, HDL, triglycerides), creatinine, urea, FBG, HbA_{1c} and albumin/creatinine ratio.

In this study, diabetics without complications hadhigh level of triglycerides, FBG and HbA_{1c} but other measured parameters including total and direct bilirubin were detected in normal range when compared to control group.

In contrast to these findings, (**Raikwar et al., 2018)** reported that direct bilirubin, ALT and AST were higher than normal in type (2) diabetes patients.

The mean level of both total and direct bilirubin in diabetics without complications was in normal range, but it was lower than that of the control group. Thus, the decrease of bilirubin level associated with development of DM which reflects the protective effect of bilirubin against progression of type (2) diabetes mellitus.

In agreement with these findings, **(Rejendran et al., 2018)** showed that low level of bilirubin was a risk factor for diabetes type (2).

In contrast to these findings, (**Wang et al., 2017)** found that elevated serum direct bilirubin was associated with an increased risk of developing type (2) diabetes.

In the current study, the diabetic nephropathy group had high mean levels of HbA_{1c}, FBG, Albumin/creatinine ratio, triglycerides, urea, and creatinine while AST, ALT, cholesterol, and HDL were in the normal range. Regarding to bilirubin, the mean level of direct bilirubin was higher than normal, whereas that of total bilirubin was in normal range.

By investigating the parameters that differed significantly between diabetics without complications and diabetic nephropathy, mean levels of direct bilirubin, creatinine, urea, Albumin/creatinine ratio, and FBG significantly increased in diabetic nephropathy than in diabetics without complications group.

These results mean that decrease of direct bilirubin level occurs with progression of diabetic nephropathy.

This agrees with (**Mashitani et al., 2013)** whoreported that baseline level of serum bilirubin correlated independently with diabetic nephropathy progression in type (2) diabetic patients and with (**Rajendran, et al., 2018)**who revealed

that a low level of bilirubin was a risk factor for the development of diabetic nephropathy

Baranano et al., 2002 suggested thatbilirubin had an anti-oxidant role and could protect cells from excess hydrogen peroxide, so it can be concluded that lower concentration of serum bilirubin is associated with increased oxidative stress which in turn accelerates the progression of diabetic nephropathy.

In other words, the high level of bilirubin has an inhibitory effect on the progression of diabetic nephropathy via its anti-oxidant effect

This study reported that total bilirubin was lower in nephritic patients than in diabetic patients, but with no significant difference in agreement with (**Toya et al., 2014)**, who showed that there was no significant increase in bilirubin between patients with diabetic nephropathy than those with diabetes without kidney disease

In contrast, a cross-sectional study (**Yasuda et al., 2011)** showed a correlation between total serum bilirubin and prevalence of diabetic nephropathy in patients with impaired glucose metabolism. another study showed that total bilirubin was higher among diabetic patients with no kidney disease than among nephritic patients (**Hamamoto et al., 2015).**

It was concluded in a meta-analysis (**Zhang et al., 2017)** that bilirubin can act as a diagnostic biomarker.

The diabetic retinopathy group showed increased mean levels of ALT, triglycerides, FBG, and HbA_{1c}, whereas other parameters were in the normal range.

The mean levels of total bilirubin, AST, albumin/creatinine ratio, FBG, and HbA_{1c} increased significantly in diabetic retinopathy than in diabetics without complications.

Although there was a significant decrease in the mean level of total bilirubin in the diabetic retinopathy group than in diabetics without complications, the mean level in diabetic retinopathy was in the normal range.

Karuppannasamy et al., 2017 found that the level of serum bilirubin was lower in diabetic patients with retinopathy than those without retinopathy and it was shown that serum total bilirubin is an independent risk factor associated with diabetic retinopathy, this was in agreement with this study findings. Also, (**Dave et al., 2015)** showed the same findings, serum total and direct and indirect bilirubin levels were higher in patients without diabetic retinopathy than those with retinopathy

Several studies (**Yasuda et al., 2011 & Cho HC 2011)** suggested an inverse correlation between serum bilirubin and diabetic retinopathy. This inverse correlation was also reported by (**Ghaffar et al., 2016)** which demonstrated that serum bilirubin can predict the progression of diabetic retinopathy over time

It seems that direct bilirubin is risky for nephropathy, whereas total bilirubin is risky for retinopathy.

This study investigated the correlation between different parameters with both FBG and HbA_{1c}. There was a significant positive correlation between ALT and FBG in diabetics without complications, whereas in diabetic retinopathy, there were a significant positive correlations between FBG and both of HbA_{1c} and albumin/creatinine ratio.

All significant correlations between HbA_{1c} and creatinine, urea, triglycerides and albumin/creatinine were positive and found in the diabetic nephropathy group only.

The previous correlations were to the best of our knowledge addressed for the first time in our study reporting that the level of bilirubin was negatively associated with FBG and HbA_{1c} in diabetic patients (**Farasat et al., 2017),** however in our study there was no significant association between bilirubin and such variables in the 4 studied groups.

5. Conclusion

The present study showed that low levels of both direct and total bilirubin were associated with increased risk of diabetic retinopathy and nephropathy, whereas increased levels (within the physiological range) can be considered as a protective factor against diabetes type (2) and its important micro-vascular complications (diabetic retinopathy and diabetic nephropathy).

References

[1] Al Bahnasy RE, Mahrous OA, El Shazli HM, Gabr HM, Ibrahem RA, Soliman SS. Prevalence of diabetes mellitus and impaired glucose tolerance among adolescents in Menoufia governorate. Menoufia Medical Journal. 2017:1;30 (1):69.
[2] American Diabetes Association (ADA). Standards of medical care. Diabetes Care 2006; 29:s4–s42.
[3] American Diabetes Association. Standards of medical care in diabetes–2010. Diabetes Care;2010: 33 (Suppl. 1), S11–S61.
[4] American Diabetes Association, 2010,clinical practicerecommendations,33 (supplement 1)
[5] Baranano DE, Rao M, Ferris CD, Snyder SH. Biliverdin reductase: A major physiologic cytoprotectant. Proc Natl Acad Sci U S A. 2002;9:16093–98.
[6] Bos M, Agyemang C. Prevalence and complications of diabetes mellitus in Northern Africa, a systematic review. BMC public health. 2013;13 (1):387.
[7] Boulton AJ, Vileikyte L, Ragnarson-Tennvall G and Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005; 366:1719-1724
[8] Cho HC. The relationship among Homocysteine, Bilirubin, and diabetic retinopathy. Diabetes Metab J. 2011;35:595-601.
[9] Dave A, Kalra P, Gowda BH, Krishnaswamy M. Association of bilirubin and malondialdehyde levels with retinopathy in type 2 diabetes mellitus. Indian J Endocrinol Metab. 2015;19:373–77.

[10] Dronavalli S, Duka I, Bakris GL. The pathogenesis of diabetic nephropathy. Nature Clin Prac Endocrinol Metab 2008; 4: 444-52.
[11] Farasat T, Sharif S, Manzoor F, Naz S. Serum Bilirubin is Significantly Associated with Hba1c in Type 2 Diabetic Subjects. Endocrinol Metab Int J 2017, 5 (6): 00142.
[12] Ghaffar T, Marwat ZI, Ullah F, Khan S. Association of serum total bilirubin level with diabetic retinopathy in type 2 diabetes mellitus. Journal of Ayub Medical College Abbottabad. 2016:28;28 (3):537-41.
[13] Hamamoto S, Kaneto H, Kamei S,. Low bilirubin levels are an independent risk factor for diabetic retinopathy and nephropathy in Japanese patients with type 2 diabetes. Diabetes Metab 2015;41:429–31.
[14] Hegazi R, El-Gamal M, Abdel-Hady N, Hamdy O. Epidemiology of and risk factors for type 2 diabetes in Egypt. Annals of global health. 2015:1;81 (6):814-20.
[15] Karuppannasamy D, Venkatesan R, Thankappan L, Andavar R, Devisundaram S. Inverse association between serum bilirubin levels and retinopathy in patients with type 2 diabetes mellitus. Journal of clinical and diagnostic research: JCDR. 2017;11 (2):NC09.
[16] Kumari S, Panda S, Mangaraj M, Mandal MK, Mahapatra PC. Plasma MDA and antioxidant vitamins in diabetic retinopathy. Indian J Clin Biochem. 2008;23:158-62.
[17] Lotfy M, Adeghate J, Kalasz H, Singh J, Adeghate E. Chronic complications of diabetes mellitus: A mini review. Current diabetes reviews. 2017:1;13 (1):3-10.
[18] Madsen-Bouterse SA, Kowluru RA. Oxidative stress and diabetic retinopathy: pathophysiological mechanisms and treatment perspectives. Rev Endocr Metab Disord. 2008;9:315-27.
[19] Mashitani T, Hayashino Y, Okamura S, Tsujii S, Ishii H, Diabetes Distress and Care Registry at Tenri Study Group. Correlations between serum bilirubin levels and diabetic nephropathy progression among Japanese type 2 diabetes patients: a prospective cohort study [Diabetes Distress and Care Registry at Tenri (DDCRT 5)]. Diabetes care. 2013 Aug 29:DC_130407.
[20] Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. JAMA 2007; 298: 902-16.
[21] Mokini Z, Chiarelli F. The molecular basis of diabetic microangiopathy. Pediatr Endocrinol Rev 2006; 4: 138-52.
[22] Najam SS, Sun J, Zhang J,Xu M, Lu J, Sun K, et al. Serum total bilirubin levelsand prevalence of diabetic retinopathy in a Chinese population. J Diabetes. 2014;6:221–27.
[23] Nathan, D. M., Turgeon, H. & Regan, S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia;2007: 50:2239–2244.
[24] Ola MS, Berkich DA, Xu Y,. Analysis of glucose metabolism in diabetic rat retinas. Am J Physiol Endocrinol Metab 2006; 290: E1057-E67.
[25] Raikwar V, Dangi V, Suran A. Liver function test parameters in patients having type 2 diabetes mellitus and hypertensive diabetes. Liver. 2018;3 (1).
[26] Rajendran S, Manju M, Mishra S, Kunar R. Association between serum bilirubin and Albuminuria in type 2 diabetes mellitus and diabetic nephropathy. International Journal of Clinical Biochemistry and Research, April-June, 2018;5 (2):232-237.
[27] Shaw, J. E., Sicree, R. A. & Zimmet, P. Z. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res. Clin. Pract;2010: 87:4–14.
[28] Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235:1043–46.
[29] Susztak K, Bottinger EP. Diabetic nephropathy: a frontier for personalized medicine. J Am Soc Nephrol 2006; 17: 361-7.
[30] Toya K, Babazono T, Hanai K,. Association of serum bilirubin levels with development and progression of Albuminuria, and decline in estimated glomerular filtration rate in patients with type 2 diabetes mellitus. J Diabetes Invest 2014;5:228–35.
[31] Wang J, Li Y, Han X, Hu H, Wang F, Li X, Yang K, Yuan J, Yao P, Miao X, Wei S. Serum bilirubin levels and risk of type 2 diabetes: results from two independent cohorts in middle-aged and elderly Chinese. Scientific reports. 2017 Feb 6;7:41338.
[32] Wild S, Roglic G, Green A, Sicree R and King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27:1047-1053.
[33] World Health Organization (WHO). Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation 1999. Part 1. Diagnosis and classification of diabetes mellitus Geneva: World Health Organization (WHO) 1999.
[34] World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation [online], http://www.who.int/diabetes/publications/report-hba1c_2011.pdf (2011).
[35] Yasuda M, Kiyohara Y, Wang JJ, Arakawa S, Yonemoto K, Doi Y,. High serum bilirubin levels and diabetic retinopathy: the Hisayama Study. Ophthalmology. 2011;118:1423-28.
[36] Zhang D, Zhu B, Zhang W, Wang W, Guo D, Yang L, Wang L. Total bilirubin level may be a biomarker of nephropathy in type 2 diabetes mellitus: a meta-analysis of observational studies based on MOOSE compliant. Medicine. 2017 Jan;96 (1).