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HBA1C AS A PREDICTOR OF DYSLIPIDEMIA IN ALGERIAN TYPE 2 DIABETIC PATIENTS

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Abstract

Background and Aims: *The aim of our study was to test whether HbA_1c can serve as a predictor of dyslipidemia in type 2 diabetic patients.* ***Materials and Methods:*** *450 type 2 diabetic patients (165 males, 285 females), mean age of 58.7±9.9 years were included in this study. Venous blood samples were collected from all patients; serum was analyzed for HbA1c, fasting blood glucose, total cholesterol (TC), triglycerides, high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-C (LDL-C). LDL-C/HDL-C and TC/HDL-C risk ratio were also calculated. For the data evaluation, Pearson's correlation coefficient and independent samples t-test were used. Statistical significance was defined by a probability level of $p < 0.05$.* ***Results:*** *399 (88.66%) of our patients had dyslipidemia. Low HDL-C was the most common form of dyslipidemia, observed in 311 patients (69.11%). Hypertriglyceridemia was found in 184 (40.88%) and elevated LDL-C in 229 (50.88%) patients. Values of HbA1c >7.0 % showed significant correlation with TC, LDL-C, TG, LDL-C/HDL-C and TC/HDL-C risk ratio, as compared to patients with HbA1c ≤ 7.0% ($p<0.05$ for all). HDL-C levels didn't differ between the two groups ($p= 0.322$).* ***Conclusions:*** *The study suggests the usefulness of HbA1c as a predictor of dyslipidemia for screening of type 2 diabetic patients at high risk of cardiovascular diseases.*

key words: *Type 2 diabetes, Dyslipidemia, Cardiovascular disease.*

Background and aims

Dyslipidemia is a major risk factor for macrovascular complications in patients with type 2 diabetes mellitus (T2DM) [1]. Macrovascular disease is the most common cause of morbidity and mortality in T2DM [2], and is defined as illnesses affecting the larger arteries supplying the heart, brain and the lower limbs, thereby causing cardiovascular disease (CVD), cerebrovascular disease and peripheral vascular disease. Type 2 diabetic patients often have an atherogenic lipid profile (high triglycerides [TG] and low high-density lipoprotein cholesterol [HDL]) which greatly increases the risk of developing CVD [3]. Early

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correction of dyslipidemia in this type of patients reduces cardiovascular risk [4].

The aim of the present study was to study the lipid profile in type 2 diabetic patients and assess the importance of HbA1c as an indicator of dyslipidemia and future risk of cardiovascular disease in this group of patients.

Materials and methods

This prospective cohort study included 450 type 2 diabetic patients: 285 (63.3%) women and 165 (36.6%) men. Patients were recruited from the Internal Medicine Hospital of Ain Defla in the Western Province of Algeria between January 2011 and January 2012. Patients were subjected to physical examination and laboratory tests. Candidates with other causes of secondary dyslipidemia (hypothyroidism, Cushing disease or steroid medication use, nephrotic syndrome, etc.) and patients on lipid-controlling drugs were not included.

Blood samples were obtained after 12-hours fasting. Fasting Blood Glucose (FBG) was assessed using colorimetric enzymatic technique (Prochima), total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) levels were measured with by enzymatic assays. Total cholesterol was determined in plasma, and HDL-C was measured in the supernatant, after precipitation of very low density lipoprotein cholesterol (VLDL-C) and low density lipoprotein cholesterol (LDL-C) with dextran sulfate in magnesium chloride. LDL-C levels were estimated using the Friedewald formula: LDL-C= TC – HDL-C - TG/5. HbA1c was measured by using an ion exchange chromatography method (Crest A Coral clinical system, USA).

According to the NCEP - ATPIII guidelines, hypercholesterolemia is defined when TC > 200 mg/dl, high LDL-C when the value is over 100 mg/dl, hypertriglyceridemia if TG >150 mg/dl and low HDL-C when the value is below 40 mg/dl in men, and 50 mg/dl in women. Patients with one or more parameters (TC, TG, HDL-C, or LDL-C) outside values recommended by the NCEP-ATPIII were considered to have dyslipidemia [5]. Dyslipidemias were classified into: mixed dyslipidaemia (three abnormal lipid parameters); combined dyslipidemia (two abnormal lipid parameters) and isolated dyslipidemia (only one abnormal parameter) [6]. The impact of glycemic control on various parameters was evaluated by categorizing all patients into two groups based on their HbA1c levels. Group I (good glycemic control; HbA1c <7%) and Group II (poor glycemic control; HbA1c ≥ 7%). The selection of these cutoff values of HbA1c was based on the current American Diabetes Association recommendations for most non-pregnant adults [7].

Statistical analysis Statistical analysis was performed using SPSS version 17.0. Pearson's correlation coefficient was used to examine the association between various continuous parameters; the linear regression model was used. Independent samples t-test was used to compare means of different variables. Data were presented as mean ± standard deviation (SD). The results were considered statistically significant when the two tailed p value was < 0.05.

Results

General characteristics of the study population are presented in Table 1. The mean age (±S.D) was 67.72 ± 10.24 versus 45.86 ± 12.08 years in males and females, respectively. The average duration of diabetes was 9.1 ± 5.1 years. The mean BMI was 29.8± 5.9 kg/m2. Also, 315 (70%) of patients were hypertensive.

Low HDL-C was the most common form of dyslipidemia and was found in 311 (69.11%)

T2DM patients; the proportion was much higher in women 234 (82.10%) as compared to men 77 (46.66%). Hypertriglyceridemia was found in 184 (40.88%) patients: 114 (69.09%) men and 70 (24.56%) women. Elevated LDL-C was found in 229 (50.88%) patients: 89 (53.93%) men and 140 (49.12%) women. Hypercholesterolemia was found in 147 (32.66%) of patients: 53 (32.12%) men and 94 (32.98%) women. Among all patients, 141 (31.33%) had only one abnormal lipid profile parameter, 117 (26%) had two abnormal lipid parameters, 120 (26.66%) had three abnormal lipid profile parameters and 21 (4.66%) had all four lipid parameters abnormal.

Table 1. General characteristics of the study population.

General characteristics	(Mean ± SD)
Duration of diabetes mellitus (years)	9.5± 5.1
BMI (kg/m^2)	29.8± 5.9 (TOTAL)
Females	30.16±0.1
Males	28±10
Waist circumference (cm)	
Females	102 ± 10.9
Males	92 ± 11.98
Age (years)	58.7± 9.9 (total)
Males	67.72 ± 10.24
Females	45.86 ± 12.08
Sex (number)	
Females	285
Male	165
Hypertension (%)	70%

The impact of gender on serum lipids is shown in Table 2. Among circulating lipids, TC, LDL-C and TG were significantly higher in male patients (TC: p=0.011, LDL-C: p=0.002, TG: p=0.031). HDL-C was also slightly lower (p=0.033) in females as compared to males. The mean value of HbA1c and FBG were slightly higher in females in comparison to male patients, but the differences were not significant.

HbA1c demonstrated significant correlations with TC (r=0.40, p = 0.01), LDL-C (r =0.84; p=0.00) and LDLc/HDL-C ratio (r =0.3, p=0.01). The correlation of HbA1c with TG was positive (p=0.16), but that with HDL-C was negative (p=0.00). HbA1c was found to be a predictor of hypercholesterolemia (p=0.01, R^2=0.16; HbA1 and TC data have adjusted to the model in a satisfactory manner, this model explained a significant proportion of the variance in HbA1c variable: TC = 10.120* HbA1c + 74.537) and LDL-C (p=0.00, R^2=0.71, HbA1c and LDL-C data have adjusted to the model in a satisfactory manner, this model explained a significant proportion of the variance in HbA1c variable: LDL-C= 24,452*HbA1c - 55,373) by linear regression analysis. Furthermore, TG showed a significant association with HbA1c in the regression analysis (p=0.00, R^2=0.54, HbA1c and TG data have adjusted to the model in a satisfactory manner, this model explained a significant proportion of the variance in HbA1c variable, TG= 51.080*HbA1c - 145.108). HDL-C (p=0.00, R^2=0.24, HbA1c and HDL-C data have adjusted to the model satisfactory manner, this model explained a significant proportion of the variance in HbA1c variable, HDL-C= 2.252* HbA1c + 49.715) showed significant negative correlation with Hb1Ac (Pearson correlation coefficient: -0.490) as detailed in Figure 1.

Table 2. Lipid profile parameters of male and female type 2 diabetic patients

Parameter	Males (n = 165) Mean ± S.D	Females (n = 285) Mean ± S.D	p-value
TC (mg/dl)	190.66 ± 6.32	179.05 ± 0.99	0.011 *
TG (mg/dl)	200.21 ± 8.37	186.61 ± 9.43	0.031*
HDL-C (mg/dl)	36.52 ± 0.97	35.93 ± 0.61	0.033*
LDL-C (mg/dl)	110.89 ± 2.27	99.86 ± 0.05	0.002 **
HbA1c (mg/dl)	9.01 ± 0.10	9.85 ± 0.17	0.105
FBG (mg/dl)	149.44 ± 5.83	159.4 ± 7.56	0.296

* P < 0.05; ** P < 0.01

The biochemical parameters categorized by patients' glycemic control (HbA1c) are presented in Table 3. Group II (Hb1Ac > 7.0%) had

significantly higher values of TC (p = 0.024), TG (P=0.030), LDL-C (P=0.011), TC/HDL-C (p=0.001) and LDL-C/HDL-C (p=0.002) as compared to Group I (HbA1c ≤ 7.0%).

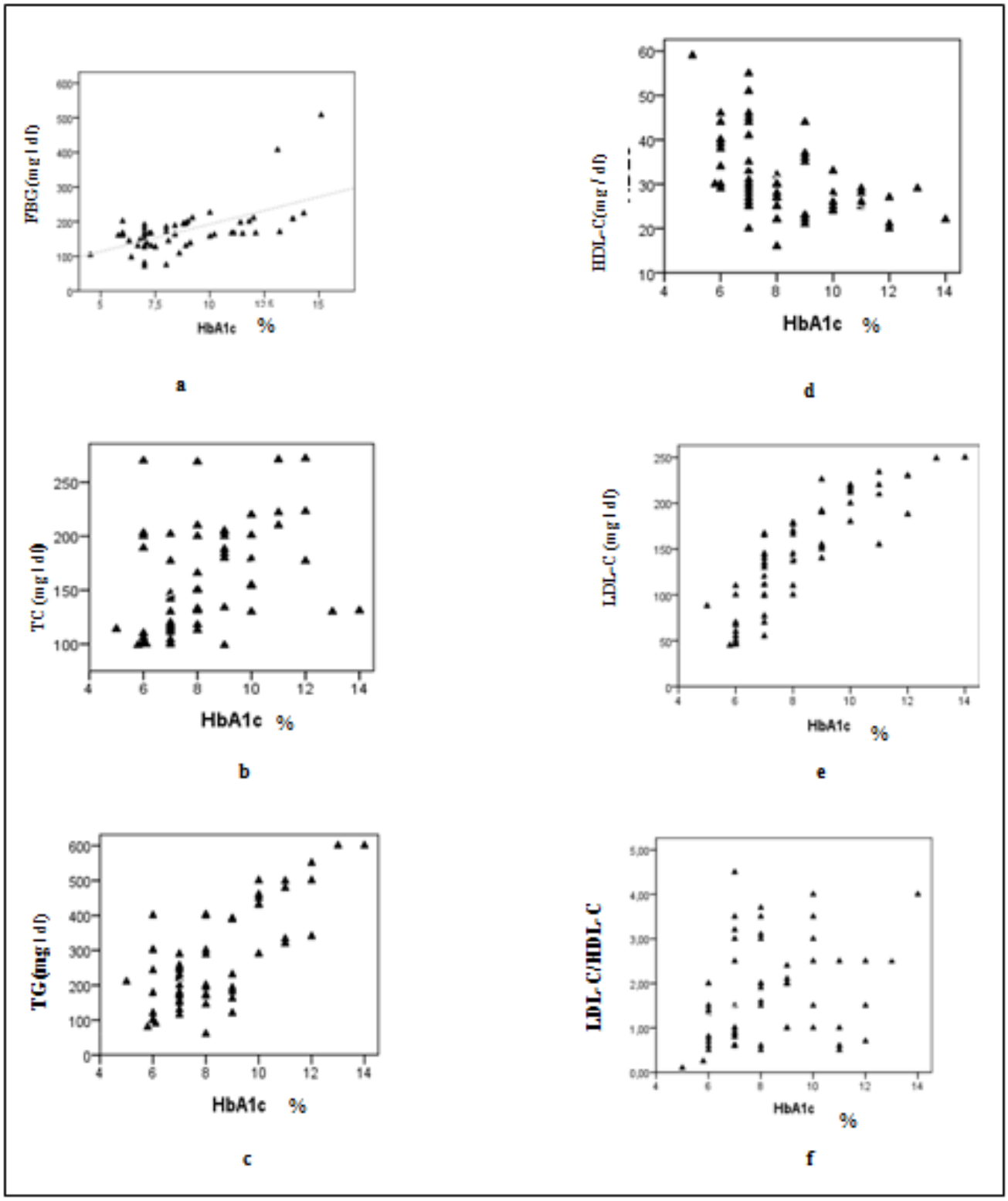

Figure 1. *Correlations between HbA1c, FBG and lipide profile parameters. (a) Positive correlation between HbA1c and FBG. (b) Positive correlation between TC and HbA1c. (c) Positive correlation between HbA1c and TG. (d) Negative correlation between HbA1c and HDL-c. (e) Positive correlation between HbA1c and LDL-c. (f) Positive correlation between LDL/ HDL ratio and HbA1c.*

Table 3. Biochemical parameters according to patients' glycemic control (HbA1c).

Parameter	HbA1c		p-value
	≤ 7.0% (*n*=165) Mean ± SD	> 7.0% (*n* = 285) Mean ± SD	
TC (mg / dl)	174.89 ± 5.29	181.78 ± 5.19	0.024 *
TG (mg / dl)	173.05 ± 7.88	199.36 ± 9.07	0.030 *
HDL-C (mg / dl)	41.79 ± 0.84	39.71 ± 0.68	0.322
LDL-C (mg / dl)	91.63 ± 4.27	107.86 ± 4.60	0.011 **
Risk ratio (TC / HDL-C)	3.76 ± 0.098	4.31 ± 0.127	0.001 ***
LDL-C/HDL-C	1.98 ± 0.089	2.43 ± 0.107	0.002 **
FBG (mg / dl)	123.56 ± 3.03	175.0 ± 6.79	0.001 ***

* P < 0.05; ** P < 0.01; *** P < 0.001

Discussion

In the present study, we evaluated the parameters of lipid profile in T2DM, and their correlation with HbA1c. HbA1c levels did not differ significantly between the two genders. However, there was a significant difference in the levels of lipid parameters between males and females (Table 2). Levels of TC, LDL-C and TG were significantly higher in men. These findings are consistent with those of previous studies [8]. Hyperlipidemia in females might be attributed to the effects of sex hormones on body fat distribution which lead to differences in altered lipoproteins [9].

A recent study, including 120 T2DM patients reported a mean HbA1c significantly higher in diabetic patients with silent myocardial ischemia [10]. The current study revealed a high prevalence of hypercholesterolemia, hypertri-glyceridemia, high LDL-C and low HDL-C levels which are all well known risk factors for cardiovascular disease. The results of our study and the reasons for dyslipidemia were comparable to a similar study reporting the patterns of diabetic dyslipidemia in Pakistani. They concluded that the pattern of dyslipidemia was characterized by high levels of LDL-C and low HDL-C [11].

Hyperglycemia and dyslipidemia generally coexist in diabetic patients with poor glucose control. The interaction of hyperglycemia and dyslipidemia increases the risk of macro- and micro-vascular complications [12]. The mechanisms by which hyperglycemia and dyslipidemia cause diabetic vascular diseases are the formation and accumulation of advanced glycation end products (AGEs) [13], increased oxidative stress, activation of protein kinase C (PKC), increased flux through the hexosamine pathway, vascular inflammation, deficiency of insulin action in the vasculature, and altered expression and action of hormones, growth factors, and cytokines [14]. In addition, chemical modification of lipoprotein in diabetic states, including peroxidation and glycation, may be an underlying pathogenic mechanism linking dyslipidemia to diabetic complications. For instance, oxidation may increase atherogenicity of the lipoproteins, whereas glycation may enhance the oxidative stress of the lipoproteins. Furthermore, chemical modification of proteins by lipids, such as formation of lipoxidation end products, has also been suggested to be a likely pathogen for vascular changes in diabetes [15].

HbA1c level of 7.0% is considered to be appropriate for reducing the risk of cardiovascular complications [16]. In the current study, diabetic patients with HbA1c > 7% had a

significant increase in TC, LDL-C, TG, TC/HDL-C and LDL-C/HDL-C ratio as compared to patients with HbA1c ≤ 7.0%. These results are similar to those of Chintamani et al. study [17]. Furthermore, Wagner and colleagues showed that the improvement in glycemic control from HbA1c of 10.54± 2.05% to HbA1c of 7.01 ±0.63% (P <0.0005) after a follow-up of 3.5 months resulted in a significant reduction in LDL-C - from 3.62± 1.15 to 3.34 ±1.02 mmol/L (p <0.05), and apo B - from 1.17 ±0.29 to 1.07± 0.25 g/L (p <0.01), with increase in LDL particle size from 25.10± 0.31 to 25.61 ±0.53 nm (P<0.005) in T2DM patients who had LDL phenotype B at baseline [18]. Their findings clearly indicate that HbA1c can provide valuable information besides its primary role in monitoring long-term glycemic control. Thus, HbA1c can be used as a predictor of cardiovascular risk in diabetics [19].

HbA1c abnormality indicates uncontrolled diabetes mellitus and dyslipidemia in diabetic patients and increases the risk of vascular complications. To prevent these complications, it is important to focus on HbA1c control and targeting lipids to avoid morbidity and mortality in diabetic patients. HbA1c measurement helps to control diabetes mellitus and helps identifying dyslipidemia [20]. In addition, another study reported that intensive glycemic control is associated with reduced cardiovascular events [21]. HbA1c is also used as a predictor of dyslipidemia in T2DM. [22]. HbA1c is associated with atherogenic dyslipidemia, particular TG and TG / HDL-C ratio, but not with TC, HDL-C or LDL-C [23].

Our data reveal a prevalence of 51.3% of LDL-C levels higher than 100 mg/dl, which is considered a risk factor for CHD and atherosclerosis similar to the results of Ahmed et al. study [24]. On the other hand, low HDL-C was found to be the most prevalent lipid abnormality, which is also associated with high risk of CHD and atherosclerosis.

Most patients with T2DM have dyslipidemia in varying degrees. With the increased levels of HbA1c, dyslipidemia becomes more severe [25]. The estimation of cardiovascular disease risk was increased by 18% for each 1% increase in absolute HbA1c value in diabetic population [5]. HbA1c is directly related to the severity of coronary artery disease (CAD) in diabetic patients [9]. Whereas improving the glycemic control can substantially reduce the risk of cardiovascular events in diabetics is debatable. Moreover, attempts to reduce cardiovascular risks resulted in the improvement of HbA1c even in the absence of any specific intervention targeting improvement of glycemic control [26]. A soluble form of receptor for advanced glycation end products (SRAGE) in type 2 diabetic patients with CAD was found to be elevated with significant association between SRAGE and HbA1c as well as serum lipids [27].

There were obvious limitations to our study, mainly being single centered and using a small sample size. Our study has also some strength since dyslipidemia is found frequently in patients with type 2 diabetes and seems to be correlated with glycemic control. Because it is a major risk factor for coronary heart disease, and one of the most important and frequent complications with a high premature mortality and morbidity rate, dyslipidemia should be better assessed, prevented, and treated as early as possible to avoid or reduce vascular damage.

Conclusion

This study showed a correlation between HbA1c and various lipid parameters or atherogenic ratios (LDL-C/HDL-C ratio). This suggests that with higher HbA1c values, the severity of dyslipidemia increases in T2DM patients. Therefore, diabetic patients with

elevated HbA1c and dyslipidemia can be considered as a very high risk group for cardiovascular diseases. Our results suggest that HbA1c may be used as indicator for early diagnosis of dyslipidemia in addition to its primary role in monitoring long-term glycemic control (HbA1c has the potential of being a dual biomarker).

Competing interests. The authors declare that they have no competing interests.

Authors' contributions. All authors read and approved the final manuscript.

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REFERENCES

1. Mooradian AD. Cardiovascular disease in type 2 diabetes mellitus: current management guidelines. *Arch Intern Med* 163: 33–40, 2003.

2. Koskinen SV, Reunanen AR, Martelin TP, Valkonen T. Mortality in a large population-based cohort of patients with drug-treated diabetes mellitus. *Am J* Public Health 88: 765–770, 1998.

3. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Circulation* 95: 69-75, 1997.

4. Ayaz KM, Ravindra M, Vivek R, Gopalakrishna Bhat P. A study on APO B100/APO A-I Ratio in uncontrolled type 2 diabetes mellitus. *Int J Appl Biol Pharma Tech* 2: 379-384, 2011. Accessed at : http://www.ijabpt.com/pdf/76063-II-Ajay%20Malik1].pdf

5. Selvin E, Marinopoulos S, Berkenblit G et al. Meta-analysis: glycosylated haemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med* 141: 421-431, 2004.

6. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. *J Diabetes Complications* 24: 84-89, 2010.

7. Gligor R, Crisnic I, Talpes S, Pilat L, Ghinga S, Maris L. Relationship between glycosylated hemoglobin and lipid metabolism in patients with type 2 diabetes. *Studia Univ. VG, SSV* 21: 313-318, 2011. Accessed at: http://www.studiauniversitatis.ro/pdf/21-2011/21-2-2011/SU21-2-2011Gligor.pdf

8. Ravipati G, Aronow WS, Ahn C et al. Association of hemoglobin A(1c) level with the severity of coronary artery disease in patients with diabetes mellitus. *Am J Cardiol* 97: 968–969, 2006.

9. Vinod Mahato R , Gyawali P, Raut P, Regmi P, Singh K, Pandeya DR. Association between glycaemic control and serum lipid profile in type 2diabetic patients: glycated haemoglobin as a dual biomarker. *Biomed Res* 22: 375-380, 2011. Accessed at: https://www.researchgate.net/publication/215774283_Association_between_glycaemic_control_and_serum_lipid_profile_in_type_2_diabetic_patients_Glycated_haemoglobin_as_a_dual_biomarker

10. Bouzid K , Ben Mami Ben Miled F, Hassine M et al. Study of cardiovascular risk factors in Tunisian patients with recent type 2 diabetes. *Ann Cardiol Angeiol (Paris)* 61: 81-87, 2012.

11. Mullugeta Y, Chawla R, Kebede T, Worku Y. Dyslipidemia associated with poor glycemic control in type 2 diabetes mellitus and the protective effect of metformin supplementation. *Ind J Clin Biochem* 27: 363–369, 2012.

12. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 287: 2570- 2581, 2002.

13. Meerwaldt R, Links T, Zeebregts C, Tio R, Hillebrands JL, Smit A. The clinical relevance of assessing advanced glycation endproducts accumulation in diabetes. *Cardiovasc Diabetol* 7: 29, 2008.

14. Pansuria M, Xi H, Li L, Yang XF, Wang H. Insulin resistance, metabolic stress, and atherosclerosis. *Front Biosci (Schol Ed)* 4: 916–931, 2012.

15. Ghani MH, Humaira M, Raqueeb A. Patterns of diabetic dyslipidemia and glycemic control at tertiary care hospital Sindh. *Med Channel* 16: 372-375, 2010. Accessed at: http://connection.ebscohost.com/c/articles/55121091/patterns-diabetic-dyslipidemia-glycemic-control-tertiary-care-hospital-sindh

16. Xu Y, He Z, King GL. Introduction of hyperglycemia and dyslipidemia in the pathogenesis of diabetic vascular complications. *Curr Diab Rep* 5: 91-97, 2005.

17. Bodhe C, Jankar D, Bhutada T, Patwardhan M, Patwardhan V. Hba1c: predictor of dyslipidemia and atherogenicity in diabetes mellitus. *Int J Med Sci* 2: 278-281, 2011. Accessed at: http://www.ijbmsp.org/index.php/IJBMSP/article/view/4/4

18. Wägner AM, Jorba O, Rigla M et al. Effect of improving glycemic control on low-density lipoprotein particle size in type 2 diabetes. *Metabolism* 52: 1576-1578, 2003.

19. Pujari SS. Hba1c as marker of dyslipedemia in type 2 diabetes mellitus patients. *SJAMS* 1: 728-731, 2013. Accessed at: http://saspublisher.com/wpcontent/uploads/2013/12/SJAMS16728-731.pdf .

20. Rohlfing CL, Wiedmeyer HM, Little RR et al. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA1c in the Diabetes Control and Complications trial. *Diabetes Care* 25: 275-278, 2002.

21. Kurukulasuriya LR, Sowers JR. Therapies for type 2 diabetes: lowering HbA1c and associated cardiovascular risk factors. *Cardiovasc Diabetol* 9: 45, 2010.

22. Raja Reddy P, Jayarama N, Shashidhar KN. Association among HbA1C and lipid profile in Kolar type 2 diabétic population. *JPSI* 2: 10-12, 2013. Accessed at: http://jpsionline.com/admin/php/uploads/271_pdf.pdf

23. Yan Z, Liu Y, Huang H. Association of glycosylated hemoglobin level with lipid ratio and individual lipids in type 2 diabetic patients. *Asian Pac J Trop Med* 5: 469-471, 2012.

24. Ahmed SE, Mustafa E, Abdul Raheem EM. Assessment of plasma levels of fasting blood glucose, triglycerides, total cholesterol, and HbA1c in patients with type 2 diabetes mellitus. *IJHSR* 3: 1-6, 2013. Accessed at: http://www.scopemed.org/fulltextpdf.php?mno=45089

25. Saaddine JB, Engelgau MM, Beckles GL et al. A diabetes report card for the United States: quality of care in the 1990s. *Ann Intern Med* 136: 565–574, 2002.

26. Woodward A, Wallymahmed M, Wilding J, Gill G. Improved glycaemic control - an unintended benefit of a nurse-led cardiovascular risk reduction clinic. *Diabet Med* 22: 1272-1274, 2005.

27. Nakamura K , Yamagishi S, Adachi H et al. Elevation of soluble form of receptor for advanced glycation end products (sRAGE) in diabetic subjects with coronary artery disease. *Diabetes Metab Res Rev* 23: 368-371, 2007.