Glycated hemoglobin health management for the patients with diabetes mellitus type 2

Elvira Đozo, Nusret Salkica, Amela Begić, Bosanko Horozić, Belma Tukić, Halil Ćorović, Safet Hadžimusić

Abstract— **Introduction:** Glycated hemoglobin is non-enzymatic compound of the glucose and hemoglbin used for tracking of the diabetes metabolic control. Diabetes increses risk of coronary artery disease (CAD) for 2 to 3 times, stroke 3 to 4 times and peripheral arterial disease for 2 to 4 times. **Research goals:** 1.Compare HbA1c parameter with macrovascular complications for patients with diabetes mellitus type 2, duration of illness up to 10 years, 2: Estimate cardiovascular risk in examined population using table for cardiovascular risk evaluation table, 3:Compare results reagrding HbA1c i SCOR of the cardiovascular risk. **Research methodology:** In this study we evaluated diabetes mellitus type 2 patients treated at the Clinic for endocrinology and diabetes Clinical Center University of Sarajevo for period of 1st January 2009 to 31st December 2012. We have been evaluating frequency of macrovascular complications comparing to HbA1c levels with disease history review and other medical documentation. Patients have been separated into 2 groups based of disease length, first group up to 5 years of disease and second group patients with 10 years of disease. Disease parameters have been compared and statistically processed. **Results:** We had 328 in our study, HbA1c values > 9% were for 197 patients. By comparing results we showed relation between cardiovascular incidence and disease length. For every patients we calculated SCOR for cardiovascular risk based on: age, sex, cholesterol, smoking status and HbA1c. Macrovascular complications had incidence of 40,6%. Most frequent complications are for patients with HbA1c 7-9% and with disease length of 6-10 years. HbA1c values are related statisticaly with increased blood glucose levels, BMI, triglycerides and HDL. HDL was at highest point for paients with HbA1c <7%. Most common SCOR is 2, lowest SCOR is for patients with HbA1c <7%. **Conclusion:** Elevated HbA1c values are related with higher frequency of macrovascular complications. Diabetes duration is related with macrovascular complications. Better diabetes management can prevent vascular comolications, increase life quality and reduce health system burdeon.

Index Terms— Diabetes mellitus, SCOR, cardiovascular risk, macrovascular complications, HbA1c, angiopathy, CVI.

1 INTRODUCTION

Diabetes mellitus is the biggest modern society pandemic and beacuse of a large number of morbidity and mortality diabetes mellitus is considered to be black death since 14th century (1).

Diabetes type 2 is dangerous and progressive disease created by at least two disorders. First impact is low number of insulin receptors in the cells and second factor is glucose transport impossibility of the insulin into the cells (insulin resistance), mostly int the fat tissue, liver and skeletal muscle cells. This is the path of increase glucose level into the blood. Now pancreas starts to produce more insulin to push glucose into the cells. In the begging increase level of the glucose is solved with this mechanism, this period is called impaired glucose tolerance. Repeated cases of increased glucole level demand even more levels of insulin production leading to damaged function of the pancreas. Final result of this situation is diabetes mellitus (2).

Early diagnosis and the treatment are essential, beacuse diabetes macrovascular complications start with impaired glucose tolerance, while microvascular diabetes complications start with high levels of the glucose in the blood (2,3).

Main mortality and disability factors persons with diabetes mellitus are its chronic complications. Every organ can be affected with diabetes. Cardiovascular complications are the most important morbidity disease of diabetes. They can occur 15 years earlier than with person without diabetes resulting with high mortality rate. Life expectancy is 5 to 10 years shorter than with non-diabetes patient. Diabetes complications are responsible for increased comorbidity (4,5).

Cardiovascular disease development is 2 to 3 times bigger for men, and 3 to 5 times for women with diabetes comparing to patients without diabetes. Diabetes increses risk of coronary artery disease (CAD) for 2 to 3 times, stroke 3 to 4 times and peripheral arterial disease for 2 to 4 times (6).

East/West Study showed diabetics without previous myocardial infarction (MI) have the same risk as nondiabtics with previous myocardial infarction (MI) (7).

Framingham Heart Study (FHS) data show 2 times increased risk for CAD, 5 times for ischaemic limb complications and 15 times for amputations of the diabetic patients group comparing to nondiabetics goup (8).

Key principles of the diabetes treatment are:

- patient education
- right diet for diabtic patient
- body activity
- therapy (oral or insulin)

Target values in diabetes mellitus type 2 medical treatment

are:

- HbA1c torange 6% 7%;
- Preprandial glucose level 4-6 mmol/L;
- 2-hour postprandial glucose level 5-8 mmol/L;
- For elderly patients clinical guidelines are from American Geriatrics Society (AGS), for persons with no strict regulation of blood glucose levels HbA1c 8% is recommended.

Glycated hemoglobin is non-enzymatic compound of the glucose and hemoglbin used for tracking of the diabetes metabolic control. It represents average glycemia levels during life time of the red blood cells (8 to 10 weeks). Physiological value is up to 6%. Value of HbA1c for <6,5% represents good level, 6,5-7,5% is border line and >7,5% is bad value (2,8).

HbA1c correlates positively with chronic diabetes complications, and lowering of annual HbA1c for just 1% can decrease risk for macrovascular complications for 37%, peripheral arterial disease for 43%, myocardial infarction for 14% and stroke for 12% (9).

Diabetes mellitus type 2 is important risk factor for development coronary artery disease and other atherosclerosis diseases. Good blood glucose leve regulation is precondition for low atherosclerosis risk and low risk of the affected organs (9).

2 RESEARCH GOALS

1. Compare HbA1c parameter with macrovascular complications for patients with diabetes mellitus type 2, duration of illness up to 10 years;
2. Estimate cardiovascular risk in examined population using table for cardiovascular risk evaluation table;
3. Compare results reagrding HbA1c i SCOR of the cardiovascular risk.

3 RESEARCH METHODOLGY

In this study we evaluated diabetes mellitus type 2 patients treated at the Clinic for endocrinology and diabetes Clinical Center University of Sarajevo for period of 1st January 2009 to 31st December 2012, average age 40-60. Disease duration is up to 10 years. This study is clinical, retrospective.

We have been evaluating frequency of macrovascular complications comparing to HbA1c levels with disease history review and other medical documentation. HbA1c and cardiovascular disease incidence has been monitord also. Patients have been separated into 2 groups based of disease length, first group up to 5 years of disease and second group patients with 10 years of disease. We compared results of these 2 groups, and results showed relationship of the cardiovascular disease with duration of the diabetes disease. For every patient we have calculated SCOR of the cardiovascular risk based on paramteres such as: sex, age, cholesterol, blood pressure, smoking status comparing to HbA1c.

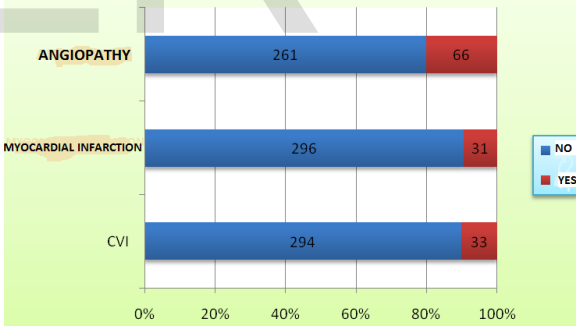
We used SPPS Windows vol. 20.0 (SPSS Inc, Chicago, Illinois, USA) for statistical analysis of the data. Nominal and ordinal variables have been analyzed with χ^2 test and Fisher's exact test. Symmetry of the continuous variables has been tested with Kolmogorov-Smirnov test (KS test).

4 RESULTS

We had 328 in our study, 53% male and 47% female patients. Average age is 53±5,1. Number of patients with diabetes type 2 is increased life years. Female patients were older (M=54,5±4,6) comparing to male patients (M=52,6±5,4).

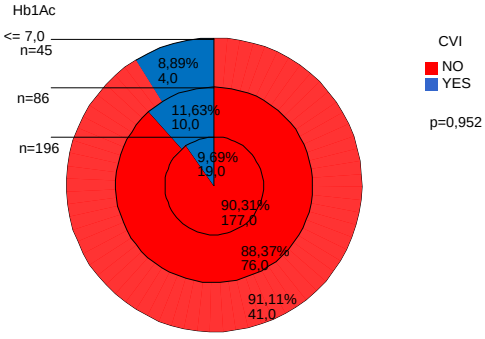
HbA1c values ≤ 7% were for 45 (13,7%) patients-diabetes wer controled, HbA1c values 7-9% were for 86 patients (26,2%)-diabetes for corection and HbA1c values > 9% were for 197 patients (60,1%)-unregulated diabetes.

Most common cardiovascular complication is peripheral angiopathy with 20,4% patients , while Myocardial infarction and stroke are equal with 10% cases.



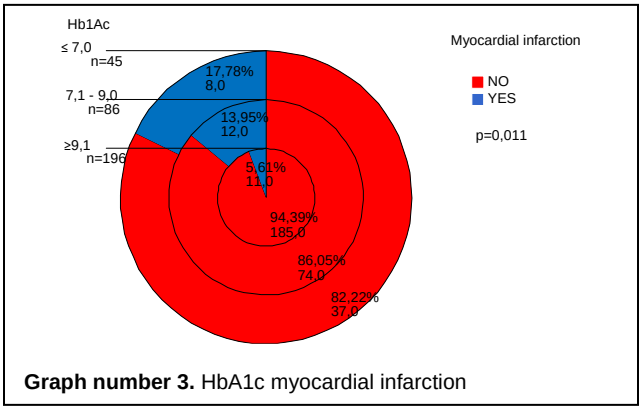
Graph number 1. Cardiovascular complictions of the patients

Based on the results of HbA1c, CVI complications have been the same for all three groups of patients (10%).



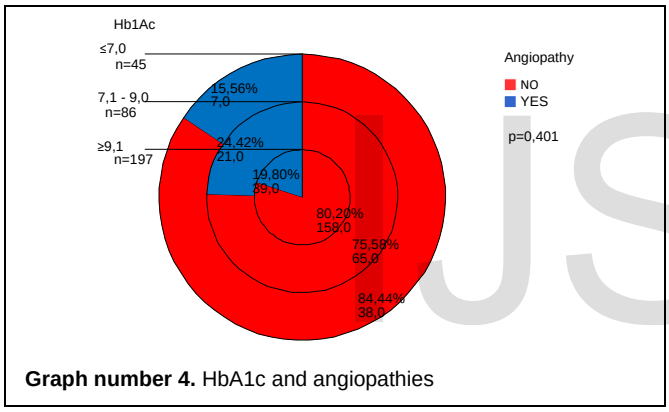
Graph number 2. HbA1c and CVI

Vast majority of patients (17,8%) with myocardial infarction had HbA1c ≤7%, 13,9% had HbA1c 7,1-9%. Myocardial infarction with HbA1c >9% had incidence of 5,6%.



Graph number 3. HbA1c myocardial infarction

Vast majority of patients (24,4%) with angiopathies had HbA1c 7,1-9%, 19,8% had HbA1c > 9%. Angiopathies with HbA1c < 7% had incidence of 15,5%.



Graph number 4. HbA1c and angiopathies

TABLE 1
CORELATION BETWEEN CEREBROVASCULAR STROKE AS A DIABETES COMPLICATION AND DIABETES DURATION

			CVI		Total
			NO	**Yes**	
Diabetes duration (Years)	6 +	N	86	19	105
		%	81,9%	**18,1%**	100,0%
	≤5	N	206	14	220
		%	93,6%	**6,4%**	100,0%
Total		N	292	33	325
		%	89,8%	10,2%	100,0%

CVI as a complication and diabetes duration are dependent χ^2= 10,723; p=0,001.

Patients with diabetes (more than 6 years) have significantly higher percentage of CVI complications (18,1%), while the group with diabetes (less than 5 years) have 6,4%.

TABLE 2
CORELATION BETWEEN MYOCARDIAL INFARCTION AS A DIABETES COMPLICATION AND DIABETES DURATION

			Myocardial infarction		Total
			NO	**YES**	
Diabetes duration (Years)	6+	N	88	17	105
		%	83,8%	**16,2%**	100,0%
	≤5	N	206	14	220
		%	93,6%	**6,4%**	100,0%
Total		N	294	31	325
		%	90,5%	9,5%	100,0%

*Myocardial infarction as a complication and diabetes duration are dependent χ^2= 7,955; **p=0,005.***

Patients with diabetes (more than 6 years) have significantly higher percentage of myocardial infarction (16,2 %), while the group with diabetes (less than 5 years) have 6,4%.

TABLE 3
CORELATION BETWEEN ANGIOPATHY AS A DIABETES COMPLICATION AND DIABETES DURATION

			Angiopathy		Total
			NO	**YES**	
Diabetes duration (Years)	6+	N	77	29	106
		%	72,6%	**27,4%**	100,0%
	≤5	N	182	38	220
		%	82,7%	**17,3%**	100,0%
Total		N	259	67	326
		%	79,4%	**20,6%**	100,0%

Angiopathy as a complication and diabetes duration are dependent χ^2= 4,456; p=0,035.

Patients with diabetes (more than 6 years) have significantly higher percentage of angiopathy complicationss (27,4 %), while the group with diabetes (less than 5 years) have 17,3%.

TABLE 4
VALUES OF THE CHOLESTEROL AND TRIGLYCERIDES IN COMPARISION WITH HBA1C

					Percentile				
Hb1Ac		N	Min.	Max	25th	50th Med.	75th	Kruskal Wallis Test	p
≤7,0	**Tot. chol.**	45	2,0	9,5	4,150	**4,900**	6,300	1,445	**0,485**
7,1 - 9,0	**Tot. chol.**	85	2,4	8,4	4,200	**5,000**	5,850		
≥9,1	**Tot. chol.**	195	1,4	22,6	4,300	**5,300**	6,300		
≤7,0	**trig**	45	,42	5,19	1,3900	**1,9600**	2,6150	6,414	**0,040**
7,1 - 9,0	**trigl**	85	,54	12,82	1,6050	**2,2000**	3,0900		
≥9,1	**trigl**	195	,50	32,40	1,5300	**2,2500**	4,2200		

Kruskal-Wallis test showed no significant relevance between total cholesterol measurements for different patient categories (p=0,485).
Kruskal-Wallis test showed significant relevance between triglycerides measurements for different patient categories (p=0,04).

Biggest triglycerides values 2,25 mmol/L (1,53-4,22) are for HbA1c >9%, then 2,2 mmol/L (1,6-3,09) HbA1c 7-9%. Lowest values are for 1,96 mmol/L (1,39-2,61) HbA1c <7%.

TABLE 5
VALUES OF THE HDLC IN COMPARISION WITH HBA1C

					Percentile				
HbA 1c		N	Min.	Max.	25th	50th Med.	75th	Kruskal Wallis Test	p
≤7,0	**HDL**	45	,12	2,90	,8150	**,9600**	1,2550	**10,865**	**,004**
7,1 - 9,0	**HDL**	80	,39	2,10	,8400	**,9550**	1,1200		
≥9,1	**HDL**	186	,10	2,15	,7100	**,9000**	1,0400		

Kruskal-Wallis test showed significant relevance between HDL measurements for different patient categories (p=0,04).

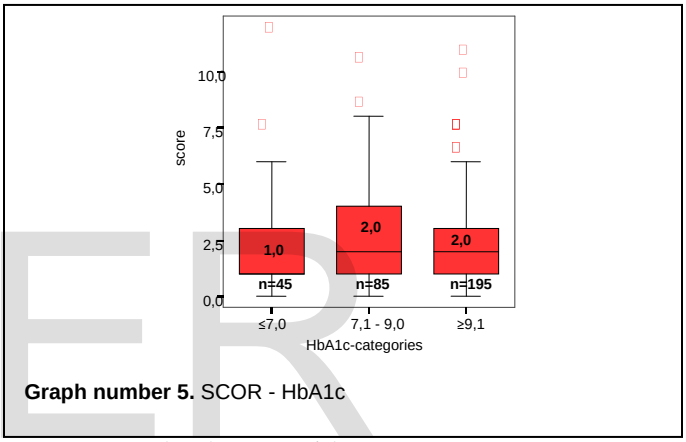
Biggest triglycerides values 0.96 mmol/L (0,81-1,25) are for HbA1c <7%, then 0,95 mmol/L (0,84-1,12) HbA1c 7-9%. Lowest values are for 0,90 mmol/L (0,71-1,04) HbA1c >9%

Average value of BMI is >25, every patient had overweight values.

TABLE 6
BODY WEIGHT FOR PATIENTS WITH DIABETES MELLITUS TYPE 2 AND HBA1C VALUES

					Percentile				
HbA 1c		N	Min.	Max.	25th	50th Med.	75th	Kruskal Wallis Test	p
≤7,0	**HDL**	45	,12	2,90	,8150	**,9600**	1,2550	**10,865**	**,004**
7,1 - 9,0	**HDL**	80	,39	2,10	,8400	**,9550**	1,1200		
≥9,1	**HDL**	186	,10	2,15	,7100	**,9000**	1,0400		

Kruskal-Wallis test showed significant relevance between body weight and HbA1c values (p=0,038).



Graph number 5. SCOR - HbA1c

Patients with HbA1c <7% have SCOR 1 (1-3), patients with HbA1c 7,1-9% have SCOR 2 (1-4) and patients with HbA1c >9% have SCOR 2 (1-3).

5 DISCUSSION

We showed incidence of microvascular diabetes type 2 complications for patients with disease duration of 10 years comparing HbA1c levels in our research. Incidence of other complications in comparision of diabetes duration is also showed.

Cardiovascular risk assessment has been estimated using charts. These results have been compared with HbA1c and SCOR. Our results showed increased incidence of diabetes type 2 with years of life, but HbA1c differences and average age are not stasticaly significant.

According to NHANES (National Health and Nutrition Examination Survery) HbA1c levels increase with years no matter sex (10).

For 40,6% patients in our study we recorded cardiovascular complications. Based on the results of Euro Heart Survey (EHS) diabetes mellitus and impaired glucose tolerance are seen on vast majority of patients with coronary artery disease, and in GAMI study (Abnormalitiens in Patients With Myocardial Infarction) scientists discovered 67% of patients

with myocardial infarction without diagnosis verified diabetes have newfound diabetes or impaired glucose tolerance (11).

In this study most common cardiovascular complication is peripheral angiopathy, while myocardial infarction and stroke are on second place. For patients with regulated diabetes type 2 stroke and angiopathy are complications independent of HbA1c levels. Myocardial infarction is most common complication for patients with HbA1c level <7% (statisticaly significant).

ACCORD study, large clinical examination has best guidelines for reduction of cardiovascular events. This study included 10 251 volunteers with type 2 diabetes. Patients had been divided in two group; group 1 HbA1c <6% and group 2 HbA1c 7-7,9%. Study ended 18 months earlier after 3,5 years because increased mortality for patients with lower levels of HbA1c (6,4%). Conclusion of this ACCORD study showed insistence in normalisation HbA1c levels <6% can be counterproductive (12).

Italian study for 15 7773 patients in 19 medical centers showed increased HbA1c levels in cardiovascular patients. HbA1c is not related with stroke but with lower limb vascular events (13).

Anthropometric data showed increased BMI (Obesity BMI> 25kg/m^2) for diabetes patients. Raz I, Wilson PWF, Strojek K, et showed only 8% diabetes patients have normal BMI while 91% patients have increase body weight or obese (14).

Risk factors analasys (age, sex, blood preasure, blood glucose leve, CRP, fibrinogen, cholesterol, triglycerides, HDLC, VDLC, LDLC, atherogenic index) regarding HbA1c levels showed blod glucose, triglycerides and HDLC are statisticaly significant. The highest levels were for HbA1c >9% for glucose and triglycerides, while HDLC is for HbA1c <7%. Helsinki Hearth Study (HHS) showed lower HDL levels and higher triglycerides and blood preasure levels with higher BMI for diabetes patients. Diabetes patients had increased incidence for myocardial infarction and cardiac death (15).

Senghor and William showed realtion between good glycemia regulation (HbA1c <6,5%) and diabetic dyslipidemia (16).

Most common SCOR in our research is 1. When analyzed HbA1c, patients with regulated diabetes had SCOR 1, while HbA1c >7% pateints had SCOR 2. In this research this is not stasticaly significant. Chronic diabetes complications analysis showed increased incidence of stroke, myocardial infarction and angiopathy for patients with longer duration of disease (6-10 years duration).

A1 Shieve study examined prevelance diabetes type 2 complications and basic physical caharacteristics for patients. Basic factors are: HbA1c, fasting glucose level, postprandial glucose level, LDL, cholesterol, blood preasure and BMI. Macrovascular complications wer for 27,2 % patients and microvascular for 53,5%. Study showed relation between age, BMI, diabetes duration, LDL, blood preasure with micro and macrovascular complications, while HDLC showed negative relation. These results are seen as a failure in reaching normal glucose level. Better diabetes management, better disease control can prevent vascular complications, increase quality of life and reduce health system burdeon (17).

Diabetes type 2 is related with high risk of complications, mostly macrovascular. Evaluation of the results 4 big studies: ACCORD, ADVANCE, VADT, UKPDS intensive glucose regulation did not result reducing cardiovascular events. HbA1c <6% levels result in increased total and cardiovascular mortality and decreased microvascular complications (mostly nephropathy). VADT study showed intensive controls for diabetes no major impact on cardiovascular gain contrary to UKPDS study results. Best diabetes type 2 stroke and cardiovascular complications protection modality is prevention on all risk factors as soon as possible and personalized approach for every patient (18, 19, 20, 21, 22).

6 Conclusion

1. By comparing HbA1c levels and macrovascular complications incidence results showed no statistical significance in case of angiopathies and stroke. Stroke and angiopathy are represented for values HbA1c <7%. Incidence of myocardial infarction is statisticaly significant.
2. While analyzing incidence of macrovascular complications comparing disease duration results showed significant presence for patients with longer period of disease (6-10 years duration).
3. Results did not show statistical significance use of charts for cardiovascular risk assessment (SCOR) comparing values of HbA1c. Lowest SCOR is related for patients with HbA1c <7%.
4. Risk factor management showed relation between HbA1c and increased blood glucose levels, BMI, triglycerides and HDL. These factors are resposnible for cardiovascular disease development.

7 References

[1] J Matthews DR, Matthews PC. Banting Memorial Lecture 2010^. Type 2 diabetes as an `infectious´ disease: is this the Black Death of the 21st century? Diabet Med. 2011; 28 (1): 2-9.

[2] Aščić-Buturović B. i saradnici: Preddijabetes i dijabetes melitus tip 2, 1 izd., Sarajevo: Institut za naučnoistraživački rad i razvoj Klinički centar Univerziteta u Sarajevu, 2009, p 76; 87; 140-145.

[3] https://www.plivazdravlje.hr/centar/200/Secerna-bolest.html.

[4] Jembrek-Gostović M. i suradnici: Metabolička inzulinska razistencija i kardiovaskularni sustav, Medicus, 2004.13(2): 67-75.

[5] Donnelly R, Emslie-Smith AM, Gardner ID, Morris AD. Vascular complications of diabetes. British Medical Journal 2000; 320: 1062-6.

[6] Anon. Dijabetes kao kardiovaskularna bolest, Kardio list, 2007. 2(2):15.

[7] Antić S.: Dijabetes melitus tip 2 i kardiovaskularna bolest, 2008.

[8] American Diabetes Association, Diagnosis and Classification of Diabetes Mellitus, Diabetes Care, volume 35, supplement1, January 2012.

[9] UKPDS group. Intensive Blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998: 352:837-53.

[10] National Health and Nutrition Examination 2007-2008.

[11] Zhang Y, Hu G, Yuan Z, Chen L: Hemoglobin in Relationship to Cardiovascular Outcomes and Death in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. Published: August 09, 2012 Glycosylated

[12] The ACCORD Study Group. Effects of intensive glucose lowering therapy in

type 2 diabetes mellitus. N. Engl, J. Med. 2008; 358:2545-59.

[13] Penno G, Solini A, Zoppini G, Orsi E, Fondelli C, Zerbini G, Morano S, Cavalot F, Lamacchia O, Trevisan R, Vedovato M, Pugliese G. Renal Insufficiency and Cardiovascular Events (RIACE) Study Group. Hemoglobin A1c variability as an independent correlate of cardiovascular disease in patients with type 2 diabetes: a cross-sectional analysis of the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. Cardiovasc Diabetol. 2013 Jul 5;12:98.

[14] Raz I, Wilson PWF, Strojek K, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diabetes Care 2009; 32: 381–6.

[15] Koskinen P, Mänttäri M, Manninen V, Huttunen JK, Heinonen OP and Frick H: Coronary Heart Disease Incidence in NIDDM patients in the Helsinki Heart Study, Diabetes Care July 1992. 15:7820-825.

[16] Senghor A, William E. Correlation of HbA1c and non-HDL cholesterol to assess diabetic dyslipidemia, International Journal of Recent Scientific Research (2014) Vol.5: 931-933.

[17] Litwak L, Goh SY, Hussein Z, Malek R, Prusty W, and Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study, Diabetol Metab Syndr. 2013; 5: 57.

[18] Litwak L, Goh SY, Hussein Z, Malek R, Prusty W, and Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study, Diabetol Metab Syndr. 2013; 5: 57.

[19] Meier M. and Hummel M, Cardiovascular disease and intensive glucose control in type 2 diabetes mellitus: moving practice toward evidence-based strategies, Vasc Health Risk Manag. 2009; 5: 859–871.

[20] Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens. 2009;27(11):2121-58.

[21] Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358 (24):2560-72.

[22] Duckworth W, Abraira C, Moritz T, et al. Glucosecontrol and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360(2):129-