VERSITA

© **2012** ILEX PUBLISHING HOUSE, Bucharest, Roumania
http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **19**(2):115-122
doi: 10.2478/v10255-012-0015-3

THE RELATIONSHIP BETWEEN HEMOGLOBIN A1c AND CHRONIC COMPLICATIONS IN DIABETES MELLITUS

Bogdan Timar [1,2], ***Oana Albai*** [1,2,✉]

[1] "Victor Babes" University of Medicine and Pharmacy, Timisoara
[2] Emergency County Clinical Hospital, Timisoara

received: February 12, 2012 *accepted*: April 20, 2012
available online: May 31, 2012

Abstract

Background. *Hyperglycemia is leading to serious chronic and acute complications in diabetes mellitus which are shortening and altering the patient's life.* ***Objective.*** *The main purpose of the study is to investigate the correlation between HbA1c values and diabetic complications.* ***Material and methods.*** *The study enrolled 2120 diabetic patients, 1174 women (55.4%) and 946 men (44.6%), mean age 58.3 ± 12.3 years, living in Timisoara.* ***Results.*** *We observed the lowest incidence of chronic complications of diabetes mellitus for the group having HbA1c values lower than 6%. Chronic complications are increasing with the HbA1c value, with a significant threshold at 7 % ($p<0.0001$).* ***Conclusions.*** *Optimizing glycemic control is the key to prevent or delay the occurrence of severe chronic complications of diabetes mellitus, complications which can be significantly reduced by achieving the ADA recommended HbA1c target (<7%).*

key words: *diabetes mellitus; chronic complications; cardiovascular risk; hemoglobin A1c; glycemic control.*

Background

Diabetes Mellitus (DM) is a heterogeneous, etiologic and pathogenic syndrome, characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action or both. Hyperglycemia and other associated abnormalities are leading to serious acute and chronic complications, which are reducing and altering the patient's life. The increasing prevalence of the disease and its main complications, micro and macrovascular, represents one of the main public health problems worldwide.

Because approximately 70-80% of diabetic patients die from cardiovascular events, DM can be considered an equivalent of cardiovascular disease (CVD) [1].

Extended epidemiological trials revealed that cardiovascular risk is two up to four times increased in DM individuals compared to non-diabetic ones, its incidence and prevalence being influenced by gender, diseases duration and association with other illnesses (arterial hypertension, dyslipidemia) [2]. The

✉ Bucium Street, No. 36, Iasi, 700282, Phone: 0742 054 311, Fax: 0232 213 211,
corresponding author e-mail: otyca95@yahoo.com

cardiovascular mortality risk in diabetic patients without a prior myocardial infarct (MI) is comparable to that of nondiabetic patients who had a MI.

The main aim of DM treatment is to maintain glycemic values in target, in order to prevent or to delay the occurrence of the extremely severe chronic complications.

According to current guidelines "*the long term objectives"* of DM therapy include:

- Prolonging life and increase its quality;
- Achieving optimal glycemic control as long as possible, defined as:
  - Fasting glycemia ≤110mg/dL;
  - Post prandial glycemia (2 hours) ≤140mg/dL;
  - HbA1c ≤7% individualized for age, disease duration and other comorbidities.
- Prevention of acute and especially chronic complications of DM;
- Attaining targets regarding associated risk factors:
  - BP <130/80mmHg;
  - Reaching desired lipid values:
    - LDLc <70mg/dL;
    - Non-HDLc <100mg/dL;
    - Apolipoprotein B <80mg%;
    - HDLc >40mg% in males and >50mg% in females;
    - Serum triglycerides (TG) <150mg%;
  - Patient education;
  - Psychotherapy [3].

Assessment of glycemic control, a key point for the management of DM, is achieved by combining the medical support with patient's self-monitoring. HbA1c is currently *"the golden standard"* for assessing the glycemic control.

Both reference studies in DM, "The Diabetes Control and Complications Trial" (DCCT) and "United Kingdom Prospective Diabetes Study" (UKPDS) proved that chronic complications of DM, especially microvascular, are significantly reduced with the lowering of the HbA1c levels [4-6].

Some studies, in recent decades, have shown close correlation between HbA1c value and the risk of chronic complications of DM [7-9], while in others this aspect wasn't revealed. Each 1% increase in HbA1c value results in a 10-20% increase in cardiovascular risk and overall mortality [10-12].

Assessing HbA1c is recommended:

- 3-4 times in an year in type 1 DM patients;
- At least twice in an year in patients with type 2 DM who haven't reached the therapeutic goals so far;
- Whenever is needed, as well as before or after changing the therapeutic regimen.

If until recently HbA1c was used only for monitoring the glycemic control, in 2009 the International Expert Committee of American Diabetes Association (ADA), International Diabetes Federation (IDF) and the European Association for the Study of Diabetes (EASD) are recommending HbA1c as a diagnosis test for DM and they are establishing the threshold for diagnosis at 6.5% [3, 13].

Using HbA1c as a diagnosis criterion provides a series of advantages namely the fact that it doesn't need a period of fasting before assessment and it is not influenced by other factors such as stress or infections of any kind.

An HbA1c value between 5.7 to 6.4% indicates individuals with increased risk of developing diabetes and CVD, this span being named by specialists as *prediabetes* [14-16].

Aims

Based on these assumptions, the objectives of the present study consisted in assessing the degree of glycemic control in a group of patients with diabetes, and to establish the correlations between chronic complications of diabetes and glycemic control assessed by HbA1c levels.

Material and method

We enrolled 2120 patients with type 2 DM, 1174 woman (55.4%) and 946 men (44.6%), with a mean age of 58.3±12.3 years (range 41 to 76 years), from Timisoara.

We investigated a series of clinical and biological parameters: age, gender, place of origin, duration of DM, therapy, body mass index (BMI), blood pressure (BP), HbA1c, total cholesterol (TC), serum triglycerides (TG), HDLc and LDLc (computed using Friedwald's formula).

We also investigated the presence of chronic complications of diabetes for the enrolled patients: microvascular (diabetic retinopathy - DR and diabetic nephropathy - DN), macrovascular (stroke, ischemic heart disease - IHD and peripheral artery disease - PAD) and neuropathic (distal sensory diabetic neuropathy - DSDN). Diagnostic of DR was based on fundoscopic examination and of DN on urine albumin/creatinine ratio.

Using SPSS, we calculated Spearman correlation coefficient, also named "the rank correlation coefficient", used to compare variables measured on ordinal scale or range.

Results

Main characteristics of the patients enrolled are shown in Table 1.

Table 1. Main characteristics of the enrolled patients.

Parameter	Value
Number of enrolled patients	2120
Men (%)	946 (44.6)
Women (%)	1174 (55.4)
Mean age (years) ± SD	58.3±12.3
DM duration (years) ± SD	8.2±7.1
BMI (kg/m^2) ± SD	29.9±5.6
HbA_1c (%) ± SD	8±1.6
TC (mg/dL) ± SD	208±28.3
TG (mg/dL) ± SD	213±99.3
HDLc (mg/dL) ± SD	42.1±5.4
LDLc (mg/dL) ± SD	124.8±41.8
Hypertensive patients: number (%)	1276 (60.2)

As shown in Table 1, the mean HbA1c in the studied group was 8%±1.6%. We observed that only 556 patients (26.2%) from the entire lot belonged to the targeted group (HbA1c ≤7%, Figure 1).

In the study group 184 patients (8.7%) were treated only with diet, 1052 (49.6%) were on oral antidiabetic drugs and 884 (41.7%) were on insulin therapy with or without oral drugs.

Chronic DM complications have been investigated both in general and in relation to HbA1c value. In 34.2% of the cases microvascular complications (DR and DN) were found; in 52.7% macrovascular complications were found (stroke, IHD, PAD),

and 38.2% had neuropathic complications (Figure 2).

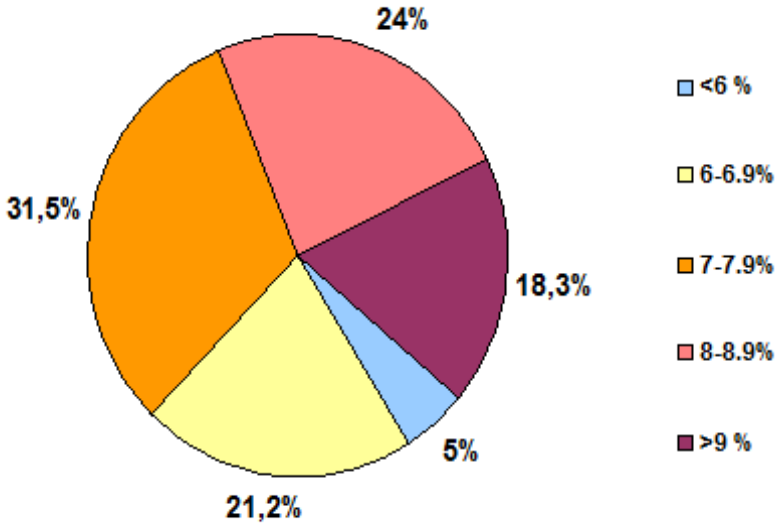

Figure 1. HbA1c categories in the study group

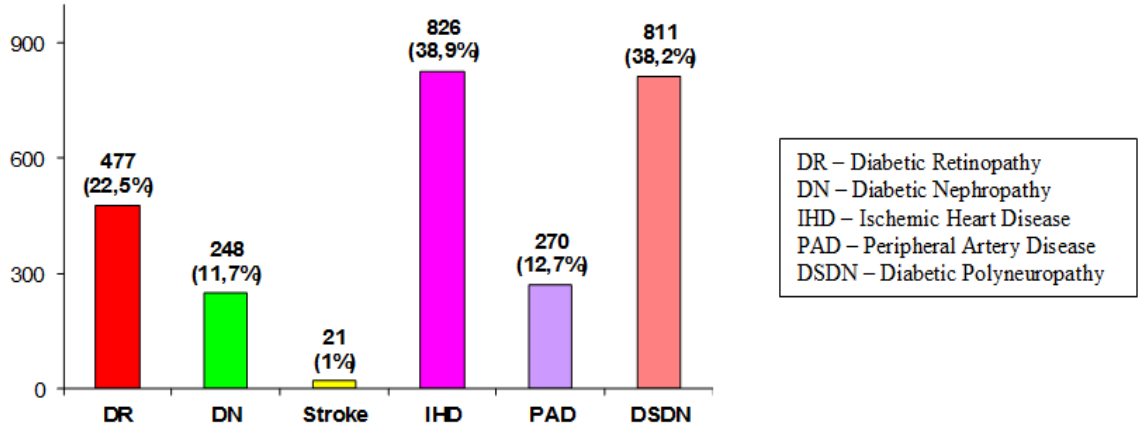

Figure 2. Prevalence of chronic complications in the study group

Analyzing different intervals of HbA1c, adjusted regarding age, diabetes duration and BMI, we observed the lowest percentage of chronic complications of DM in the group with HbA1c values lower than 6%. We also found that their number increases with HbA1c, with a statistically significant raise in patients with HbA1c between 7 and 7.9% compared to those with values between 6 and 6.9% ($p<0.0001$) (Table 2).

In the group of patients treated with insulin, 321 (36.3%) followed conventional treatment (regimens with 2 or 3 shots), and 563 (63.7%) were under intensive treatment (4 or 5 shots). HbA1c was significantly higher in patients under conventional treatment compared to those under intensive treatment: 9.1±1.7 % versus 8.2±1.2 % ($p<0.0001$). By comparing the occurrence of chronic complications in patients under conventional

treatment versus those with intensive therapy, we found that the percentage is significantly higher in the first group (p<0.0001, Figure 3).

Table 2. Chronic complications of DM in the enrolled individuals according to HbA1c value.

HbA_1c (%) Studied parameter	<6	6-6.9	7-7.9	8-8.9	≥9
Diabetic Retinopathy *	12 (11,2)	47 (10,5)	168 (25,1)	132 (25,9)	118 (30,5)
Diabetic Nephropathy *	6 (5,6)	28 (6,2)	78 (11,7)	71 (13,9)	65 (16,8)
Stroke *	0	1 (0,2)	4 (0,6)	9 (1,8)	7 (1,8)
Ischemic Heart Disease *	34 (31,8)	164 (36,5)	257 (38,5)	234 (45,9)	137 (35,4)
Peripheral Artery Disease *	10 (9,3)	43 (9,6)	78 (11,7)	70 (13,7)	69 (17,8)
Diabetic Polyneuropathy *	20 (18,7)	107 (23,8)	215 (32,3)	182 (35,7)	287 (74,2)

* Values represent numbers and (prevalence in subgroup – percentage).

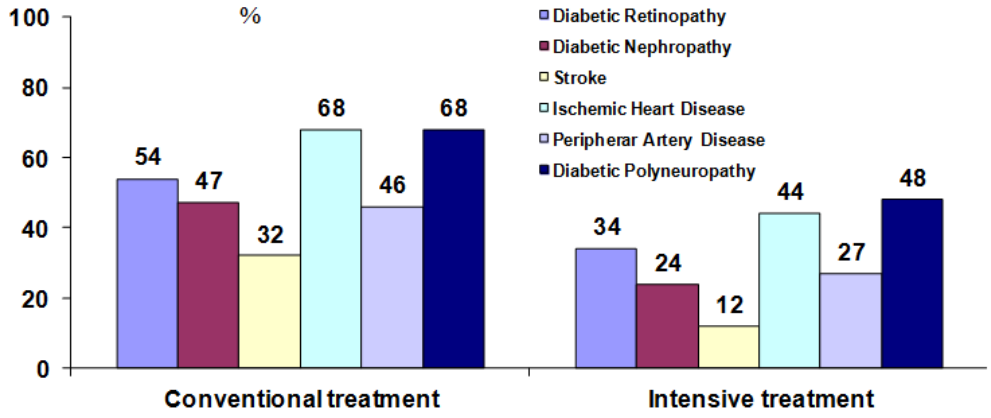

Figure 3. Chronic DM complications regarding treatment scheme.

We found positive correlations between all investigated chronic complications (after adjusting regarding age, BMI and diabetes duration) of DM and the levels of HbA1c. Among them, the strongest correlations were between DR and HbA1c (r=0.64, p<0.001) and between DN and HbA1c (r=0.61, p<0.001). A moderate correlation was observed between DSDN and HbA1c (r=0.46, p<0.001 ES).

Discussions

Measuring the HbA1c value is commonly used in DM patients as a marker of glycemic control and also as a marker for changing the treatment or even for initiating insulin therapy when needed [17, 18].

In 1993, DCCT proved that intensive insulin therapy reduced with 73% the risk of progression of DR compared to conventional treatment. In our study the prevalence of retinopathy was merely twofold higher in patients treated conventionally compared to those on intensive treatment: 54% versus 34% [4, 19, 20].

These observations led to the recommendations of international societies to reduce HbA1c target from 7% to 6.5% in

order to prevent chronic microvascular complications. An article by Mazzone M et al. proved that cardiovascular events are reduced in direct proportion with the improvement of the glycemic control: "A lower than 7% HbA1c is reasonable and safe", concluded Mazzone [21].

A meta-analysis performed by a group from University of Cambridge, UK, suggests that a better glycemic control reduces the risk of myocardial infarct and cardiovascular disease, with no other influence regarding other causes of mortality.

The Action in Diabetes and Vascular Disease (ADVANCE) study, revealed the reduction of albuminuria progression with the improvement of the glycemic control, while Action to Control Cardiovascular Risk in Diabetes (ACCORD) was halted before planned date, due to increasing in mortality risk, in diabetic patients with very low HbA1c values [22].

Like other important trials, UKPDS proved that improving glycemic control is reducing not only the main microvascular complications of DM but also the incidence of MI or other causes of mortality [23, 24, 25].

It is known that a patient with DM dies mainly because cardiovascular events, and approximately 10 years earlier than non-diabetics.

Ray et al. enrolled 33.040 patients and compared the effects of standard treatment to the intensive one on the cardiovascular events and mortality in DM patients. Average HbA1c was 0.9% lower and the number of cardiovascular events was with 15% and MI with 17% lower in intensive treated patients [10].

The Atherosclerosis Risk in Communities (ARIC) study revealed that HbA1c is a significant predictor for cardiovascular diseases (stroke, IHD or even death), even in patients having a normal value of HbA1c. In ARIC study, which included non-diabetic patients, HbA1c gained a higher level of trust for assessing long term cardiovascular diseases than fasting plasma glucose, especially in levels higher than 6%. HbA1c is therefore not only a key indicator of glycemic control for patients with diabetes, but also an important marker for cardiovascular disease (CVD). Taking these into accout, HbA1c was included as a diagnosis criterion in DM patients; therefore, patients with HbA1c values higher than 6.5% are classified as having DM, and those with values between 5.7% and 6.4% are considered having prediabetes.

A study conducted in Norfolk, which enrolled 4662 men and 5570 women aged between 45 and 79 years and analyzed the relationship between HbA1c, CVD and overall mortality, proved that individuals with HbA1c lower than 5% had the lowest incidence of cardiovascular events and global mortality. An increasing with 1% of HbA1c was associated with an increased relative risk of overall mortality with 1.24 in men and with 1.28 in women. This relative risk increase was independent of age, BMI, systolic blood pressure values, TC, smoking or history of CVD, but in our study we haven't found any significant correlation between HbA1c and macrovascular complications [26, 27].

Similar to other trials, in our patients, the percentage of chronic microvascular complications of diabetes is increasing together with HbA1c, being significantly higher (about three times) in patients with values above 7%.

Conclusions

Improving the glycemic control is the key for preventing or delaying chronic DM complications; these can be significantly reduced by achieving and maintaining the target recommended by ADA: HbA1c less than 7%.

The significantly increase of micro-vascular complications in patients with HbA1c above 7% in our study, confirms this value as a therapeutic target in the therapy of DM patients.

REFERENCES

1. **Gerstein HC, Miller ME, Byington RP, Goff DC, Jr, et al**. Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358(24): 2545-2559, 2008.

2. **Zhang X, Patel A, Horibe H, Wu Z, Barzi F, et al.** Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol* 32(4): 563-572, 2003.

3. **American Diabetes Association.** Standards of medical care in diabetes – 2009. *Diabetes Care* 32 (Suppl.1): S13-61, 2009.

4. **DCCT Study Group**. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 44(8): 968-983, 1995.

5. **Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ et al**. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353(25): 2643-2653, 2005.

6. **Stratton IM, Adler AI, Neil HA et al.** Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321(7258): 405-412, 2000.

7. **Cohen RA, Hennekens CH, Christen WG et al.** Determinants of retinopathy progression in type 1 diabetes. *Am J Med* 107(1): 45-51, 1999.

8. **Kilpatrick ES, Rigby AS, Atkin SL**. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 29(7): 1486-1490, 2006.

9. **Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group**. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy: the Epidemiology of Diabetes Interventions and Complications (EDIC) study. *JAMA* 290(16): 2159-2167, 2003.

10. **Ray KK, Seshasai SR, Wijesuriya S et al.** Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomized controlled trials. *Lancet* 373: 1765-1772, 2009.

11. **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* 358: 2560-2572, 2008.

12. **Ceriello A, Kilpatrick E, Akalin S et al.** Intensive glucose therapy and clinical implications of recent data: a consensus statement from the Global Task Force on glycaemic control. *Int J Clin Pract* 63: 1421-1425, 2009.

13. **Hoelzel W, Weykamp C, Jeppsson JO et al.** IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. *Clin Chem* 50: 166-174, 2004.

14. **Jeffcoate SL**. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. *Diabet Med* Jul 21(7): 657-66, 2004.

15. **Kovatchev BP, Otto E, Cox D, Gonder-Frederick L, Clarke W**. Evaluation of a new measure

of blood glucose variability in diabetes. *Diabetes Care* 29(11): 2433-2438, 2006.

16. Lind M, Odén A, Fahlén M, Eliasson B. A Systematic Review of HbA1c Variables Used in the Study of Diabetic Complications, Diabetes & Metabolic Syndrome: *Clinical Research & Reviews* 282–293, 2008.

17. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *JAMA* 295 (14):1707-1708, 2006.

18. Österbrand M, Fahlén M, Odén A, Eliasson B. A method to predict the metabolic effects of changes in insulin treatment in subgroups of a large population based patient cohort. *European Journal of Epidemiology* 22: 151-157, 2007.

19. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329 (14): 977-986, 1993.

20. Lachin JM, Genuth S, Nathan DM, Zinman B, Rutledge BN, DCCT/EDIC Research Group. Effect of glycemic exposure on the risk of microvascular complications in the Diabetes Control and Complications Trial-revisIted. *Diabetes* 57(4): 995-1001, 2008.

21. Mazzone T. Hyperglycaemia and coronary heart disease: the meta picture. *Lancet* 373: 1737-1738, 2009.

22. Calles J, Banerji M, Bonds D et al. Baseline characteristics and mortality in ACCORD. Abstract No: 88-OR. *American Diabetes Association, 69th Scientific Sessions, New Orleans*, June 5–9, 2009.

23. Holman RR, Paul SK, Bethel MA et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359(15): 1577-1589, 2008.

24. Stevens R, Kothari V, Adler A, Stratton I, Holman R. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clinical Science* 101: 671-679, 2001.

25. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352 (9131): 837-853, 1998.

26. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352 (9131): 837-853, 1998.

27. Tamborlane WV, Beck RW, Bode BW et al. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 359 (14): 1464-1476, 2008.