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TREATMENT AND ASSESSMENT OF GLYCEMIC COMPENSATION OF PATIENTS WITH DIABETES MELLITUS IN THE LIGHT OF A NEW REFERENCE SYSTEM FOR HbA_{1C}

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ABSTRACT

Diabetes mellitus is a chronic incurable disease (so far) with permanent impaired glucose conversion. Is results from a total or partial lack of insulin in the body or its underutilization in organs. Selection of investigative procedures based on recommendations of the International Federation of Clinical Chemistry (IFCC) and the National Glycohemoglobin Standardization Program (NGSP). Objective of the study was to highlight the advantages and disadvantages of these methods and their mutual comparability. The relation and comparison of the measured values of the IFCC, NGSP methods and recommendations of International diabetes organizations is described. Transition of measurements of HbA1c from DCCT standard to the new IFCC reference standard will not be problematic. Stable relationship was confirmed between the two systems. The relationship can be expressed mathematically with the "master equation". The results of the study of glucose, which is derived from HbA1c, confirmed the existence of a linear relationship between HbA1c and mean level of blood glucose. In light of these findings, ADA has proposed a new concept in the management of diabetes, which they called Estimated Average Glucose (eAG). eAG allows the results of measurement of HbA1c express in the same units as the glucose concentration (mg/dl or mmol/l). Uniform system of expressing concentration of current and long-term glucose control can streamline and simplify the educational process of diabetes.

Keywords: ***Glycated haemoglobin (HbA1c), Diabetes Control and Complications Trial (DCCT), International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), IFCC reference method, estimated average glucose (eAG)***

1. INTRODUCTION

Diabetes mellitus is a group of metabolic diseases caused by insulin deficiency, insulin resistance or a combination of both. It is manifested by an elevated blood glucose levels (the hyperglycaemia). Failure of insulin action in tissues is reflected in disorder of carbohydrate, protein and fat metabolism. Currently, the most serious diabetes-specific problems are late complications, which have serious consequences for the whole organism and essentially determines the length and quality of life of diabetic (Perušičová J et al. 1996).

Hemoglobin is a protein that has the ability to bind with glucose molecules. This process is called glycation of proteins. Blood glucose is covalently bound to the N-terminal residue of valine, β-chain of the hemoglobin of red blood cells. Spontaneous chemical change (Amadori) irreversibly forms the product HbA1c. HbA1c concentration of the formed depends on the concentration of blood glucose. The higher the blood glucose concentration is, the higher the amount of HbA1c in the blood is created. HbA1c circulates in the blood for the life span of red blood cells. Glycated hemoglobin thus serves as a measure of individual risk of long-term complications of diabetes. Control measurements of HbA1c provide insight on the management of glucose concentration, management efficiency and risk of complications of diabetic patients (Rácz O. et al.1989). The current method of determining HbA1c are set according to DCCT reference system. DCCT HbA1c target level is 6.5 to 7.5% and can be set

individually for each patient, taking into account the risk of hypoglycemia, cardiovascular condition and overall morbidity. The new IFCC reference system will gradually replace the old DCCT measurement system. The IFCC reference system brings unit change from the original % to SI unit **mol**. HbA1c values measured according to the new IFCC standardization will be expressed as **mmol per mole of hemoglobin HbA1c (mmol HbA1c / mol HbA)** (J. Balla, 2004).

2. DCCT AND IFCC

The transition of measurements of HbA1c DCCT measurement system to the new IFCC reference system will not be problematic. Stable relationship between the two systems was confirmed. Relationship can be expressed mathematically by so-called master equation. If the results of measurements by HbA1c DCCT method expressed in %, then the equation expressing the relationship between the two measurement systems is **IFCC-HbA1c (mmol/mol) = [DCCT-HbA1c (%) - 2.15] x 10,929.**

Using this equation for the target values of DCCT 6.5% - 7.5%, the equivalent IFCC values can be determined as 48 mmol/mol - 59 mmol/mol for diabetics and for DCCT reference value of 4.0% - 6.0% , the IFCC values are 20 mmol/mol - 42 mmol/mol for non-diabetics.

HbA1c units are currently given in %. Because of that, the percentage decline seems minimal (eg. from 6.5% to 5.2% is an improvement of 1.3 percentage points). If units mol and mmol are used instead, the equivalent decrease of HbA1c (from 65 mmol HbA1c /mol Hb to 52 mmol HbA1c /mol Hb) is an improvement of 20%. This would remove misunderstanding about the percentages, given that diabetologists are not informed as which reference system is used for the results of glycated hemoglobin - whether they are values measured by IFCC, or DCCT system (Hoelzel et al 2004).

The aim of our research was to statistically compare the values of glycated hemoglobin measured in the laboratory by IFCC method and the values converted to the DCCT standard on the selected sample of 84 patients. The aim was to determine how selected patients are compensated, if IFCC standard values and its criterias are used.

Main diagnose of the sample patients, was Type 2 Diabetes Mellitus. Patients were selected from two private diabetological clinics (*Prešov* and *Stropkov*). The patients are treated with oral antidiabetic agents (PAD), combinated therapy and/or treated with insulin. The sample size was **84 patients aged 34-89 years.** The sample was divided into 2 groups (men and women) (Figure 1).

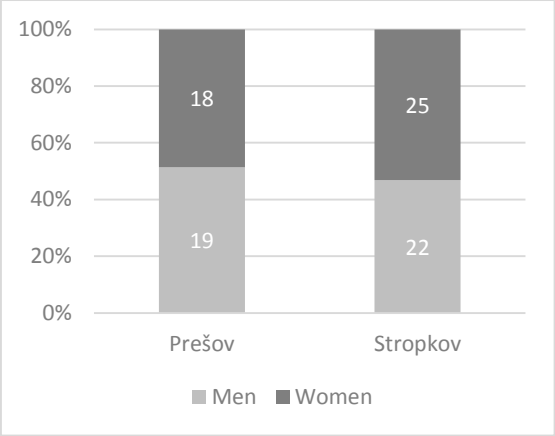

Figure 1. Gender Distribution of Patients from Two Diabetological Clinics.

Measurments of hemoglobin A1c was performed at accredited clinical biochemistry laboratory - Analyticko-diagnostického laboratória, s.r.o. – in Prešov, Slovakia. Immunological method was calibrated according to the standard IFCC with standard working procedure. Measurements were performed with biochemical analyzer Roche Hitachi 912 using a diagnostic kit HbA1c Roche Tina-quant II Hemoglobin A1c II. Using master equation, the DCCT (NGSP) values were calculated. The results have undergone statistical hypothesis testing on the probability distribution. As the test samples are dependent (paired), we have performed a statistical evaluation of the measured DCCT and IFCC values of HbA1c in the blood of men and women at the start of treatment, and after one year of treatment. The paired t-test was used.

Measured values are also processed using descriptive statistical methods (frequency, arithmetic mean, standard deviation and relative standard). Results are arranged in paired DCCT – IFCC values.

The effect of treatment of men in first group in DCCT units (%) shows relative decrease of the mean of HbAc 26% (from 9.6% to 6.8%), as expressed in IFCC units (mmol / mol), the decrease is 33% (from 81 mmol / mol to 51 mmol / mol). Similar differences in favor of a higher relative decline in the mean HbA1c expressed in IFCC units, were also observed in second group of males - in the DCCT units median dropped from 9.8% to

7.9%, which is 19% relative decline, while in IFCC units, the relative decrease was up to 24% (from 84 mmol / mol to 62 mmol/l). An analogous situation shows both groups of women. In the first group, decrease in DCCT units was from 8% to 6.7% thus a relative decrease of 15%. In IFCC units values decreased from the initial 64 mmol/mol to 50 mmol/mol, which represents a relative decrease of 20%. The second set of women shows the same trend: DCCT mean value declined from an initial value of 10.3% to 7.9%, a relative decrease of 22%, while the relative decrease in the mean of the IFCC was from 89 mmol / mol to 63 mmol / - relative decrease of 28%. The fact that the relative percentage decrease in IFCC system is always higher than in the DCCT is caused by mathematically simple reason – in IFCC, the denominators are numerically lower numbers than in the DCCT. This fact is a clear counter-argument against such a view that IFCC standardization is introducing very low numerical representation of the results that will motivate patients to treat unruly.

The results of the statistical analysis clearly confirmed statistically highly significant decrease in hemoglobin A1c levels in the blood of patients treated with oral antidiabetic agents or insulin, after one year of treatment, regardless of whether or not the measurement results were expressed in DCCT and IFCC system. It is a further confirmation that the new IFCC system has no effect on clinical outcomes of patients and evaluation of diabetic complications based on targeted risk criteria for the IFCC system (see Table 1 and Table 2).

We did not find even one patient with a discrepancy in the evaluation with regard to the appropriate targets. This small sample of patients, although not enough for the scientific evidence, can be considered as a confirmation of the assumption that the expression of results in IFCC reference system cannot harm patients due to an incorrect classification by the newly proposed classification criteria for determining the risk of diabetic complications.

3. eAG

HbA1c has become an invaluable tool for the control of diabetes and the directive when deciding on treatment of diabetes. American diabetologists constantly remind that the HbA1c is very difficult to clarify to the patients. They confuse glycosylated hemoglobin as indicator of haematological disease instead of diabetes. The results of the research of estimation of the mean glucose, which is derived from HbA1c (the A1c -Derived Average Glucose Study (ADAG), published in Diabetes Care, confirmed the existence of a linear relationship between HbA1c and the average blood glucose levels. In view of these findings, American Diabetes Association (ADA) in cooperation with the European Association for the Study of Diabetes (EASD) and International Federation of Diabetes (IDF), suggested the new concept in the management of diabetes, which they called Estimated Average Glucose, the eAG. eAG can express the results of measurements of HbA1c in the same unit as glucose (mg/dl and mmol/l). The eAG terminology is familial to a patient and may help to simplify the discussion and explanation of the performance of the treatment process and control of diabetes, between the patient and doctor (Kuenen et al. 2008).

The study of linear dependence of HbA1c and average glucose estimation was, currently, carried out only on limited sample of the population and has not been confirmed on a larger scale. Therefore many professional societies, particularly in Europe, are still very cautious and restrained in recommendations of eAG. However, they expect another wide research in this area and the results in practice with interest.

Glycated hemoglobin diabetics is measured at least two times a year. Any change in the results of HbA1c by 1% up or down is a big change of risk of diabetic complications. At this point it must therefore stressed the fact, that in reality it is a change of one percentage point and not a 1% change, as is in the practice often unfortunately and wrongly understood and interpreted by patients. If HbA1c increased from 6% to 7% the relative change is 17% (7 - 6 = 1/6 = 0.166 * 100 = 17%) and not just 1%. This mistake is made by patients quite often. It is caused by small numerical values and result in underestimation of treatment. Therefore, in recent years, especially in the circles of American diabetologists, increasingly intense discussion is ongoing on a new "means of communication" of diabetes among patients and physicians.

For many years, determination of HbA1c was harmonized with the method, which was based on clinical studies of diabetes management DCCT (NGSP) and UKPDS. However, the past decade showed that the NGSP system that correlates with ion exchange method according to Goldstein (Goldstein method is not metrologicaly standardized) is not sufficient for global harmonization and must be replaced with genuine

reference measuring system. IFCC appointed expert group for HbA1c standardization, which developed the new IFCC reference system

Diabetological companies' representatives agree that the IFCC reference procedure should become a global standard and all manufacturers should calibrate their methods based on the IFCC reference system. However, they believe that it is necessary to change benchmarks, target values for the control, management and treatment of diabetes, which can bring a number of problems such as increase in costs, confusion between 'old' and 'new' values and long time to re-educate patients and physicians. Paradoxically, this could lead to a lowering the level of diabetes care. Therefore they suggest that the results of HbA1c tests should be reported worldwide in new units. IFCC has agreed to this request and suggested replacing the current HbA1c % with new (SI) units of mmol HbA1c / mol HbA. As it turned out, the true denominator is the mole [HbA0 + HbA1c] as confirmed by the IFCC-NCPU and recently also by NHS Diabetes Group.

It turned out that the relationship between HbA1c and eAG is the same regardless of whether patient is diabetic or not, whether patient has type 1 diabetes or type 2 diabetes, without distinction on smoking status, gender, age, race or ethnicity but with a trend towards higher values per average HbA1c glucose of Africans or African Americans compared with whites.

The following equations:

eAG (mg/dl) = 28,7 x A1C (%) – 46,7,

or

eAG (mmol/l) = 1,59 x A1C (%) – 2,59

may be used by laboratories and other health care providers to calculate the eAG. Health care providers (laboratories, POCT) can express the results in units which are more familiar to patient and thus simplify communication and avoid misunderstanding. The chance of acceptance of eAG was increased by acceptance of new concept eGFR (estimated glomerular filtration rate) by medical community. This proposal is regarded as a kind of "precedent" and represents the hope that the growing acceptance of eGFR will give a boost to understanding the similar concept eAG.

For the calculation of the eAG, the mathematical equations recommendations of the American Diabetes Association were used. Calculated eAG values show a high degree of correlation with hemoglobin A1c. The high degree of correlation (R2 = 1.000) is only illusory, because correlation is between two dependent values - values of measured concentration of glycated hemoglobin (HbA1c) and mathematical calculated value of the average concentration of glucose (eAG). This correlation has no scientific validity and is only a graphic demonstration of the confidence intervals (± 15%), which is the true value of the eAG, respectively HbA1c. In such a wide confidence interval is eAG virtually losing their original meaning. We recognize that the present study does not include a randomized selection of patients and therefore important scientific findings can not be made on the basis of the results achieved (see Figure 2).

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Table 1. Statistical Results of Sample From Prešov

	At baseline				After one year			
	DCCT		**IFCC**		**DCCT**		**IFCC**	
	% HbA1c		mmol/l		% HbA1c		mmol/l	
Gender	Men	Women	Men	Women	Men	Women	Men	Women
n	19	18	19	18	19	18	19	18
arithmetic average	9.6	8.0	81	64	6.8	6.7	51	50
Standard Deviation	2.431	1.660	26.57	18.15	0.642	0.578	7.01	6.32
relative standard deviation	25%	21%	33%	28%	9%	9%	14%	13%
relative decline of % HbA1c due to treatment					26%	15%	33%	20%

Table 2. Statistical Results of Sample From Stropkov

	At baseline				After one year			
	DCCT		**IFCC**		**DCCT**		**IFCC**	
	% HbA1c		mmol/l		% HbA1c		mmol/l	
Gender	Men	Women	Men	Women	Men	Women	Men	Women
n	22	25	22	25	22	25	22	25
arithmetic average	9.8	10.3	84	89	7.9	7.9	62	63
Standard Deviation	1.414	1.874	15.45	20.48	1.001	1.100	10.94	12.02
relative standard deviation	14%	18%	18%	23%	13%	14%	17%	19%
relative decline of % HbA1c due to treatment					19%	22%	24%	28%

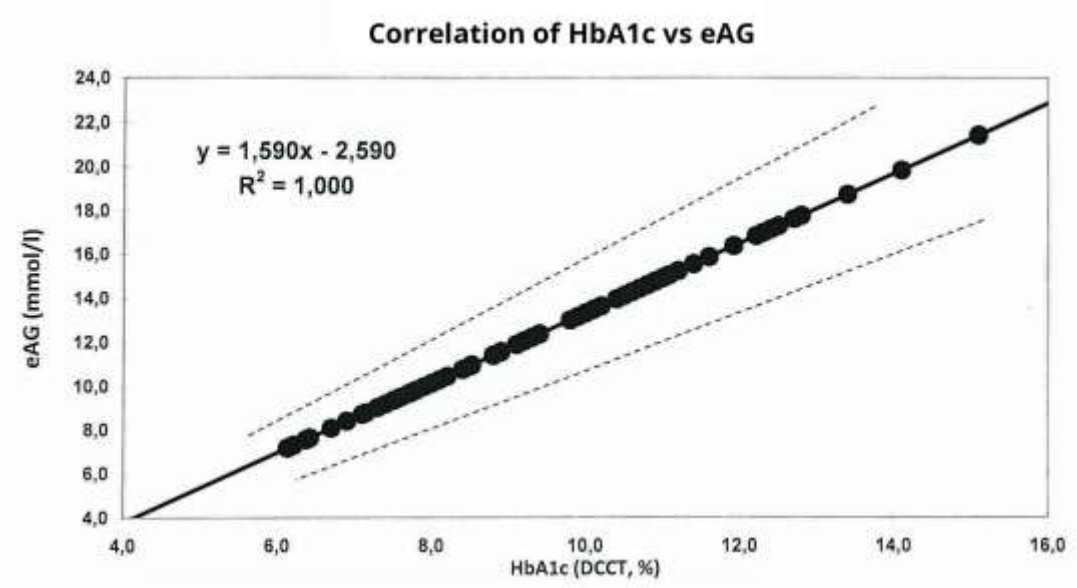

Figure 2. Correlation of HbA1c vs. eAG