SOUTHEAST EUROPE JOURNAL OF SOFT COMPUTING
Available online at www.scjournal.com.ba

Study Of HbA_{1c} As A Reliable Indicator For Metabolic Syndrome In Non Diabetic Patients

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Abstract

With the metabolic syndrome and diabetes mellitus increase in the recent decade, the importance of early detection of insulin resistance is essential. However, a simple method is not currently available for precise measurements. Therefore the aim of this study was to elucidate the association of HbA_{1c} with metabolic syndrome as a constellation of cardiovascular risk factors.
The study population consisted of 45 subjects with metabolic syndrome and 45 free of metabolic syndrome (control group).Total cholesterol, triglycerides, glucose, HbA_{1c}, body mass index (BMI), waist circumference (WC), systolic and diastolic blood pressure were measured in both groups. HbA_{1c} levels are found much more in MS group than the control group, 8,7% and 6,2%, respectively. The sensitivity and specificity of HbA_{1c} is significantly higher in metabolic syndrome patients, 86,7% and 46,67%, respectively. Additionally, subjects with metabolic syndrome exhibited significantly higher blood glucose, triglyceride, systolic/diastolic blood pressure and cholesterol. Our results suggest that HbA_{1c} may be a marker for metabolic syndrome and may identify in a certain degree insulin resistance subjects.

Keywords: Metabolic syndrome, glycated haemoglobin, Diabetes mellitus

Abbreviations: BMI, body mass index; CVD, cardio vascular diseases; IDF, International diabetes federation; ATPIII, Adult treatment panel III; HbA_{1c}, glycated haemoglobin 1c; SBP; systolic blood pressure; DBP, diastolic blood pressure

1. Introduction

Metabolic syndrome (MS) is the name for a group of risk factors that raises the risk for heart disease and other health problems, such as diabetes and stroke. The most common factors for metabolic syndrome are high glucose levels, obesity, high cholesterol and high blood pressure [1]. It is estimated that around 20-25 per cent of the world's adult population have the metabolic syndrome and they are twice as likely to die from it and three times as likely to have a heart attack or stroke compared with people without the syndrome. In addition, people with metabolic syndrome

have a five fold greater risk of developing type II diabetes [2].

Around the world, diabetes diseases start to take an epidemic character, especially in developed countries. Diabetes mellitus affects 5% of the world's population and its prevalence is doubling in Federation of Bosnia and Herzegovina Diabetes mellitus type II is widely spread. Between 2006 and 2012, the number of people diagnosed with diabetes in the increased from 44.168 thousand to 50,9 thousand, most of them diagnosed with type 2 diabetes[3].

Diabetes is associated with many cardiovascular risk factors, which may be present before the onset of hyperglycaemia or develop after the diagnosis of diabetes. In metabolic syndrome, insulin resistance plays a key pathogenic role, and it has been proposed that this syndrome is a powerful determinant of diabetes and cardiovascular disease (CVD) [4,5].

Glycated haemoglobin (HbA_{1c}) is widely accepted as a useful measure of mean blood glucose and therapeutic guideline of diabetes. HbA_{1c} is a form of haemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.HbA_{1c} may also predict incident cardiovascular events, even in individuals without diabetes mellitus . Recent work suggests the utility of HbA_{1c} as the predictor of future risk for diabetes mellitus in diverse ethnic groups [6,7,8]. Evenhtough insulin resistance is one of the major aetiological factors in the development of MS, direct quantitative measurement of insulin sensitivity is not readily available and thus cannot be used as the diagnostic tool for the syndrome. Therefore , various diagnostic criteria for MS have been suggested [9].It is shown that patients with high HbA_{1c} significantly define the MS [10].

Further research needs to be performed in order to investigate the cut-offs of HbA_{1c} in the diagnosis of MS. Therefore, we examined the association of HbA_{1c} with the components of metabolic syndrome and tried to determine whether high HbA_{1c} levels are significant in the diagnosis of MS. Therefore, we tried to determine whether HbA1c levels are linearly correlated to other risk factors of metabolic syndrome within our group of MS patients and within the control group, confirming its status as a possible indicator of MS in patient. .

2. Patients and methods

Patients

In this case-control study 90 subjects were involved and according the ATPIII criterion divided into two groups: subjects with the metabolic syndrome risk factors and a group without metabolic syndrome risk factor (control group). Data collection was done at the public health centre of municipality Novi Grad in Sarajevo, Bosnia and Herzegovina. Subjects were diagnosed and analysed with metabolic syndrome for at least 6 month prior to this study.

Primarily selection of the patients was based on medical history data and laboratory findings of metabolic syndrome, taken and analyzed in a family medical practice of the health centre.

Subjects were divided into two groups:

1. Group of patients with metabolic syndrome (n=45 subjects)
2. Group of patients without metabolic syndrome (n=45 subjects)

The criterion for involvement for this study was:

- Both sexes
- Measurements of HbA1c

Patients with known diabetes mellitus type II were excluded from this study.

Anthropometric measurements

Research instrument were anthropometric measurements, done during the medical checkups. Furthermore, question whether patients smoke or not was asked and noticed. Height, weight, waist circumference, systolic and diastolic blood pressure were measured. Blood pressure was measured with a standardized sphygmomanometer after at least 5 min of rest, according to the Hypertension Detection and Follow up Program protocol. Body mass index (BMI) was calculated by dividing weight (kg) by height (m) squared.

Biochemical parameters

After a 12-h fast, blood glucose, total cholesterol and triglyceride were measured. The photometry method (Hitach 907, Hitach, Tokyo, Japan) was used to measure blood glucose levels and an enzymatic colorimetric test was used to measure total cholesterol and triglyceride levels, using Biosystem reagents.

HbA_{1c} levels were measured by photometric method with a reference value of 4.4-6.8 %. The methodology was aligned with the Diabetes Control and Complications Trial (DCCT) and National Glycohemoglobin Standardization Program (NGSP) standards [11].

Diagnostic criteria

We applied two different definitions of MS in this population: the minor modification version of Third Report National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) and Diagnosis and

management of the metabolic syndrome guidelines [13,14] and the newly recommended Guideline by the International Diabetes Federation (IDF) [1].

The NCEP-ATP III definition is satisfied when more than three of the following five criteria are met:

1. Waist circumference: ≥90 cm in men, ≥80 cm in women
   (defined by the WPRO) criteria [15])
2. Hypertriglyceridaemia: ≥1.7 mmol/l.
3. Total cholesterol: ≥5.1mmol/l, Low HDL-C:<1.0 mmol/l in males and <1.3 mmol/l in females.
4. Hypertension: ≥130/85 mmHg.
5. Fasting hyperglycaemia; ≥5.6 mmol/l.
6. Obesity (BMI) : ≥25kg/m^2

Fasting hyperglycaemia is the sugar level in fasting period of 8 hours .

According to the new IDF definition[1], for a person to be defined as having MS they must have central obesity defined with ethnicity-specific values (≥ 90 cm in men, ≥80 cm in women) plus any two of the following four factors:

1. Hypertriglyceridaemia:≥ 1.7 mmol/l, or specific treatment for this lipid abnormality.

2. Total cholesterol: ≥5.1mmol/l, Low HDL-C: <1.0 mmol/l in males and <1.3 mmol/l in females, or specific treatment for this lipid abnormality.

3. Hypertension: ≥130/85 mmHg, or treatment of previously diagnosed hypertension.

4. Fasting hyperglycaemia: ≥ 5.6 mmol/l.

Statistical methods

All analyses were carried out with the statistical program SPSS for Windows v. 20 (SPSS Inc., Chicago, IL, USA), the level of significance was set at $P<0.05$. The correlation tests were performed to examine various interactions and correlations. The level of correlation between variables was calculates by Pearson coefficient correlation. Multiple linear regression analysis was used for assessing the relationship of HbA_{1c} with age, gender and smoking habits of patients. HbA_{1c} was used as dependent variable and all metabolic syndrome risk factors as independent variables. One-way analysis of variance (ANOVA) tests was used to examine the significance levels for various HbA_{1c} parameters in all groups. Covariance analysis was performed to evaluate the effects of glucose, triglycerides, total cholesterol levels, systolic and diastolic blood pressure, body mass index and waist circumference on the level of Glycated haemoglobin (Hba_{1c}).To investigate the possibility of effect modifications, analyses were repeated, with inclusion of an interaction between Hab1c and all mentioned variables.

3. Results and Discussion

Forty five patients and 45 controls were included in this study. Patients with MS include 21 (46.7 %) were males and 24 (53.3%) females , with mean age of 52 years . Patients without the metabolic syndrome have 21 (46.7%) males and 24 (53.3 %) females with the mean age of 45 years. Based on results, there was no significant age difference between two groups. Metabolic syndrome group showed significantly higher HbA_{1c}, glucose, Systolic and diastolic blood pressure, body mass index, waist circumference, triglycerides and total cholesterol levels (Table1).The control group Hba_{1c} levels have no significant co correlation to other risk factors .

The mean of HbA_{1c} in MS patients increased significantly with the increase of age, BMI and glucose levels (Table1, see Appendix). This study confirmed the positive correlation between body mass index, waist circumference , systolic and diastolic blood pressure. Within the group of MS patients HbA_{1c} percentage linearly increases with glucose, systolic and diastolic pressure (Table2, see Appendix).

There was no significant correlation between patients age and HbA_{1c} within the MS patients, whereas a highly significant correlation was observed between glucose and HbA1c (Table 3, see Appendix).

In general the HbA_{1c} concentration significantly correlates with all the risk factors in metabolic syndrome ($p = 0.004$) (Table3, see Appendix).HbA_{1c} also demonstrated direct and significant correlations with systolic and diastolic blood pressures (Table2, see Appendix).

In Table 2 we can see that Body mass index in all of our patients is significantly correlated to Waist circumference, confirming previous studies [8,10,16]. Therefore BMI and W.C represents good indicators for MS and Insulin resistant patients. In table 1 we observe a notable difference and this strengthen the position of BMI factor as an good indicator of metabolic syndrome .Strong relationship is observed between W.C and triglycerides as with systolic/diastolic blood pressure. Furthermore, glucose levels and triglycerides are shows strong correlation coefficient.

Both male and female diabetic patients exhibited different patterns of glycemic control depending on three criteria values of HbA_{1c}. The distribution of subjects according to gender and specific HbA_{1c} cut-offs showed that most of the MS patients experience poor or worse glycemic control irrespective of their gender (Table 4, see Appendix).

In table 5 we observe strong relationship between HbA_{1c} and glucose in all MS patients. Additionally HbA_{1c} significantly correlates with systolic and diastolic blood pressure in the tested group.

Table 6 represents the results of linear regression all patients, using HbA_{1c} as a depended variable, smoking, age and gender as independent variables, respectively. HbA_{1c} shows a significant correlation to age and especially to the smoking variable (p=0.001), leading to the conclusion that the patients consuming nicotine have the tendency to have higher percentages of HbA_{1c} in their blood. In general, the ANOVA between HbA_{1c} and the factors in table 6 (see Appendix) resulted in a significant value of 0.004. However, here was no significant correlation between patients HbA_{1c} levels and the age within the group of MS patient, but compared to the set of all 90 patients significant correlation exists.

In this study we can observe high systolic and diastolic blood pressure as glucose levels in all MS patients, together with very high waist circumference being the most often accepted risk factors for metabolic syndrome (Table3,see Appendix).

Furthermore, high blood pressure in males is the most common risk factor in all age groups .In females this factors becomes significant with aging. Blood pressure increase is linearly connected with the increase of obesity and insufficient physical activity .However, the connection between these parameters leading to Metabolic syndrome is very difficult to measure and explain .Basically the linear increase of some factors the risk of getting the metabolic syndrome increases.

Recent studies have shown that the metabolic syndrome increases the risk of cardio vascular disease and diabetes mellitus type II [16]. The NCEP (National Cholesterol Education Program) ATP III guidelines recognized metabolic syndrome as a risk factor for CVD, and this is confirmed by several studies [20]. In this study, HbA_{1c} levels increased with the number of components of the metabolic syndrome.

Every single factor increases the risk, but due to the synergies existence the risk of getting CVD increases. There is no study that has refused this fact.

The American Diabetes Association recommended the use of the HbA_{1c} test for the diagnosis of diabetes mellitus and to identify categories at increased risk of diabetes (prediabetes) [18]. HbA_{1c} assays are now highly standardized and accurate as the glucose assays with less intra-individual variability. Also, the HbA_{1c} samples can be obtained at any time, because they do not require fasting or an oral glucose load [19]. HbA_{1c} range of 5.7% to 6.4% is well accepted in defining subjects at a high risk of diabetes. The mean HbA_{1c} value in our MS group is 8.7mmol/l. This values is very high compared to the accepted level of HbA_{1c} ($\geq$5.7%), that is accepted to predicted fasting hyperglycaemia. HbA_{1c} has been considered a very convenient and practical screening tool or high-risk populations for primary diabetes and cardiovascular prevention programmes [17]. Our results could be tested prospectively in long-term studies in other and in higher number populations at high risk of developing Type 2 diabetes and MS.

4. Conclusions

The average age of our patients with metabolic syndrome is 55 years , and without MS 45 years .The difference between MS and control group is statistically significant .The gender difference is not significant in this study between Metabolic syndrome group and control group of patients .

During our daily work obligations , especially during today's office work and much of passive sitting, which is followed by poor and fast meals, saturated with a lot of carbohydrates and fats, is causing deterioration of immunity and the occurrence of Metabolic syndrome. The MS level increases the ratio of BMI (Body mass index) through the years. The Body mass index with metabolic syndrome patients has an average 38kg/m^2 and within the control group it is 26 kg/m^2. This represents a notable difference these strengthen the position of BMI factor as a good indicator of metabolic syndrome.

Cholesterol levels in MS have 7.5 mmol/1 and in the control 4.9 mmol/1.Therefore we can conclude a significant difference between the control and the MS patients. Observing the results of cholesterol levels, it is obvious that there is a high significant difference between the MS and control group, 4.2 mmol/l and 1.5 mmol/l respectively.

Having the glucose level of 8.7 mmol/l in MS represents a crucial criteria for metabolic syndrome and insulin resistance disease. Comparing the MS cholesterol level to the control group, having 6.2 mmol/l, we can see a significant difference. In the HbA_{1c} levels we observe a big difference between metabolic syndrome and the control groups. Males with MS have in average of 8 mmol/l and females 9,5 mmol/l , whereas male patients without MS have 6,4 mmol/l and females 6,2 mmol/l. Within the HbA_{1c} levels in MS there is a significant difference between sexes, whereas in the control group it is 0.2mmol/l, less significant.

The mentioned approach increases the possibility of early detection of metabolic syndrome and diabetes mellitus for on time treatments. In summary, this study reports that among patients in Sarajevo, public health centre Novi Grad, who is known to have high risk of premature CVD and MS, a linear relationship exists between HbA_{1C} levels, CVD, and metabolic syndrome factors. The findings of this study clearly suggest that HbA_{1c} endures the ability of predicting MS and insulin resistance patients.

Acknowledgments

The authors are thankful to Prof.Dr.Mehmet Can from International University of Sarajevo, Bosnia and Herzegovina, for his support and guidance during the course of this study .

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APPENDIX

Table1. General characteristic of the study participants in public health centre Novi Grad Sarajevo

	MS patients	*Control*
N =90	*Mean (range)*	
Male %	21 (46.7 %)	21 (46.7 %)
Female%	24 (53.3%)	24 (53.3%)
Age (years)	55 (20-83)	45(23-78)
Glucose levels (mmol/l)	8.7 (6-22)	5.6 (3-6.4)
Total Cholesterol (mmol/l)	7.5 (3.3-15)	4.9 (1.4-8.3)
Triglycerides (mmol/l)	4.2 (2-14)	1.5 (0.8-6.5)
Systolic blood pressure (mmHg)	153 (120-240)	120 (70-150)
Diastolic blood pressure (mmHg)	98 (80-130)	80 (50-100)
Body Mass Index (kg/m^2)	38(22-35)	26,3 (19-30)
Waist circumference (cm)	109 (87-173)	88 (65-100)
HbA_{1c} (%)	8,7 (6-22)	6.2 (4-7)

Table2. Pearson correlation coefficient in MS group.

M.S patients	*HbA_{1c}*	*B.M.I*	*W.C*	*S.B.P*	*D.B.P*	*Cho.*	*Triglycerides*	*Glucose*
HbA_{1c}	1.000	.210	.158	.359	.320	.234	.127	.584
B.M.I	.210	1.000	.732	.405	.490	.165	.230	.279
W.C	.158	.732	1.000	.466	.439	.149	.507	.090
S.B.P	.359	.405	.466	1.000	.776	.360	.488	.368
D.B.P	.320	.490	.439	.776	1.000	.380	.326	.525
Cho.	.234	.165	.149	.360	.380	1.000	.514	.436
Triglycerides	.127	.230	.507	.488	.326	.514	1.000	.197
Glucose	.584	.279	.090	.368	.525	.436	.197	1.000

Note : significance set at P<0.05,2-tailed

Table3. Pearson correlation coefficient within in MS group.

M.S patients	*HbA_{1c}*	*B.M.I*	*W.C*	*S.B.P*	*D.B.P*	*Cholesterol*	*Triglycerides*	*Glucose*
HbA_{1c}		.083	.151	.008	.016	.061	.202	.000
B.M.I	.083		.000	.003	.000	.140	.064	.032
W.C	.151	.000		.001	.001	.165	.000	.277
S.B.P	.008	.003	.001		.000	.008	.000	.006
D.B.P	.016	.000	.001	.000		.005	.014	.000
Cholesterol	.061	.140	.165	.008	.005		.000	.001
Triglycerides	.202	.064	.000	.000	.014	.000		.097
Glucose	.000	.032	.277	.006	.000	.001	.097	

Note : significance set at P<0.05,2-tailed

Table4. Distribution of subjects according to gender and HbA_{1c} cut-offs in MS group.

Glycemic control	*HbA_{1c} criteria (cut offs)*	*Males*		*Females*		*Total*	
		Number	*Percentage*	*Number*	*Percentage*	*Number*	*Percentage*
Good	≤ 6 %	2	10%	4	17%	6	13%
Poor	>6-9%	12	52%	17	70%	29	65%
Worst	>9	7	33%	3	13%	10	22%
Total		21	100%	24	100	45	100%

Note : significance set at P<0.05,2-tailed

Table 5 .Pearson correlation coefficients and significant values of HbA_{1c} with metabolic syndrome risk factors in MS group.

Correlation	*r*	*P*
B.M.I	0.210	0.083
W.C	0.158	0.151
S.B.P	0.359	0.008
D.B.P	0.320	0.016
Cho.	0.234	0.061
Triglycerides	0.127	0.202
Glucose	0.584	0.000

Note : significance set at P<0.05,2-tailed

Table 6. Pearson correlation coefficients and significant values of HbA_{1c} with age, smoking and gender.

Correlations	***r***	***P***
Age	0.220	0.019
Gender	0.179	0.092
Smoking habits	0.398	0.001

Note : significance set at P<0.05 ,2-tailed, (MS + Control).