International Journal of Nutrition Sciences

Journal Home Page: ijns.sums.ac.ir

ORIGINAL ARTICLE

Evaluating Components of Metabolic Syndrome and Cardiovascular Risk Factors in Patients with Type 2 Diabetes Based on HbA1C Levels

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ARTICLE INFO

Keywords:
Metabolic Syndrome
Diabetes mellitus
Hemoglobin A1c
Blood glucose

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Received: 19 December 2016
Revised: 13 February 2017
Accepted: 13 March 2017

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is one of the most prevalent diseases in the present century that is associated with various complications, such as cardiovascular diseases, caused by metabolic syndrome in these patients in the long term. We aimed to assess components of metabolic syndrome in patients with controlled and uncontrolled T2DM based on serum levels of hemoglobin A1c (HbA1c).

Methods: In this cross-sectional study, after screening 1158 patients who referred to screening centers, 204 patients with T2DM were identified, and evaluated for anthropometric (weight, height, waist circumference, and body mass index), biochemical (fasting blood sugar [FBS], glucose tolerance test [GTT], lipid profile, and HbA1c) markers, and blood pressure. Patients with HbA1c>7% were considered as uncontrolled diabetes and patients with HbA1c≤7% were considered as controlled diabetes. Independent sample t-test was used for comparing markers between two groups and the association of HbA1c with the markers was checked by Pearson correlation coefficient.

Results: In patients with controlled T2DM, serum FBS (P<0.001), GTT (P<0.001), Triglycerides (P=0.04), total cholesterol (P=0.003) and LDL cholesterol (P=0.001) were significantly lower than patients with uncontrolled T2DM. There was asignificant association between HbA1c and FBS (P=0.03, r=0.15), GTT (P=0.003, r=0.21) and systolic blood pressure (P=0.02, r=0.15).

Conclusion: Appropriate treatment of T2DM, when HbA1c reduced to <7%, would prevent chronic complications of metabolic syndrome and cardiovascular risk factors, such as total and LDL cholesterol.

Please cite this article as: Mazloom Z, Hejazi N, Ekramzadeh M, Raeisi-Dehkordi HR, Hezaveh E, Jalilpiran Y. Evaluating Components of Metabolic Syndrome and Cardiovascular Risk Factors in Patients with Type 2 Diabetes Based on HbA1C Levels. Int J Nutr Sci 2017;2(1):33-38.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common endocrine diseases across the world (1). With a prevalence of about 135 million people worldwide in 1995, it is expected to reach over 300 million by 2025 (2). This disease is known as a proven risk factor for atherosclerosis. Various complications of diabetes, including hyperlipidemia, hypertension, hyperglycemia, inflammation and endothelial dysfunction, are involved in the initiation and progression of atherosclerosis (3-5). Increased levels of oxidative stress caused by increased levels of free radicals due to hyperglycemia are the main cause of atherosclerosis (6). Insulin resistance, moreover, is considered the main cause of

numerous metabolic changes in T2DM, such as metabolic syndrome (7), which is the risk factor for cardiovascular disease (8). The components of metabolic syndrome, including increased serum level of triglyceride, hypertension, and decreased high-density lipoproteins (HDL) cholesterol, have a direct relationship with cardiovascular disease (9). It seems that appropriate treatment of T2DM can postpone the incidence of metabolic syndrome and the resulting cardiovascular disease. Such treatment may include appropriate diet, medication, exercise, and behavioral therapy (10) that are intended to reduce fasting blood glucose to 70-130 mg/dl, postprandial blood sugar below 180 mg/dl, and hemoglobin A1c (HbA1c) levels below 7% (7). Since HbA1c reflects mean blood glucose levels of the previous month (11) and is a potent predictor of diabetes complications (12, 13), using HbA1c besides the daily monitoring of blood glucose by the patient is the best predictor in the treatment of T2DM (14). We aimed to evaluate the components of metabolic syndrome as the main risk factors leading to cardiovascular diseases in patients with controlled vs. uncontrolled T2DM, based on serum levels of HbA1c.

Materials and Methods

In this cross-sectional observational study, 204 patients with T2DM were selected by screening 1158 adults who referred to Diabetes Screening Centers in Shiraz, southern Iran. Patients were recruited into the study by census method and after confirmation of T2DM, the objectives of the study and details of the study phases were explained to patients and they were included in the study after obtaining informed consent.

Patients who were diagnosed with T2DM, were >18 years and gave consent to participate in the study. The recorded data included age, sex, educational level, marital status, physical activity (1-3 days/week: light, 3-5 days/week: moderate, 6-7 days/week: heavy, more than 7 days/week: very heavy), smoking, duration of T2DM, history of chronic diseases, such as hypertension, cardiovascular diseases, dyslipidemia, renal disease, and stroke, and consumption of anti-diabetic drugs (including metformin, glibenclamide, acarbose, regular or NPH insulin) were recorded.

Then, anthropometric indices were measured as follows. Weight was measured in kilogram (kg) using Seca scale, Germany, with minimum clothing. Patients' height was measured in meters without shoes using Seca meter, Germany, with an accuracy of 0.1 cm. Body mass index was calculated as weight in kilograms divided by squared height in meters by SPSS. Waist circumference (WC) and hip circumference (HC) were measured with a tape meter in cm; WC was measured at the midpoint between the lowest rib and the iliac crest and HC was measured at the largest width of the buttocks over light clothing by using non-stretchable tape; waist-to-height ratio (Wc/Ht) also were calculated and recorded.

Then, patient's blood pressure was measured using a mercury sphygmomanometer, twice, with an interval of half an hour, and the mean of the two measurements was recorded. Measurements were performed in a calm room in sitting position after the patient relaxed for 15 minutes.

In the next step, 5 ml venous blood sample was collected from each patient in 12 hours fasting status and 2 ml after oral glucose tolerance test with scalp vein in sitting position. The blood samples were centrifuged at 3000 rpm for 10 minutes and the serum was separated. Also, 2 ml of fasting blood of each patient was poured in the heparinized tube to prevent clotting and sent to the laboratory for measurement of HbA1c levels by colorimetric method. Serum levels of fasting blood sugar (FBS), glucose tolerance test (GTT), lipid profile, including triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol, creatinine and blood urea nitrogen (BUN) were measured for each patient using Auto-analyzer BT1500 (Italy). All serum measurements were performed in the local laboratory in the school of nutrition and food sciences.

Statistical analysis of the data was performed using SPSS 16 software. For this purpose, patients'HbA1c levels were compared between two groups controlled (HbA1c≤7%) and uncontrolled diabetes (HbA1c>7%). The components of metabolic syndrome (abdominal circumference, serum triglyceride, HDL cholesterol, systolic and diastolic blood pressure, and fasting blood sugar) were compared between the two groups using independent t-test. Pearson correlation coefficient was used to examine the

relationship between HbA1c level and serum components of metabolic syndrome. In this study, P values less than 0.05 were considered as significant level.

Results

Of 1158 patients with different types of diabetes, 204 patients with T2DM were enrolled into the present study. About 71.6% of patients were female. The mean±SD age of participants was 56.53±10.96 years. Demographic characteristics, mean values of clinical markers and anthropometric measurements of patients with type 2 diabetes have been reported in tables 1 and 2, respectively.

Table 1: Demographic and anthropometric characteristics of patients with T2DM

Variable	Frequency (%) or Mean±SD
Sex	
Female	146 (71.6%)
Male	58 (28.4%)
Educational level	
Illiterate	63 (30.9)
Low literate (before high school)	99 (48.5)
High school graduate	32 (0.7)
Associate Degree	4 (2)
Bachelor	6 (2.9)
Higher than bachelor	0 (0)
Other diseases	
Hypertension	89 (43.6)
Cardiovascular disease	86 (42.2)
Stroke	2 (1)
Hyperlipidemia	135 (66.2)
Renal disease	15 (7.4%)
Marital status	
Single	27 (13.3)
Married	177 (86.8)
Positive history of Smoking	26 (12.7)
Physical activity	
Light	136 (66.7)
Moderate	67 (32.8)
Heavy	0 (0)
Very heavy	1 (0.5)
Weight (kg)	70.84±12.43
BMI (kg/m²)	28.32±4.57
Waist-to-height ratio	0.62±0.08
Duration of diabetes (years)	8.80±7.59
Antidiabetic drugs usage	
Metformin (g/d)	1.01 ±0.82
Glibenclamide (mg/d)	8.28±9.24
Acarbose (mg/d)	5.01±23.26
Insulin NPH (units)	6.17±19.14
Regular insulin (units)	1.04±4.48

Quantitative variable were expressed as Mean±SD; Qualitative variables were expressed as number (percent)

Table 2: Clinical markers in patients with T2DM

Variable	Mean±SD
FBS (mg/dl)	171.88±66.29
A two-hour blood glucose GTT (mg/dl)	246.06±87.86
Glycosylated hemoglobin HbA1c (%)	8.60±5.63
Serum total cholesterol (mg/dl)	183.20±46.36
Triglycerides (mg/dl)	169.81±83.86
HDL (mg/dl)	45.44±13.80
LDL (mg/dl)	106.00±31.77
BUN (mg/dl)	15.57±6.34
Creatinine (mg/dl)	0.98±0.32
Systolic blood pressure (mmHg)	127.07±18.30
Diastolic blood pressure (mmHg)	77.09±9.26

FBS: Fasting blood sugar; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BUN: Blood urea nitrogen

After dividing the patients into two groups based on HbA1C levels, the results showed that patients with higher levels of HbA1C (>7) had a significantly lower BMI (P=0.02) and Wc/Ht (P=0.03), and higher FBS (P<0.001), GTT (P<0.001), cholesterol (P=0.003), triglycerides (P=0.04), and LDL (P=0.001). So, higher levels of HbA1c increased the components of metabolic syndrome (FBS, GTT, and TG levels). Patients with higher HbA1c had higher cholesterol, and LDL, which are major risk factors for cardiovascular diseases and atherosclerosis in patients with T2DM, resulting in higher risk of cardiovascular and atherosclerosis in patients with higher HbA1c (table 3).

As shown in table 4, there was a weak positive relationship between HbA1c level and serum levels of FBS (P=0.03), GTT (P=0.003), and systolic blood pressure (SBP) (P=0.02), which means that higher HbA1c levels increase FBS, GTT, and SBP.

Discussion

As mentioned in the results section, our findings showed that in patients with T2DM, the higher HbA1c levels are associated with higher risk of metabolic syndrome by increasing the level of FBS, GTT, total cholesterol, triglycerides, and LDL. But contrary to the expectations, anthropometric indices, including BMI and waist-to-height ratio were lower in individuals with higher levels of HbA1c that is conflicting with the mechanisms of overweight and obesity in the pathogenesis and progression of T2DM. The results also indicated a significant positive relationship between HbA1c level with FBS, GTT, and SBP, as lower HbA1c levels control

Table 3: Clinical and nutritional parameters in diabetic patients based on the level of hemoglobin A1C

Parameter	HbA1C≤7 (N=70)	HbA1C>7 (N=126)	*p*-value
BMI (kg/m^2)	29.16±0.51	27.70±0.41	0.02*
FBS (mg/dl)	139.97±4.71	189.49±6.20	<0.001*
GTT (mg/dl)	196.54±7.49	274.01±7.80	<0.001*
Total Cholesterol (mg/dl)	170.2±4.65	191.07±4.40	0.003*
Triglycerides (mg/dl)	153.39±8.66	11.54±2.99	0.04*
LDL (mg/dl)	96.26±3.29	111.54±2.99	0.001*
HDL (mg/dl)	44.17±1.16	45.85±1.37	0.35
Waist-to-height ratio	0.64±0.008	0.62±0.007	0.03*
Waist circumference (cm)	101.52±1.21	98.47±1.12	0.06
Systolic blood pressure (mmHg)	125±2.33	127.61±1.54	0.35
Diastolic blood pressure (mmHg)	75.50±1.20	77.57±0.740	0.14

The data are reported as mean±standard error; *Indicates statistically significant difference; BMI: Body mass index; FBS: Fasting blood sugar; GTT: Glucose tolerance test; LDL: Low-density lipoprotein; HDL: High-density lipoprotein

Table 4: The association between hemoglobin A1C and clinical markers measured in patients with diabetes

Variable	The correlation coefficient	*p*-value
Age	0.05	0.42
Duration of diabetes (years)	0.03	0.59
Weight (kg)	-0.02	0.78
Waist circumference (cm)	0.03	0.6
BMI (kg/m2)	0.03	0.65
FBS (mg/dl)	0.15	0.03*
GTT (mg/dl)	0.21	0.003*
Total Cholesterol (mg/dl)	0.01	0.85
LDL (mg/dl)	0.01	0.88
HDL (mg/dl)	-0.002	0.97
Triglycerides (mg/dl)	0.02	0.71
Creatinine (mg/dl)	-0.03	0.62
BUN (mg/dl)	0.05	0.44
Systolic blood pressure (mmHg)	0.15	0.02*
Diastolic blood pressure (mmHg)	0.04	0.51

*Indicates statistically significant difference; BMI: Body mass index; FBS: Fasting blood sugar; GTT: Glucose tolerance test; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; BUN: Blood urea nitrogen

FBS, GTT, and SBP that will ultimately help to improve the overall condition of the patients.

As mentioned in the introduction, HbA1c is a marker reflecting the mean blood sugar in the past months in patients with T2DM and, in combination with FBS level, is a good predictor of developing diabetes in people who have no obvious risk factors (15). In fact, according to studies, this marker can diagnose many cases of undiagnosed diabetes cases and in patients whose diabetes is diagnosed on the basis of HbA1c, abnormal lipid profile indicates the process of atherosclerosis (16). Acute hyperglycemia increases the glycosylation of red blood cells 'membrane and reduce their ability to change its shape when passing vessels that strengthen the probability of anthogenesis (17, 18).

There is evidence that hyperglycemia leads to tissue damage and complications of diabetes through advanced glycation end products (AGEs) and inflammation. Moreover, according to the studies, AGEs have a significant association with age and HbA1c (19). Previous findings have shown significant associations of HbA1c with various risk factors for atherosclerosis (20). Lipid disorders are frequently observed in patients with diabetes. Hyperglycemia is associated with increased total cholesterol, LDL cholesterol, triglycerides and low levels of HDL cholesterol and normalization of blood glucose will correct all these disorders (21). A higher level of fasting plasma glucose is a strong predictor of hypertension in diabetic patients (22). Hypertension is a major risk factor for

cardiovascular diseases in patients with T2DM that is often associated with other cardio-metabolic risk factors (23).

Based on the results of the present study and scientific evidence, controlling blood sugar and HbA1c can play a significant role in reducing complications of diabetes, delay the onset of metabolic syndrome and decrease cardiovascular disease and hypertension.

Therefore, measures to control and decrease HbA1c, as a valuable marker in controlling T2DM, such as medication, diet, lifestyle changes, and increased physical activity can all reduce the adverse effects of T2DM such as hyperlipidemia and hypertension, which are both components of metabolic syndrome.

Besides the markers measured in the present study, measurement of serum levels of inflammatory markers and oxidative stress, such as C-reactive protein (CRP), interleukin-6 (IL-6) and Malondialdehyde (MDA) and their relationship with HbA1c and other blood glucose markers will be of great value. A closer study of body composition of patients with type II diabetes in terms of skin fold, fat mass, lean body mass, body cell mass, and etc. can definitely provide precise associations between HbA1c, as a marker of diabetes control, and anthropometric indices. It is also recommended that the significance of HbA1cbe evaluated in other types of diabetes, such as type 1 diabetes, gestational diabetes, and pre-diabetic patients. It is suggested that other markers of diabetes, such as insulin resistance index, serum insulin levels, as well as AGEs, also be measured in future studies.

Conclusion

Appropriate treatment of T2DM, when HbA1c reduced to <7%, would prevent chronic complications of metabolic syndrome and cardiovascular risk factors, such as total and LDL cholesterol.

Acknowledgment

We are grateful of those who participated in this study.

Conflict of Interest

None declared.

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