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Criterion validity of metabolic and anthropometric predictors in diabetic foot syndrome

Kriterijumska validnost metaboličkih i antropometrijskih prediktora u sindromu dijabetesnog stopala

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Abstract

Background/Aim. The diabetic foot syndrome (DFS) appears in 15% of diabetes mellitus (DM) patients and is the most common cause of hospitalization, prolonged hospital stay and lower extremity amputation. This study assesses the discriminant validity of the indicators of glycemic control, lipoprotein status and the body mass index (BMI) in diagnosing DFS in the DM patients. **Methods.** A comparative observational study was conducted with the study group composed of patients diagnosed with DM and DFS and a control group, composed of healthy volunteers. Metabolic predictors measured in the study were: fasting glycaemia (FG), postprandial glycaemia (PPG), glycated hemoglobin (HbA1c), total cholesterol, total triglyceride, low density lipoprotein (LDLc) and high density lipoprotein (HDLc). The BMI was measured as an anthropometric variable. The validity criterion of both metabolic and anthropometric variables was estimated by the Receiver Operating Characteristic (ROC) procedure. **Results.** A total of 70 patients with DM and 60 healthy volunteers were observed. Using the ROC procedure, five significant predictors of DFS were proved. The validity criterion for HbA1c, FG, PPG, LDLc and the BMI were in the following order: 6.3%, 6.3 mmol/L, 7.1 mmol/L, 4.39 mmol/L and 25 kg/m^2, respectively. Significantly larger surfaces were found under the curve for all glycometabolic variables, compared to the surface under the curve for LDLc, as well as relative to the surface under the curve for BMI. **Conclusion.** Preventing DFS in patients with DM has to include intensification of diet measures along with the treatment of the increased value of fasting glycaemia, postprandial glycaemia and LDLc, even when they lower compared to the current recommended values for the patients with DM. Lowering body fat in the patients with DM has to be approached in the period of their pre-obesity.

Key words:
diabetes mellitus; diabetic foot; syndrome; glycated hemoglobin; body mass index; prognosis.

Apstrakt

Uvod/Cilj. Sindrom dijabetesnog stopala (SDS) javlja se kod skoro 15% pacijenata sa dijabetes melitusom (DM) i najčešći je uzrok njihove hospitalizacije, prolongiranog bolničkog lečenja i amputacija donjih ekstremiteta. U studiji je procenjena diskriminaciona validnost pokazatelja glikoregulacije, lipoproteinskog statusa i indeksa telesne mase (ITM) u detekciji SDS kod pacijenata sa DM. **Metode.** U uporednoj, opservacionoj studiji, ispitivanu grupu sačinjavali su pacijenti sa DM i SDS, a kontrolnu zdravi dobrovoljci. Metabolički prediktori izmereni u studiji bili su: glikemija našte (GN), post-prandijalna glikemija (PPG), glikozilirani hemoglobin (HbA1c), ukupni holesterol, ukupni trigliceridi, lipoproteini male gustine (LDLc) i lipoproteni visoke gustine (HDLc). ITM je izmeren kao antropometrijska varijabla. Kriterijumska validnost metaboličkih i antropometrijskih varijabli procenjena je procedurom prijemno operativnih karakteristika. **Rezultati.** Ukupno je opservirano 70 pacijenata sa DM i 60 zdravih dobrovoljaca. Procedurom prijemno operativnih karakteristika dokazano je pet značajnih prediktora SDS. Kriterijumske vrednosti za HbA1c, GN, PPG, LDLc i ITM, iznosile su, redom: 6.3%, 6.3 mmol/L, 7.1 mmol/L, 4.39 mmol/L i 25 kg/m^2. Pronađene su značajno veće površine ispod krivih kod svih glikometaboličkih varijabli u odnosu na površinu ispod krive za LDLc, kao i u odnosu na površinu ispod krive za ITM. **Zaključak.** Prevencija SDS kod obolelih pacijenata sa DM, mora da uključi intenziviranje dijetetskih mera uz tretman povišenih vrednosti glikemije našte, postprandijalne glikemije i LDLc i to, pri

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njihovim nižim vrednostima u odnosu na aktuelne preporučene vrednosti za pacijente sa DM. Smanjenju telesne mase kod pacijenata sa DM, neophodno je pristupiti još u periodu njihove pre-gojaznosti.

Ključne reči:
diabetes melitus; dijabetesno stopalo; sindrom; hemoglobin, glukozilovan; telesna masa, indeks; prognoza.

Introduction

The term diabetes mellitus (DM) describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. The diabetic foot syndrome (DFS) is a major problem in people suffering from diabetes DM with a tendency for ulcers, infection or damage to the deep soft tissues of the foot [2]. DFS occurs in about 15% of the patients with DM, and the most common risk factors are male gender, long-termed DM, foot deformities and diabetic polyneuropathy (DPN) [3–5]. Despite its high incidence, DFS has not been classified according to the International Classification of Diseases (ICD-10). This may indicate that the incidence of DFS is significantly higher. The patients with DM are at a high risk of developing microvascular complications, especially DPN, which further leads to the DFS development [6]. It occurs in almost 50% of the patients with DM who suffer longer than 10 years and in the patients with diabetic peripheral neuropathy, which is the most common chronic complication in the type 2 diabetes [7]. In some developed countries, DFS is the most common cause of hospitalization, prolonged hospitalization and lower extremity amputation in the patients with DM [8–10].

Former investigations indicated that the level of glycosylated haemoglobin (HbA1c), postprandial glycaemia and dyslipidemia are believed to be of a particular importance for DPN [11]. There are reports that reducing hyperglycaemia decreases the onset and progression of microvascular complications [12, 13]. However, in the above mentioned studies, the examined patients were those with DM (with or without DFS) in the absence of a control group of healthy volunteers, so that the roles of actual and retrograde glucoregulation, lipid metabolism and obesity in DFS have remained insufficiently understood. The elevated HbA1c levels indicate poor chronic glycemic control and are directly related to hypoxemia in the vasa vasorum and microvascular complications in the diabetic patients [14]. Christman et al. [15] reported that glycaemia, as assessed by HbA1c, may be an important biomarker in predicting the wound healing rate in the diabetic patients. Obesity with insulin resistance and hypoadiponectinemia associated with dyslipidemia and the elevated levels of systemic inflammatory markers are also a significant factor in the pathogenesis of DFS. Previous studies showed that the prevalence of diabetic foot ulceration is higher in people with the body mass index (BMI) > 30 kg/m^2 [11]. However, other authors suggest that the BMI is not significantly associated with DFS [16].

The objectives of this study were to assess the discriminant validity of the indicator of the glycemic control, lipoprotein status and BMI in diagnosing DFS.

Methods

Study design, time and place

To estimate the risk factors in the development of DFS, we conducted a comparative observational study. The study group was composed of the patients diagnosed with DM with DFS. DM was diagnosed by the World Health Organization (WHO) criteria. DFS in these patients was observed as the presence of microscopically confirmed lesions (cracks, fissures, clavus) or macrolesions on foot, or following the history of previously diagnosed trophic ulcers. The control group consisted of the healthy volunteers. The study was approved by the Ethics Committee of the Clinical Centre in Kragujevac and was conducted in the period January 2014 – May 2015 at the Centre for Endocrinology, Diabetes and Metabolic Diseases, Department of Internal Medicine, Clinical Centre in Kragujevac. Both groups involved the adult people of both genders who signed the consent form of participation in the research on a voluntary basis.

Variables

The study tracked the demographic variables (gender and age), anthropometric variables (BMI) and metabolic variables (fasting blood glucose, glucose 2h after food intake, total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and total triglycerides – all expressed in mmol/L). The levels of HbA1c (%) were also determined.

The measurements of weight and height were obtained for each individual, and the BMI was calculated according to the following formula: BMI (kg/m^2) = body weight (kg) / high^2 (m^2)

Fasting blood glucose (FBG) and postprandial plasma glucose (PPG) were determined spectrophotometrically by the glucose oxidase test (GOD-PAP) with the commercial reagent 'Bioanalitica'and Aeroset Abbott analyzer. The level of HbA1c was determined by using the imunoturbidimetric method of inhibition microparticle agglutination using the reagent produced by the Abbottand Aeroset-Abbott analyzer. The level of the total triglycerides was measured spectrophotometrically by the glycerol phosphate oxidase test (GPO-PAP) using the commercial reagents produced by the Abbott and Aeroset-Abbott analyzer. The level of the total cholesterol was measured spectrophotometrically by the cholesterol oxidase test (CHOD-PAP), using the commercial reagents produced by the Abbott and Aeroset-Abbott analyzer. The level of high density lipoprotein cholesterol (HDLc) was determined by the ultracentrifugation HDLc test, a homogeneous method for directly measuring HDLc, using two commercial reagents and detergent produced by the Abbott and

Aeroset-Abbott. The level of low density lipoprotein cholesterol (LDLc) was calculated by the Friedewald formula: LDLc (mmol/L) = Total cholesterol (mmol/L) – HDLc (mmol/L) – Total triglycerides (mmol/L) / 2.2

Statistical methods

The continuous numerical data sets were represented by the mean and standard deviation. The categorical variables were defined by the relative frequency of outcomes. The independent samples *t*-test was used to assess the differences among continuous numerical variables. The criterion validity of metabolic and anthropometric variables for the detection of DFS was estimated by the Receiver Operating Characteristic (ROC) procedure. The cut-point value, sensitivity, specificity, positive predictive value and negative predictive value were obtained applying the maximum Youden index: $J = max\ [SE_i + SP_i - 1]$, where SE_i denotes sensitivity and SP_i denotes specificity for each potential cut-point value of the resulting variable. Comparison of the areas under the ROC curves was done using the method of Hanley and McNeil. The accepted level of significance was 0.05. The analysis was done with the statistical package IBM SPSS Statistics 20 (NY) and MedCalc 12.5.0 (Belgium).

Results

Among the entire cohort of 130 volunteers, 70 had DFS and other volunteers were in the control group. The study included 80 women and 50 men aged 54.56 ± 14.22 years. In the study group, there were 36 women, and in the control group there were 44 women. Compared to the control group, the patients with DFS were significantly older (t = -12.531, p = 0.000). The patients with DFS were 60.17 ± 12.40 years old on average while in the group of the healthy volunteers the mean age was 47.64 ± 13.31 years. In the group of the patients with DFS, 23 of them had previous ulcer and other patients had the actual micro and/or macro foot lesions.

The student *t*-test showed that the patients with DFS exhibited significantly elevated values of FBG, HbA1c and LDLc in comparison to the control group. In other metabolic parameters no differences were noted between the groups (Table 1). In comparison with the controls, the patients with DFS had a significantly higher BMI (Table 1).

Using the ROC procedure, 5 significant predictors of DFS were proved (FBG, PPG, HbA1c, LDLc and BMI). The ROC procedure parameters are shown in Table 2.

All area under the curve (AUC) values of glycometabolic variables were higher in comparison to the AUC for BMI, and the AUC for LDLc (Table 3 and Figure 1). Also, the AUC for FBG was larger in comparison to the AUC for PPG. Between the AUC for HbA1c related to the AUC for FBG and the AUC for HbA1c related to the AUC for PPG no statistically significant difference was found.

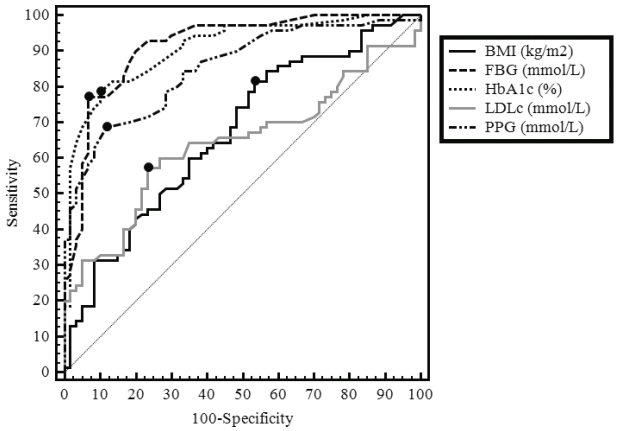

Fig. 1 – Receiver operating characteristic curve (ROC) of the metabolic and anthropometric variables in diabetic foot syndrome detection.
BMI – body mass index; FBG – fasting blood glucose; PPG – 2-h postprandial plasma glucose; HbA1c – glycated hemoglobin; LDLc – low density lipoprotein cholesterol.

Table 1

Descriptive statistics for antrophometric and metabolic variables with the significance of differences between groups (healthy volunteers – HV vs. diabetic foot syndrome – DFS)

Variables	Group		*p* (Student *t*-value)
	HV(n_1=60) Mean ± SD	DFS (n_2=70) Mean ± SD	
BMI (kg/cm^2)	25.89 ± 4.55	28.82 ± 4.66	0.000 (-3.610)
FBG (mmol/L)	5.18 ± 0.94	7.55 ± 1.69	0.000 (-10.056)
PPG (mmol/L)	6.06 ± 1.04	8.54 ± 2.57	0.000 (-7.425)
HbA1c (%)	5.55 ± 0.78	7.48 ± 1.33	0.000 (-10.236)
Total cholesterol (mmol/L)	5.38 ± 0.78	5.95 ± 1.28	0.002 (-3.120)
HDLc (mmol/L)	1.14 ± 0.28	1.16 ± 0.54	0.811 (-0.239)
LDLc (mmol/L)	3.90 ± 0.83	4.41 ± 1.32	0.009 (-2.661)
Triglycerides (mmol/L)	1.68 ± 0.97	1.90 ± 0.80	0.168 (-1.388)

BMI – body mass index; FBG – fasting blood glucose; PPG – 2h post prandial plasma glucose; HbA1c – glycated hemoglobin; HDLc – high density lipoprotein cholesterol; LDLc – low density lipoprotein cholesterol; SD – standard deviation.

Table 2

Receiver operating characteristic (ROC) curve analysis of the significant metabolic and anthropometric variables in the detection of diabetic foot syndrome

Variables	AUC	SE for AUC	95% CI for AUC	*p* (z)	Cut point	SN (%) (95% CI)	SP (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
FBG	0.915	0.025	0.854–0.957	0.000 (16.452)	> 6.3	77.14 (65.6–86.3)	93.33 (83.8 – 98.2)	93.1 (83.3–98.1)	77.8 (66.4–86.7)
HbA1c	0.908	0.026	0.845–0.952	0.000 (15.808)	> 6.3	78.57 (67.1–87.5)	90.00 (79.5–96.2)	88.7 (77.5–95.6)	80.8 (69.8–89.1)
PPG	0.851	0.033	0.779–0.908	0.000 (10.731)	> 7.1	68.57 (56.4–79.1)	88.33 (77.4–95.2)	85.5 (72.9–93.7)	73.8 (62.5–83.1)
LDLc	0.642	0.049	0.553–0.724	0.004 (2.899)	> 4.39	57.14 (44.7–68.9)	76.67 (64.0–86.6)	71.0 (56.8–82.7)	64.1 (52.4–74.8)
BMI	0.669	0.047	0.582–0.750	0.000 (3.574)	> 25	81.43 (70.3–89.7)	46.67 (33.7–60.0)	60.4 (49.4–70.8)	71.5 55.5–84.4

AUC – area under the curve; SE – standard error; CI – confidence interval; z – normal distribution zed value; SN – sensitivity; SP – specificity; PPV – positive predictive value; NPV – negative predictive value; BMI – body mass index; FBG – fasting blood glucose; PPG – 2h postprandial plasma glucose; HbA1c – glycated hemoglobin; LDLc – low density lipoprotein cholesterol.

Table 3

Difference between the area under curves (AUC) pairs with the metabolic and anthropometric variables in the diabetic foot syndrome prediction

	Difference between AUC	SE	95% CI	z	*p*
BMI vs FBG	0.246	0.050	0.147–0.345	4.869	0.000
BMI vs HbA1c	0.239	0.051	0.138–0.339	4.649	0.000
BMI vs LDLc	0.027	0.066	0.102–0.157	0.416	0.678
BMI vs PPG	0.182	0.056	0.072–0.292	3.232	0.001
FBG vs HbA1c	0.007	0.027	0.046–0.060	0.263	0.792
FBG vs LDLc	0.273	0.052	0.172–0.375	5.265	0.000
FBG vs PPG	0.064	0.032	0.001–0.126	2.002	0.045
HbA1c vs LDLc	0.266	0.050	0.168–0.365	5.289	0.000
HbA1c vs PPG	0.057	0.029	0.001–0.115	1.918	0.055
LDLc vs PPG	0.210	0.055	0.102–0.317	3.816	0.000

AUC – area under the curve; SE – standard error; CI – confidence interval; z – normal distribution zed value; BMI – body mass index; FBG – fasting blood glucose; PPG – 2h postprandial plasma glucose; HbA1c – glycated hemoglobin; LDLc – low density lipoprotein cholesterol.

Discussion

In this study, we dealt with the assessment of the validity of metabolic and anthropometric parameters as the predictors of the DFS. DFS is a late-diagnosed DM complication, mainly due to the lack of instruments for a reliable early diagnosis in primary care. Due to the multidisciplinary approach to this problem, the possible risk factors have been selectively investigated in the research so far, and due to the non-standardized instruments no consensus over the prevention of DFS has been achieved within the World Health Organization.

Former studies dealing with DFS were mostly related to the cost-effectiveness of treatment of the patients suffering from foot ulcers, morbidity, mortality and a treatment for the special care patients if compared to those who were the diabetic patients without DFS, while no research with the healthy populations as the control group was undertook [17].

Our results showed that HbA1c is the most important independent predictor of DFS among the metabolic parameters, which is consistent with other studies [18]. According to our analysis, the cut-point for HbA1c is 6.3%. The resulting value is lower than the value according to the American Diabetes Association (ADA) guidelines for HbA1c (threshold ≥ 6.5%) and the recommended values for HbA1c (threshold = 7.0%) according to the European Association for the Study of Diabetes (EASD) criteria [19].

When the HbA1c ≥ 6.5 %, the PPG levels contribute to a large portion of this value. If we take into account that sudden increases in blood glucose cause oxidative stress and induce endothelial dysfunction, which leads to the chronic complications of DM, then special importance is attached to PPG. According to the ADA recommendations, the PPG value was higher and measured at 11.1 mmol/L. Having analyzed the results presented in Diabetes Epidemiology: collaborative analysis in Europe (DECODE) and Diabetes Epidemiology: collaborative analysis in Asia (DECODA) studies, the PPG is given priority over FBG regarding their predictive values in predicting chronic complications [20]. The results of our study showed the lower PPG values if compared

to the recommendations. The cut-point we obtained was at 7.0 mmol/L and closer to the ADA pre-diabetes criteria. Concerning the PPG testing, in this study, we got a larger area under the curve for fasting blood glucose. These three parameters – FBG, HbA1c and PPG – make the three most important therapeutic goals of achieving the optimal glycemic control.

The experts on the diagnosis and classification of DM defined the criteria for impaired fasting glucose (IFG) at 5.6–6.9 mmol/L, and the World Health Organization set IFG cutoff at 6.1 mmol/L. According to the American Diabetes Association (ADA) criteria, the DM value is slightly higher – at 6.5 mmol/L, and the European Association for the Study of Diabaetes (EASD) suggested the value of 7.0 mmol/L. In our results, the FBG cut-point is at 6.3 mmol/L which requires starting the treatment much earlier in order to prevent DFS, even, in accordance with the current FBG criteria, in the pre-diabetes phase [19].

LDLc in our study appeared to be an important metabolic predictor of DFS. The values obtained are consistent with the results of the Framingham Heart Study, the Multiple Risk Factor Intervention Trial (MRFIT), where LDLc was identified as a risk factor of the utmost importance along with FBG and PPG [21]. In the current guidelines for the prevention of coronary heart disease in the diabetic patients, elevated LDLc is the primary target of the lipid-lowering therapy.

In the patients with low cardiovascular risk, the target LDLc value was at 2.6 mmol/L and in those with a high cardiovascular risk, it was at 1.8 mmol/L.

In our results, the validity of LDL in the prediction of DFS is lower than the validity of the BMI. We obtained the cut-point value of 4.39 mmol/L. Following the ADA criteria, some studies showed that only 58.5 % of the patients reached the target LDLc value during treatment, while 7.2% achieved the target values for both LDLc and HbA1c simultaneously [22]. In favor of and in addition to previously stated, the treatment of dyslipidemia in the DM patients should be commenced earlier, from the very onset of the disease.

In our study, the BMI was singled out as an important anthropometric parameter and, according to its validity in relation to the metabolic parameters; it had the smallest area under the curve, the cut-point being at 25 kg/m^2. Previous studies showed that the prevalence of diabetic foot ulceration is higher in the people with BMI > 30 kg/m^2. In the RICH-ARD investigators study conducted on 2,339 patients the mean BMI was 29.9 kg/m^2, and even 42.9% had the BMI ≥ 30 kg/m^2 [23]. Our results showed that body weight regulation is significant in the prevention of DFS which is consistent with the results of Gray et al. [24], who showed that elevated BMI is associated with the progressively higher risk of complications from DM, specifically for DFS, and cardiovascular risk in men when the BMI from 27.5 kg/m^2 to 29.9 kg/m^2, or when 25 kg/m^2 to 27.49 kg/m^2 in women.

Previous studies pointed out the need for better approach to prevent DFS, including the intensive patient education and specialist nurse education in primary health care under the supervision of the diabetologists. Such investment is certainly justified, but one should not ignore the importance of the biochemical markers known as the predictors of DM-related complications.

Our study's limitations are connected to a relatively small study population. Additionally, in regards to the age of the patients in the group with DFS, there was no equity, compared to the control group, considering the fact that the patients with DFS were significantly older.

Conclusion

According to the results of our study, if we are to forestall the emergence of diabetic foot syndrome as a diabetes mellitus related complication, the treatment of the patients with elevated values of fasting blood glucose, postprandial plasma glucose, glycosylated haemoglobin and low density lipoprotein cholesterol should begin much earlier, at the lower values than currently recommended in diagnosing diabetes mellitus, and the reduction of the body mass index should be given even greater emphasis in the period of pre-obesity. Of course, we need and expect additional studies to be conducted on the larger groups of patients.

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