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Diagnosis and predictive clinical and para-clinical cutoffs for diabetes complications in Lur and Lak populations of Iran; a ROC curve analysis to design a regional guideline

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ABSTRACT

Introduction: American Diabetes Association updates its guideline every year. However this guideline can be changed for different populations based on their cultural and genetic status.
Objectives: We intend to design a regional study in Lur and Lak populations of Iran using receiver operating characteristics (ROC) curve model.
Patients and Methods: A total of 133 diabetes mellitus (DM) patients were enrolled in this study. The collected information for each patient were gender, age, body mass index (BMI), DM type, DM duration, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), lipid profile, type of treatments, type of statin and dose, documented neuropathy, documented nephropathy, symptomatic retinopathy, peripheral vessel disease (PVD), documented cardiovascular disease (CVD), food ulcer history, dawn effect, systolic blood pressure (SBP), and diastolic blood pressure (DBP). ROC curve was used and area under curve (AUC) was reported.
Results: For neuropathy, age was the most accurate diagnostic index (area under curve [AUC] = 79%). For nephropathy SBP was the most accurate diagnostic index (AUC= 88%). For symptomatic retinopathy DM duration was the most accurate diagnostic index (AUC= 81%). For PVD, HDL-C was the most accurate diagnostic index (reverse AUC= 67%). For CVD age was the most accurate diagnostic index (AUC= 81%). For foot ulcer history age was the most accurate diagnostic index (AUC= 85%).
Conclusion: The final suggested guideline is like the international guidelines. However some unique points should be regarded. Blood pressure >165/110 mm Hg is diagnostic of diabetic nephropathy. Additionally serum high-density lipoprotein (HDL-C) >48 mg/dL is strongly suggested.

Implication for health policy/practice/research/medical education:
Diabetes management guidelines can be changed for different populations based on their cultural and genetic status. In this region, blood pressure >165/110 mm Hg is diagnostic of diabetic nephropathy. Additionally serum HDL-C >48 mg/dl is strongly suggested for the prevention of diabetes complications.
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Introduction

Diabetes mellitus (DM) as a global health issue, is a complex multifactorial chronic disease and a growing epidemic illness with chronic macro- and microvascular complications (1-4) as well as psychological problems (5). DM and its complications account for 5% of all deaths worldwide annually (6,7). Hyperlipidemia and dyslipidemia increase the risk of microvascular complications including retinopathy, nephropathy and neuropathy as well as macrovascular complications such as cardiovascular disease (CVD). CVD is the major cause of mortality and morbidity in type 2 DM (T2DM)

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patients, which is responsible for near to 50% of all deaths globally (1,3,8-10). In patients of type 2 DM, the risk of CVD is 2 to 4 times of people without DM (3,11). Insulin resistant increases free fatty acid levels and lipoproteins in the blood which potentiate the risk factor of dyslipidemia and atherosclerosis (12-15). Dyslipidemia is responsible for 1/2 cases of ischemic heart disease and 1/5 cases of strokes (8,16). Hence, early diagnosis of dyslipidemia in high-risk patients with DM is necessary for reducing the risk of acute and chronic complications (6,8). Hemoglobin A1c (HbA1c) predicts both macro and microvascular complications of DM which indicates the mean glycemic values in the recent three months (17,18). The positive correlation between HbA1c with total cholesterol (TC), triglyceride (TG), low-density lipoprotein (LDL-C) and very low-density lipoprotein (VLDL) levels were detected. Additionally, the negative correlation of HbA1c with high-density lipoprotein (HDL-C) levels has shown in both male and females (6-8,19). Hemoglobin A1c can be used to predict dyslipidemia and glycemic values and diabetics complications (6,8).

Objectives

American diabetes association updates its guideline every year. This guideline is obtained based on evidence-based medicine. Various parts of this guideline are based on systematic reviews and meta-analyses. They include various populations an ethnicities. However, this guideline can be changed for different populaces based on their cultural and genetic status. Therefore, we intend to design a regional study in Khorramabad, Lorestan province, west of Iran, emphasizing on blood pressure and lipid profile cutoffs.

Patients and Methods

Design

This analytic cross-sectional study was conducted based on Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (available from http://www.equator-network.org/reporting-guidelines/stard/). This study has been done in the Khorramabad hospitals having endocrinology/internal medicine ward or clinics (Shahid Rahimi, and Sohadaye Ashayer). The sampling method was census in the second half of 2017.

Participants

Totally 150 known cases of type 1 and type 2 diabetes were found. However according to some incomplete information, only 133 patients were enrolled in this study. The ethnicities of the patients were Lur and Lak as their gene pools of human leukocyte antigen (*HLA*) have been previously reported (20, 21). History taking and physical examination were done. The collected information for each patient were gender, age, body mass index (BMI), DM type, DM duration, fasting blood sugar (FBS), HbA1c, LDL-C, HDL-C, TG, type of DM treatment, type of statin and dose, documented neuropathy, documented nephropathy, symptomatic retinopathy, peripheral vessel disease (PVD), documented CVD, food ulcer history, dawn effect, systolic blood pressure (SBP), and diastolic blood pressure (DBP). In addition, the cumulative daily equivalent dose of atorvastatin, and estimated level of LDL-C without statin therapy were calculated in Excel 2013 (Microsoft, USA).

Test methods

The gold standard definition of each term is based on the following points; neuropathy (documented cases based on history and physical examination); nephropathy (documented cases based on micro-albuminuria); retinopathy (merely symptomatic cases with the history of laser or surgical therapy or being candidates of such procedures); PVD (documented cases based on history and physical examination); CVD (documented cases based on cardiology consultant); dawn effect (nausea during night sleep and morning hyperglycemia merely based on portable glucometer); cumulative atorvastatin equivalent [calculated based on (22)]; real LDL-C (estimation of LDL-C if there is not administration of statin based on the lower limit of LDL-C reduction in each statin dose) (22).

Ethical issues

The research followed the tenets of the Declaration of Helsinki. This study has been registered in the ethics committee of Lorestan University of Medical Sciences with registration number IR.LUMS.REC.1393.19. The informed consent was obtained. The raw data are originally obtained and available online (https://data.mendeley.com/datasets/k62fdsnwkg/1).

Statistical analysis

Based on central tendency and enough sample size of each possible group (>30), we considered normal distribution for numerical data. Independent *t* test with equal variance was used. Receiver operating characteristics (ROC) curve was used for $P<0.05$. Thereafter if area under curve (AUC) was >65% the cutoffs of that parameter would be reported. Three cutoffs would be reported; 1) one of the optimal cutoffs in the northwest of the ROC curve; 2) the most median cutoff with sensitivity 100%; 3) the most median cutoff with specificity 100%. Sensitivity 100% was considered as negative predictive value (NPV)~100%, and specificity 100% considered as positive predictive value (PPV)~100%. STATA14 software (StataCorp LLC, US) was used.

Results

T test results

Two-tailed *P* values are reported in Table 1. The relations (significant at $P<0.05$) are considered for ROC curve analysis. For *t* test-based judgement we used Bonferroni's correction because of 70 simultaneous analysis. Then $P<0.0007$ was considered as a corrected significance level. After correction, age and DM duration was the

Table 1. T test analysis results

Complication	Age (y)	BMI kg/m²	DM duration (y)	FBS (mg/dL)	HbA1c (%)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	SBP (mm Hg)	DBP (mm Hg)
Neuropathy	<0.0001[b]	0.1648	<0.0001[b]	0.0042[a]	0.1585	0.3365	<0.0001[b]	0.0185[a]	0.0153[a]	0.0073[a]
Nephropathy	<0.0001[b]	0.0000[b]	<0.0001[b]	0.0001[b]	0.0555	<0.0001[b]	0.0148[a]	0.0001[b]	<0.0001[b]	<0.0001[b]
Retinopathy	<0.0001[b]	0.1276	<0.0001[b]	0.0006[b]	0.0306[a]	0.0140[a]	0.0037[a]	0.0125[a]	<0.0001[b]	<0.0001[b]
PVD	<0.0001[b]	0.3410	<0.0001[b]	0.0195[a]	0.0528	0.4782	0.0004[b]	0.0129[a]	0.2161	0.1026
CVD	<0.0001[b]	0.0635	<0.0001[b]	0.0003[b]	0.0409[a]	0.1659	<0.0001[b]	<0.0001[b]	0.0002[b]	<0.0001[b]
Foot ulcer	<0.0001[b]	0.0012[a]	<0.0001[b]	0.2259	0.0289[a]	0.1576	0.0001[b]	0.0142[a]	0.0003[b]	0.0002[b]
Dawn effect	0.7799	0.1493	0.2494	0.3914	0.3962	0.0001[bc]	0.2109	0.7339	0.0231[ac]	0.2408

Abbreviations: PVD, peripheral vessel disease; CVD, cardiovascular disease.
Each numerical parameter is evaluated in each nominal complication.
[a] Significant at $P<0.05$; [b] Significant at $P<0.0007$; [c] LDL-C and SBP had protecting effect for dawn effect.

most associated parameters with diabetes complications. FBS was associated with nephropathy, symptomatic retinopathy and CVD. Blood pressure was associated with nephropathy, symptomatic retinopathy and CVD and also foot ulcer history. Among the lipid profile, HDL-C was associated with neuropathy, PVD, CVD and foot ulcer history. TG was associated with nephropathy and CVD. LDL-C was only associated with nephropathy. HbA1C was not an independent associated factor. LDL-C was a protecting factor for dawn effect.

Linear regression results

The *P* values and effect directions are shown in Table 2. For regression-based judgement we applied Bonferroni's correction because of 45 simultaneous analysis. Then $P<0.001$ was considered as a corrected significance level. After applying the correction, age versus DM duration and SBP versus DBP had positive correlations. A negative correlation was found for HDL-C versus TG (Table 2). Real LDL-C was associated with age, LDL-C and cumulative atorvastatin equivalent. In contrast to LDL-C versus age, the positive correlation of real LDL-C with age was statistically significant (Figure 1).

ROC curve results

The cutoffs obtained from ROC curve analysis are shown in Table 3. The graphs of these ROC curves are shown in Figure 2A-F. The ROC curve of dawn effect is not shown due to its inconclusive results. For neuropathy, age was the most accurate diagnostic index (area under curve [AUC] = 79%). For nephropathy SBP was the most accurate diagnostic index (AUC= 88%). For symptomatic retinopathy DM duration was the most accurate diagnostic index (AUC= 81%). For PVD, HDL-C was the most accurate diagnostic index (reverse AUC= 100-33%). For CVD age was the most accurate diagnostic index (AUC= 81%). For foot ulcer history, age was the most accurate diagnostic index (AUC= 85%).

Discussion

This study was aimed to reach a regional guideline. Generally our results were similar to international guidelines; however there were some unique results. Mainly our dissimilarities were related to HbA1c. This can be justified through this fact that results of HbA1c evaluation are methodological and technical dependent (23,24). Moreover, based on the World

Table 2. Linear regression matrix (*P* value and effect direction)

Numerical parameter	Age (y)	BMI (kg/m²)	DM duration (y)	FBS (mg/dL)	HbA1c (%)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	SBP (mm Hg)	DBP (mm Hg)
Age	NA									
BMI	0.040[a] +	NA								
DM duration	0.000[b] +	0.464	NA							
FBS	0.930	0.029[a] -	0.238	NA						
HbA1c	0.223	0.221	0.484	0.131	NA					
LDL-C	0.744	0.623	0.393	0.106	0.845	NA				
HDL-C	0.250	0.203	0.528	0.582	0.554	0.007[a] +	NA			
TG	0.077	0.731	0.121	0.069	0.610	0.044[a] +	0.000[b] -	NA		
SBP	0.090	0.007[a] +	0.009[a] +	0.084	0.430	0.008[a] +	0.589	0.499	NA	
DBP	0.195	0.516	0.371	0.458	0.103	0.088	0.463	0.343	0.000[b] +	NA

Abbreviations: BMI, body mass index; DM, diabetes mellitus; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; TG, triglyceride; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure.
All numerical parameters are compared two by two for correlation.
[a] Significant at $P<0.05$; [b] Significant at $P<0.001$.

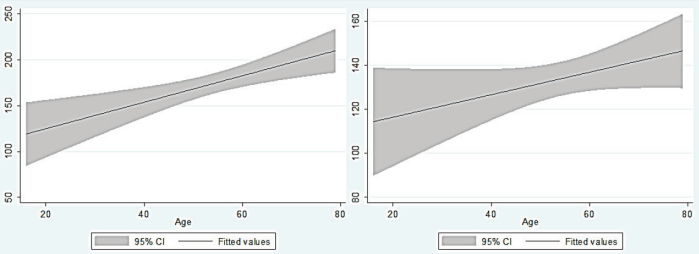

Figure 1. Regression of real LDL-C VS age (left) and LDL-C VS age (right). The left one is statistically significant ($P < 0.05$).

Health Organization report, HbA1c needs an accurate evaluation (25). In contrast to our study, a study in Egypt showed significant results for HbA1c (26). Regarding our t test analysis results, age and DM duration were the most associated parameter with diabetes complications as expected. Among the lipid profile, HDL-C was more important than TG. Additionally, TG was more important than LDL-C. This finding confirms this fact that LDL-C is not included as a metabolic syndrome criterion (27). Regarding dawn effect, while LDL-C was a protecting factor, it should not be regarded as a protecting factor because of its harmful effects. Regarding our regression analysis, the only notable finding was the negative correlation of HDL-C with TG. Positive correlation of

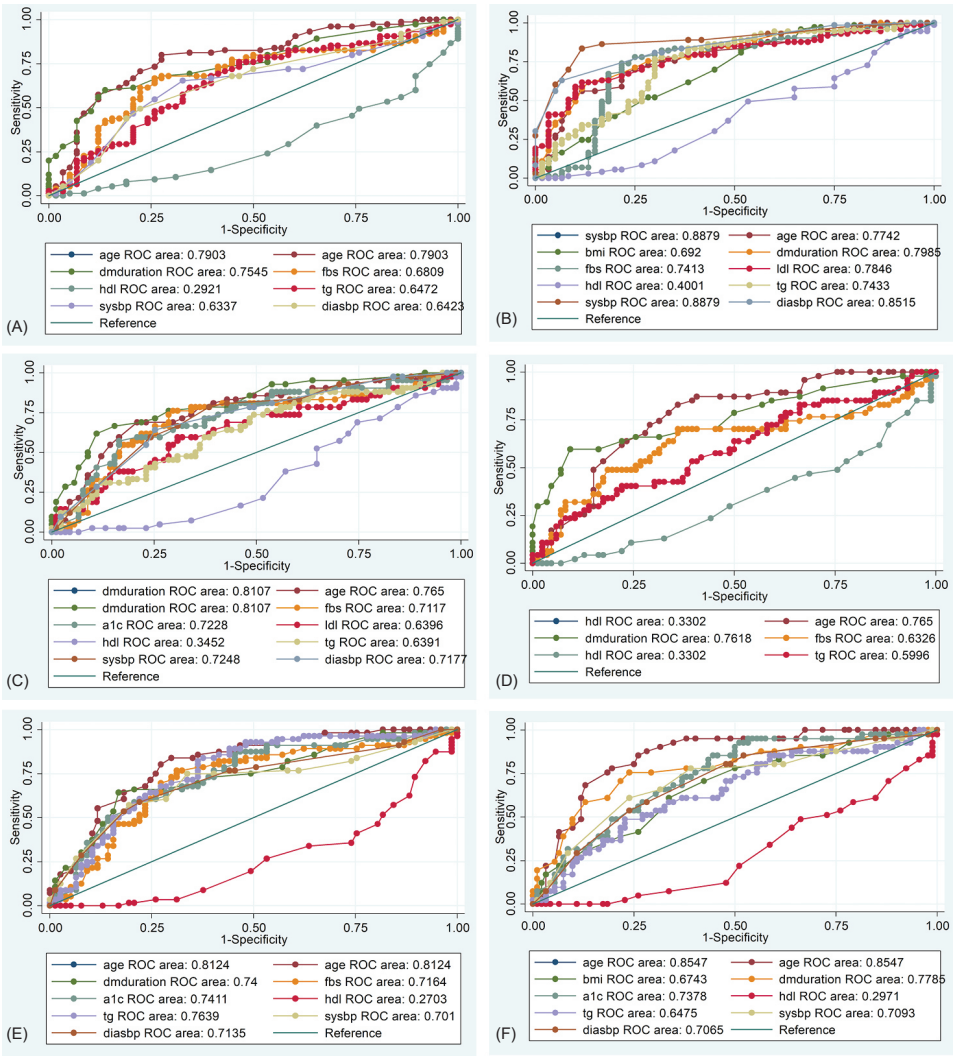

Figure 2. ROC curves for (A) diagnostic accuracy of neuropathy, (B) diagnostic accuracy of nephropathy, (C) diagnostic accuracy of symptomatic retinopathy, (D) diagnostic accuracy of PVD, (E) diagnostic accuracy of CVD and (F) diagnostic accuracy of foot ulcer history.

real LDL-C with age (not shown in Table 2) in spite of lack of this correlation in LDL-C with age, shows that administration of statin can prevent LDL-C increasing due to cumulative effect of age. Regarding our ROC curve analysis, only SBP for nephropathy and HDL-C for PVD took over cumulative effect of age and DM duration.

Among the predictive cutoffs (Table 3), FBS and HbA1c had a negative predictive value of around 100% cutoffs, However, they should not be considered for prevention of diabetes complications because of hypoglycemia danger. Additionally, blood pressure negative predictive value of around 100% cutoffs should not be considered for the prevention of diabetes complications because of renal hypoperfusion and syncope danger. However, HDL-C at 44 mg/dL, 46 mg/dL, 48 mg/dL and 48 mg/dL can be considered for prevention of foot ulcer, CVD, PVD and symptomatic retinopathy, respectively. FBS cutoffs seem not to be reliable because of their wide distribution values and susceptibility to insulin regimen. Among the positive predictive value of about 100% cutoffs, age of 79 years and DM duration 20-28of years should be considered for prediction of all diabetes complications. SBP >165 mm Hg should be considered for diagnosis of nephropathy. SBP >180 mm Hg should be considered for diagnosis of symptomatic retinopathy, CVD and prediction of foot ulcer. DBP >110 mm Hg should be considered for

Table 3. Cutoffs obtained from ROC curve analysis

	Parameter	ROC curve cutoff	PPV- 100% cutoff	NPV- 100% cutoff
Neuropathy	Age (y)	53 (80%/72%)*	79	33
	DM duration (y)	12 (60%/86%)	20	<1
	FBS (mg/dL)	200 (68%/72%)	510	80
	HDL-C (mg/dL)	40 (76%/53%)	28	60
Nephropathy	Sys BP (mm Hg)	150 (83%/88%)	165	110
	Dias BP (mm Hg)	95 (63%/93%)	110	70
	DM duration (y)	9 (75%/71%)	26	2
	LDL-C (mg/dL)	128 (79%/63%)	188	36
	Age (y)	54 (75%/68%)	79	36
	FBS (mg/dL)	198 (78%/75%)	510	100
	BMI (kg/m^2)	25 (95%/33%)	41	19
Retinopathy	DM duration (y)	15 (61%/89%)	26	2
	Age (y)	61 (69%/79%)	79	31
	Sys BP (mm Hg)	160 (59%/75%)	180	110
	A1C (%)	10.9 (57%/83%)	13.3	6.8
	Dias BP (mm Hg)	95 (64%/74%)	120	70
	FBS (mg/dL)	250 (54%/82%)	510	110
	HDL-C (mg/dL)	39 (78%/51%)	21	48
Peripheral vessel disease	Age (y)	60 (63%/76%)	79	43
	DM duration (y)	15 (59%/90%)	21	<1
	HDL-C (mg/dL)	35 (51%/75%)	21	48
Cardiovascular disease	Age (y)	55 (83%/70%)	76	39
	TG (mg/dL)	181 (83%/62%)	565	96
	A1C (%)	10.1 (58%/79%)	13.3	7.1
	DM duration (y)	13 (64%/83%)	29	<1
	FBS (mg/dL)	200 (76%/68%)	510	80
	Dias BP (mm Hg)	95 (58%/77%)	120	70
	Sys BP (mm Hg)	160 (57%/80%)	180	110
	HDL-C (mg/dL)	35 (80%/53%)	22	46
Foot ulcer history	Age (y)	63 (68%/86%)	79	45
	DM duration (y)	15 (58%/86%)	28	<1
	A1C (%)	12.2 (31%/91%)	13.3	6.6
	Sys BP (mm Hg)	165 (29%/91%)	180	110
	Dias BP (mm Hg)	110 (29%/89%)	120	60
	BMI (kg/m^2)	36 (17%/96%)	41	19
	HDL-C (mg/dL)	35 (48%/72%)	21	44

Three cutoffs are reported; a selected cutoff with high accuracy, cutoff with the highest PPV, and cutoff with the highest NPV.
* (sensitivity/specificity)

diagnosis of nephropathy. DBP >120 mm Hg should be considered for diagnosis of symptomatic retinopathy, CVD and prediction of foot ulcer and finally LDL-C >188 mg/dL can be considered for diagnosis of nephropathy. It should be regarded that these cutoffs are merely reliable for diabetic patients.

Conclusion

The final suggested guideline is like the international guidelines. However some unique points should be regarded. HbA1c evaluation in this region should be used only for evaluation of diabetes control and is not suitable as diagnostic or predictive marker of diabetes complications. Diabetic patients at the age of 79 years or with DM duration of more than 20-28 years have a potential to have all diabetes complications. Blood pressure >165/110 mm Hg is diagnostic of diabetic nephropathy. HDL-C >48 mg/dL is strongly suggested. A cohort study should be performed in our region in order to reevaluate predictive values.

Study limitations

The limitations of our study are lack of evaluation of other diabetes complications and lack of subgroup analysis (e.g. for diabetes type). It is suggested that such missing analysis to be performed in future based our freely available data supplements.

Conflicts of interest

We declare that there is no commercial conflict of interest for the manufactures of laboratory products such as A1c kits, and there is no cultural or political conflict of interest for the mentioned ethnicities. This study will be used to program a registry system in this region by Babak Khodadadi, Nazanin Mousavi and Mahshad Mousavi, members of talented students committee, educational development center (EDC), Lorestan University of Medical Sciences.

Authors' contribution

BK and NM are equal first authors. BK designed the idea. BK, NM and MM conducted clinical practice. PB was epidemiological supervisor. SAYA prepared the primary draft and finalized the manuscript.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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