Correlation of metabolic syndrome markers and parameters of UVA-induced skin autofluorescence in children with type 1 diabetes mellitus

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Introduction: Type 1 diabetes mellitus is a disease that develops in genetically susceptible individuals due to chronic inflammation and destruction of beta-cells of the pancreas. Today, type 1 diabetes is one of the most common chronic diseases, and vascular complications of diabetes are among the most important medical and social problems of modern medicine. Mainly invasive and expensive techniques are currently used to assess the carbohydrate metabolism in children with diabetes mellitus. Thus, clinicians need in new markers of carbohydrate metabolism compensation that would allow getting novel approaches to the diagnostics and monitoring of diabetes mellitus in children with non-invasive or minimally invasive examination methods. Our study focuses on the assessment of UVA-induced skin autofluorescence spectra in children aged 5-18 years with type 1 diabetes mellitus (n=50).

Materials and methods: Clinical and biochemical parameters have been assessed: age, gender, disease duration (DD), skin phototype (PHT), glycated hemoglobin (HbA1), creatinine (CR), triglycerides (TG), and cholesterol levels (CL) in the peripheral blood, urine microalbumin (MA) levels. Autofluorescence spectra were recorded with the original compact spectrofluorimeter based on the STS-VIS OCEAN OPTICS © USA microspectrometer, with UVA excitation produced by the LED (365 nm) (Fig.1). The recording time of the spectra was 30 s. The autofluorescence spectra of the skin of the inner side of the forearm after smoothing with a Gaussian filter with a half-width of 10 nm and linear (Ax)(SR-data) and (Ax+B) (LR-data) standardization to averaged spectra (Fig. 2) have been analyzed in the range of 400–670 nm. Statistical analysis was carried out with the Statsoft Statistica 12.0.

Fig.2. Spectrofluorimeter with UV LED excitation for skin autofluorescence recording

Results and discussion: Significant correlations of clinical and biochemical parameters, but not of the PHT, were found (Table 1). Factor analysis revealed two factors with significant dependence: i) on age, creatinine levels; ii) on glycated hemoglobin, cholesterol levels (Table 2). Reference wavelengths have been established by general regression analysis (general linear model, using default effect for between design, forward stepwise) where autofluorescence intensity demonstrated maximum correlation with clinical and biochemical parameters as well as with the above-mentioned factors (Table 3). All selected wavelengths were further used for the analysis. With the general regression analysis (general linear model, using factorial and polynomial to 4 degree for between design, best subset to no more than 5 parameters), statistical models have been established. We found that the levels of glycated hemoglobin could be predicted by measuring the fluorescence intensity at 5 wavelengths only (431, 558, 584, *623, 626 nm*) (Fig. 3) with Multiply R=0.90 (F=32.1) corresponding to 11% average relative error of the observed value (Fig. 4). Intensity of the autofluorescence measured at 5 wavelengths (431, 481, 558, 584, 604 nm) and age allowed predicting creatinine levels (Fig. 5) with the same accuracy (Multiply R=0.88, F=31.6) corresponding to 5% average relative error of the measured data (Fig. 6). Intensity of skin autofluorescence at 3 wavelengths (462, 590, *631 nm*) and age together with the disease duration (DD) allowed predicting triglycerides levels (Fig.7.) with less accuracy (Multiply R=0.85, F=16.3) corresponding to 31% average relative error of the measured data (Fig. 8). Intensity of skin autofluorescence measured at 8 wavelengths (410, 481, 558, 590, 604, *623, 626, 631 nm*) (Fig. 9) allowed predicting cholesterol levels with good accuracy (Multiply R=0.84, F=20.2) corresponding to 8% average relative error of the measured data (Fig. 10). Intensity of skin autofluorescence at 7 wavelengths (423, 427, 462, 498, 598, 604, 628 nm) (Fig. 11) and age allowed predicting urine microalbumin levels with less accuracy (Multiply R=0.88, F=21.7) corresponding to 30% average relative error of the measured data (Fig. 12).

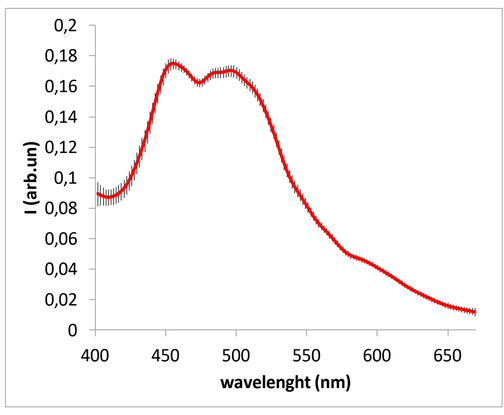

Fig. 1. Averaged skin authofluorescence spectra

Table 1. Correlations of clinical and biochemical parameters. Marked correlations are significant at p < ,05 N=50

Variable	Means	Std.Dev.	Age	PHT	DD	HbA1	CR	TG	CL	MA
Age (Year)	12,292	4,110	1,000	0,259	0,456	0,070	0,606	0,202	0,248	0,350
PHT	2,479	0,545	0,259	1,000	0,268	0,045	0,084	0,086	-0,085	-0,080
DD (Year)	4,208	2,939	0,456	0,268	1,000	0,151	0,403	0,145	0,289	0,101
HbA1 (%)	8,583	2,757	0,070	0,045	0,151	1,000	-0,094	0,329	0,278	-0,146
CR (µM/L)	60,250	8,038	0,606	0,084	0,403	-0,094	1,000	0,098	-0,017	0,417
TG(mM/L)	0,877	0,584	0,202	0,086	0,145	0,329	0,098	1,000	0,197	0,044
CL(mM/L)	4,519	0,935	0,248	-0,085	0,289	0,278	-0,017	0,197	1,000	-0,118
MA(mg/L)	21,681	33,990	0,350	-0,080	0,101	-0,146	0,417	0,044	-0,118	1,000

Table 2. Factor Loadings (Varimax raw). (Marked loadings are >,70)

Variable	Factor I	Factor II
Age	**0,824**	0,227
DD	0,593	0,405
HbA1	-0,098	**0,749**
CR	**0,856**	-0,089
TG	0,173	0,584
CL	0,100	**0,705**
MA	0,645	-0,326

Table 3. Best predictors (wavelengts) of general linear model, use default effect for between design.

Variable	Multiple R	F	LR (nm)			SR (nm)
AGE	0,585	21,895				498
DD	0,383	7,237				506
HbA1	0,549	8,838	591	598		
CR	0,629	27,547	481			
TG	0,696	12,518	463	591	631	
CL	0,685	11,794	416	431		427
MA	0,514	15,077	604			
Factor I	0,679	17,576	604			498
Factor II	0,869	19,050	411	558	585	
			623	*627*	*629*	

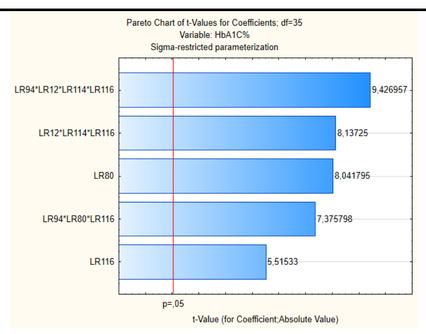

Fig. 3. Best predictors of HbA1C levels by skin autofluorescence intensity
(LR12-431 nm, LR80-558 nm, LR94-584 nm, LR114-623 nm, LR116-626 nm)

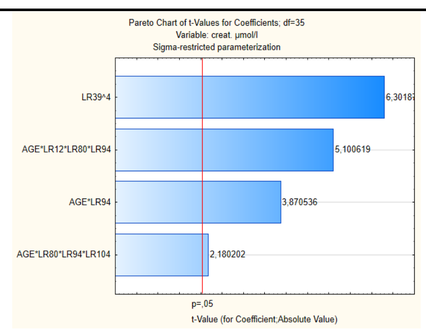

Fig. 5. Best predictors of creatinine levels by skin autofluorescence intensity
(LR12-431 nm, LR39-481 nm LR80-558 nm, LR94-584 nm, , LR104-604 nm)

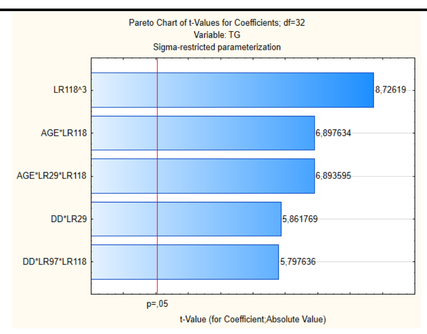

Fig. 7. Best predictors of triglycerides levels by skin autofluorescence intensity
(LR29-462 nm, LR97-590 nm, LR118-631 nm)

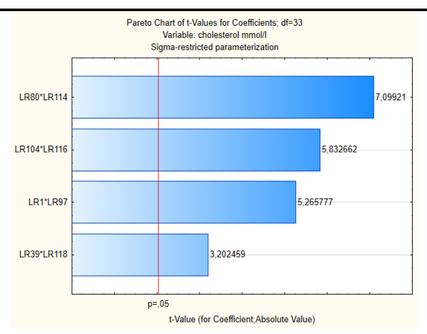

Fig. 9. Best predictors of cholesterol levels by skin autofluorescence intensity
(LR1-410 nm, LR39-481 nm)

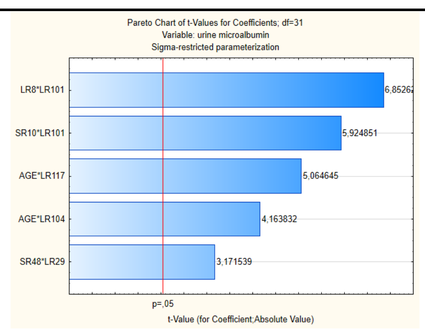

Fig. 11. Best predictors of microalbumin levels by skin autofluorescence intensity
(LR8-423 nm, LR10-427 nm, LR29-462 nm, SR48-498 nm, LR101-598 nm, LR104-604 nm, LR117-628 nm)

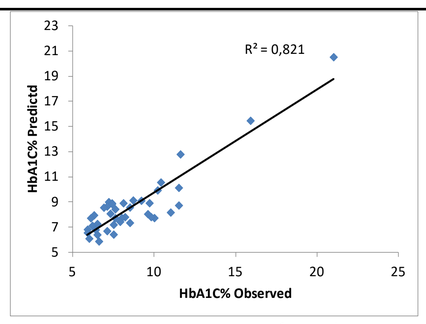

Fig. 4. Accuracy of HbA1C level spreadiction by skin autofluorescence intensity

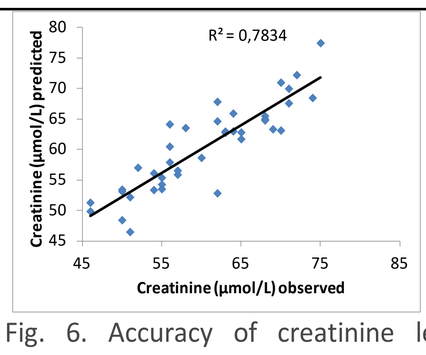

Fig. 6. Accuracy of creatinine levels prediction by skin autofluorescence intensity

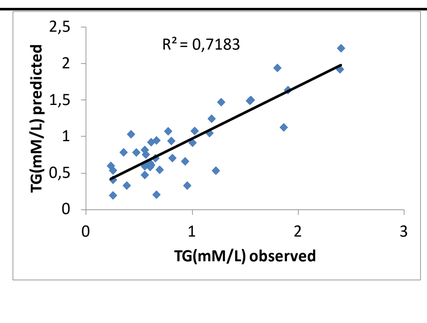

Fig. 8. Accuracy of triglycerides levels prediction by skin autofluorescence intensity

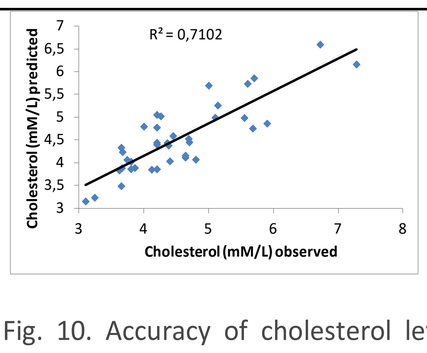

Fig. 10. Accuracy of cholesterol levels prediction by skin autofluorescence intensity

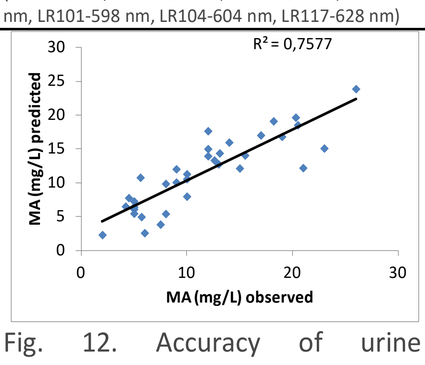

Fig. 12. Accuracy of urine microalbumin levels prediction by skin autofluorescence intensity

Significant correlations found in biochemical and clinical parameters in children with diabetes mellitus as well as grouping of parameters as the factors of factor analysis suggest the possibility to solve the problem of biochemical diagnostics in patients with diabetes mellitus type 1. Using simplified linear regression models, we found reference wavelengths that correspond to the particular parameters of metabolism. Then, due to the presence of significant correlations of the parameters, we were able to find the regressions models utilizing crossed reference wavelengths which is important for getting the models with higher accuracy. The high accuracy achieved was also due to the non-linear dependence of the parameters on fluorescence intensity up to 4^{th} order at these wavelengths. The best Pearson's correlation coefficient r=0.9 was found for the glycated hemoglobin, whereas in other cases, it was not less than 0.8. However, due to the difference in the ratio of ranges to the average values of the parameters, scattering of the average relative error of the prediction varies from 5% (for creatinine) to 31% (for triglycerides). The accuracy of the model was 11% for the glycated hemoglobin. Probably, application of non-linear scales for some parameters would result in the reduction of the model's relative error.

Conclusion: We found that in a case of diabetes mellitus, solving the problem on non-invasive assessment of biochemical parameters could be in taking into the consideration the correlations between them. The approach used in this study allows reducing the frequency of invasive biochemical assessments. It is particularly important for the parameters assessed in the peripheral blood and for achieving the highest accuracy of non-invasive measurements. Figure 2 clearly shows that forearm skin autofluorescence spectra that were linearly standardized demonstrate high stability of their shape. Average in relative variability was 4% within the indicated range, whereas analytically significant changes usually take place exactly within such range. For getting 100-rank scale within 4% of the signal range, the relative error in recording the spectra must be not worse than 0.04% which corresponds to the dynamic range not less than 2500:1 (Ocean Optics spectrometer demonstrates 4600:1). Since the shape of the spectrum shows 4-5 times as a difference of maximums and minimums, the dynamic range should be not worse than 10000:1. It is an absolute requirement not only for the capacity of the ADC in the spectrometer (not less than 14 bits), but also for the stability and brightness of the luminescence excitation source, and for the conditions of spectra recordings under the external lighting.