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PREDICTORS OF CHANGES IN PHYSICAL PROPERTIES OF SKIN IN PATIENTS WITH DIABETES MELLITUS

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Abstract

Introduction: *The skin, the largest human organ, is often affected by diabetes mellitus (DM). We know that DM affects the hydration of stratum corneum (SC), the sebum content of the skin and to some extent, the barrier function of the epidermis and elasticity, but we do not know the factors leading to these changes.* ***Objectives:*** *The objectives of this study were to determine the factors associated with changes in physical properties of the skin (skin hydration degree, sebumetry, transepidermal water loss and skin elasticity) in patients with diabetes.* ***Materials and methods:*** *The physical properties of the skin were assessed using the Multi Probe Adapter Systems MPA ® (Courage-Khazaka, Germany) in 57 patients with diabetes and 46 non-diabetic.* ***Results:*** *Statistical analysis of the entire group of 103 subjects showed a significant association between female gender and decreased SC hydration ($p<0.05$ in all cases), decreased values of transepidermal water loss (TEWL) (ß=-0.282, $p=0.006$) and decreased elasticity of the skin in forearm (ß=-0.216, $p=0.043$). Also, the presence of DM was negatively associated with levels of SC hydration measured on the forearm (ß=-0.281, $p=0.005$). Furthermore, in patients with diabetes, the presence of diabetic neuropathy (DNP) was negatively associated with the hydration of SC measured at all levels (forearm: ß=-0.465, $p<0.001$; leg: ß=-0.590, $p<0.001$; tight: ß=-0.198, $p<0.001$). The observed relationship was independent of age and sex of the participants ($p<0.05$ after adjustment for age and sex). Regarding skin elasticity, increasing age was associated with lower levels of skin elasticity both in entire group and in patients with DM, at all sites of measurements ($p<0.05$ in all cases). Additionally, in patients with diabetes, elasticity of the skin measured at forearm and tight was negativelly associated with type of DM (forearm: ß=-0.335, $p=0.023$; tight: ß=-0.522, $p<0.001$). In our study, nor diabetes neither DNP were not associated with TEWL values.* ***Conclusions:*** *The presence of DNP seems to be the main predictor of decreased SC hydration in all measuring points and skin elasticity is significantly associated with age. There are some gender-related modification in physical properties of the skin. Surprisingly, type 2 DM was associated with reduced elasticity in the thigh, and this association was independent of age and sex.*

key words: *diabetes mellitus, diabetic neuropathy, skin hydration, TEWL, sebum content, elasticity.*

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Background

The skin serves as an interface between the body and the environment and it is structured to prevent the loss of essential body fluids and to protect the body against the penetration of toxic chemicals from the environment. SC, with its cells and overlapping intercellular lipids, makes water diffusion in the external environment very difficult and prevent dehydration [1]. Maintaining an optimal level of hydration of the SC depends largely on several factors: intercellular lamellar lipids, integrity and arrangement of the layers of SC, natural moisturizing factors (NMF - aminoacids with hydrophilic structure, with wetted properties and retain water in the SC). A good hydration is essential for normal desquamation and ensuring an appropriate environment for conducting metabolic processes [2, 3]. The hydro-lipid film has a minor role in the prevention of transepidermal water loss (TEWL), but it has a major role in the protection against fungal and bacterial biological, while the intercellular lipid cement from the SC plays a major role in preventing TEWL. The hydro-lipid film on the surface of the skin, by its occlusive effect, may improve the water content of SC [4].

DM is responsible for a variety of skin damages, some studies showing the link between diabetes and various skin manifestations ranging between 11.4% and 71% [5]. Xerosis (low degree of hydration of the SC) is the most common non-infectious skin damage in patients with diabetes [6]. Common causes of skin xerosis are: decreased hydration, use of hot water and soaps with acid *p*H for personal hygiene, genetic factors, age, ambient factors (pollution, cold, low air humidity), and pathological conditions such as atopic dermatitis, malnutrition, renal failure or diabetes.

DM is characterized by an alteration in the insulin secretion and/or action, which results in increasing levels of plasma glucose. Hyperglycemia induces cell injury by various mechanisms: non-enzymatic glycation, increased oxidative stress [7], activation of aldozo-reductase, activation of diacilglicero-phosphate kinase [8] etc. Through advanced glycation end products (AGE), hyperglycemia induces collagen glycation in the dermis [9], which is normally associated with increasing age [10]. These products lead to alterations in the skin elasticity [11] and delayed wound healing [12].

Objectives

The objective of this study is to determine the factors associated with changes in physical properties of the skin (skin hydration degree, sebumetry, TEWL and skin elasticity) in patients with diabetes.

Materials and Methods

In total 57 patients with diabetes and 46 non-diabetic subjects were included in a cross-sectional study. Physical properties of the skin: hydration of SC (in the forearm, leg and thigh), sebumetry (in the forearm and thigh), TEWL (the forearm) and elasticity (in the hand, forearm and thigh) were assessed using Multi Probe Adapter System (product of Courage-Khazaka, Germany) with appropriate probes: Corneometer® CM 825 (for hydration of SC); Tewameter ® (for TEWL), Sebumeter ® SM 815 (for sebumetry) and Cutometer ® MPA 580 (for skin elasticity). Data collected through this device are downloaded in a a computer using Windows based applications.

Before measurements, participants were kept for about 15 minutes at 20-24 ºC and humidity of 30-45%.

Anthropometric data were collected: age, gender, height, weight. In diabetic patients a foot exam was performed - screening for diabetic neuropathy (DNP), and glycosylated hemoglobin (HbA1c) was determined.

The study was conducted in compliance with the priciples of the Declaration of Helsinki and approved by the Ethics Comittee of "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca. All the subjects were informed about the objectives and methods of the study and gave their written consent.

Statistical analysis was performed using the SPSS v.17.0 package. Mean and standard deviation were used to describe numerical variables. Student t-test was used to compare variable with normal distribution. Both in diabetic and non-diabetic subjects, the values determined for sebumetry in all regions and TEWL were transformed logarithmically to achieve normal distribution. Also, values obtained for hydration of SC at tight level in diabetics were transformed logarithmically. Linear regression was used to identify factors associated with changes in the physical properties of the skin. A p-value ≤0.05 was considered statistically significant.

Results

The subjects characteristics are shown in Table 1. The diabetic group included both patients diagnosed with type 1 (30.4%) and with type 2 (69.6%).

Among the subjects without diabetes included in the study, 39% were obese, 26.82% were overweight (66% of controls were overweight or obese), 31.7% were normal weight and 2.3% were underweight.

In the diabetic group, mean body mass index (BMI) was not statistically different from the control group (p=0.06). In the group with diabetes, about ¾ of the cases were type 2 diabetes mellitus (73.2%) and 75.6% of patients were insulin treated.

Table 1. Subjects characteristics.

Parameter	Entire group (n=103)	Group without diabetes (n=46)	Group with diabetes (n=57)
Age (years)*	52.57±13.2	50.73 ± 14.91	54.08 ± 11.2
Women (%)	63.10%	69.56%	75.43%
Men (%)	36.89%	30.44%	24.57%
BMI (kg/m^2) *	29.42±6.50	28.12±6.12	30.76 ± 6.68
Presence of DNP (%)	-	-	54.38%
Insulintherapy (%)	-	-	65.2%
Type 2 diabetes (%)	-	-	69.6%

*****Data are presented as mean±SD; BMI – body mass index; DNP - diabetic neuropathy

In order to estimate how age, sex, diabetes, diabetic polyneuropathy and age influence the hydration of SC, simple univariate regression was used. For the diabetic group we added type of diabetes, treatment and HbA1c to the variables for the univariate regression. Regression coefficients and p-value (indicating statistical significance) are presented in Table 2.

Table 2. The association between physical properties of the skin and anthropometric and clinical parameters in the entire group and in the diabetic group – simple univariate regression

Entire group (n=103 cases)			Diabetic group (n=57 cases)		
	ß	p		ß	p
SC hydration - forearm			SC hydration - forearm		
Age	- 0.101	0.319	Age	- 0.018	0.895
Gender	-0.298	0.003*	Gender	-0.218	0.114
Diabetes mellitus	-0.281	0.005*	DNP	-0.465	<0.001*
			Type of diabetes	0.070	0.617
SC hydration - leg			SC hydration - leg		
Age	-0.158	0.121	Age	-0.020	0.888
Gender	-0.285	0.004*	Gender	-0.151	0.275
Diabetes mellitus	-0.158	0.121	DNP	-0.590	<0.001*
			Type of diabetes	0.073	0.599
SC hydration - thigh			Lg SC hydration - thigh		
Age	0.055	0.592	Age	0.162	0.248
Gender	-0.412	<0.001*	Gender	-0.378	0.005*
Diabetes mellitus	-0.198	0.051	DNP	-0.198	<0.001*
			Type of diabetes	-0.267	0.188
Lg sebumetry - forearm			Lg sebumetry - forearm		
Age	- 0.065	0.672	Age	0.093	0.674
Gender	-0.427	0.003*	Gender	-0.507	0.014*
Diabetes mellitus	-0.158	0.301	DNP	-0.328	0.127
			Type of diabetes	0.147	0.502
Lg sebumetry - leg			Lg sebumetry - leg		
Age	-0.100	0.533	Age	0.198	0.391
Gender	-0.422	0.006*	Gender	-0.676	0.001*
Diabetes mellitus	-0.285	0.070	DNP	-0.510	0.018*
			Type of diabetes	0.288	0.205
Lg TEWL - forearm			Lg TEWL - forearm		
Age	- 0.160	0.128	Age	-0.228	0.108
Gender	-0.282	0.006*	Gender	-0.438	0.001*
Diabetes mellitus	-0.065	0.536	DNP	-0.221	0.119
			Type of diabetes	-0.194	0.172
Elasticity - hand			Elasticity - hand		
Age	- 0.455	<0.001*	Age	- 0.417	0.004*
Gender	-0.081	0.451	Gender	-0.174	0.247
Diabetes mellitus	-0.111	0.304	DNP	-0.012	0.937
		0.485	BMI	-0.369	0.029*
			Type of diabetes	-0.125	0.407
Elasticity - forearm			Elasticity - forearm		
Age	-0.441	<0.001*	Age	-0.441	0.002*
Gender	-0.216	0.043*	Gender	-0.211	0.159
Diabetes mellitus	-0.031	0.773	DNP	0.117	0.441
			Type of diabetes	-0.335	0.023*
Ln elasticitaty - thigh			Ln elasticitaty - thigh		
Age	-0.337	0.001*	Age	-0.543	<0.001*
Gender	0.103	0.343	Gender	-0.028	0.852
Diabetes mellitus	0.142	0.192	DNP	0.061	0.688
			Type of diabetes	-0.522	<0.001*

*-statistically significant regression coefficient; ln,lg - natural logarithm, respectively base 10 logarithm; DNP-diabetic polyneuropathy; SC - stratum corneum; TEWL- transepidermal water loss

Statistical analysis of the entire group of 103 subjects showed a significant association of the female gender with decreased SC hydration, decreased values of transepidermal

water loss and decresed elasticity of the skin in forearm. Also, the presence of diabetes mellitus was associated with decreased SC hydration on the forearm. Furthermore, in the diabetic group the presence of DNP was associated with reduced the hydration of SC at all levels and reduced sebum secretion on the leg (Table 2).

Regarding skin elasticity, increasing age was associated with lower levels of skin elasticity was both in entire group and in patients with diabetes, at all sites of measurements (Table 2). Additionally, in patients with diabetes, elasticity of the skin measured at forearm and tight was negativelly associated with type 2 diabetes (Table 2).

Table 3. The association between physical properties of the skin and anthropometric and clinical parameters in patients with diabetes – model adjusted for age and gender

Parameters	ß	p
SC hydration - forearm		
DNP	-0.438	0.001*
Treatment	0.028	0.849
Type of diabetes	0.122	0.474
SC hydration - leg		
DNP	-0.585	<0.001*
Treatment	0.036	0.809
Type of diabetes	0.128	0.457
Lg SC hydration - thigh		
DNP	-0.422	0.001*
Treatment	-0.190	0.159
Type of diabetes	0.151	0.342
Lg sebumetry - forearm		
DNP	-0.147	0.505
Diabetes treatment	-0.104	0.642
Type of diabetes	0.068	0.793
Lg sebumetry - leg		
DNP	-0.221	0.279
Diabetes treatment	-0.415	0.024*
Type of diabetes	0.273	0.192
Lg TEWL - forearm		
DNP	-0.137	0.298
Diabetes treatment	-0.140	0.308
Type of diabetes	-0.083	0.603
Elasticity - hand		
DNP	0.008	0.957
Diabetes treatment	-0.063	0.666
Type of diabetes	0.103	0.533
Elasticity - forearm		
DNP	0.152	0.278
Diabetes treatment	0.066	0.644
Type of diabetes	0.184	0.254
Ln elasticity - thigh		
DNP	0.042	0.753
Diabetes treatment	0.086	0.527
Type of diabetes	-0.334	0.027*

*-statistically significant regression coefficient; ln,lg - natural logarithm, respectively base 10 logarithm; DNP-diabetic polyneuropathy; SC - stratum corneum; TEWL- transepidermal water loss

No association was detected between physical properties of the skin and BMI, diabetes treatment and diabetes control (data not shown).

Further, we tested the associations between properties of the skin and the anthropometric and clinical parameters after adjustment for age and gender both in the entire group and separately in patients with diabetes. In the entire group, after adjustment for age and sex, the presence of diabetes mellitus remained statistically significant associated with decreased SC hydration on the forearm (ß=–0.244, p=0.012) (data not shown).

In patients with diabetes, the adjustment for age and sex did not influenced the association between the presence of DNP and lower levels of hydration of SC (Table 3). Additionally, decreased skin elasticity of the thigh was associated with the presence of type 2 diabetes and diabetes treatment was negatively associated with sebum secretion measured at leg level (ß=–0.415, p=0.024) (Table 3).

In this model, no parameter associated with TEWL was identified.

Discussion

The main finding of this study was the association between the presence of DNP and decreased SC hydration in patients with diabetes mellitus. This relationship was independent of age and sex of the participants. A decrease in SC hydration in diabetic patients has been noticed in previous studies and the presence of DNP augmented this modification [13]. Medium-term glycemic control is another factor that seems to influence the hydration of SC [14]. This association was not identified in our group of patients. Dehydrated SC is the precursor of pressure ulcers and it was demonstrated that these can be prevented by application of moisturizing products [15, 16]. Skin xerosis, with callus formation, plays a key role in diabetic foot pathology, one of the major complications of diabetes [17]. Gefen et al. [18] showed that pressure under the distal end of the first metatarsal is 4 times greater in diabetics than in non-diabetic and even 8 times higher in the end of the second metatarsus. Also, due to motor neuropathy, contact of the plant with the soil during walking is extended by 38% to 50%, which favors the occurrence of pressure ulcers in patients with diabetes. There are many mechanisms which lead to skin xerosis. Nerve damage leads to atrophy of sebum and sweat glands. Another reason for the occurrence of skin xerosis would be redistribution of blood flow to the legs through the opening of arteriovenous shunts and "stealing" blood from the skin. These changes lead to impaired skin elasticity, with cracks and penetration of bacteria.

Impaired skin hydration is accompanied by changes in barrier function of SC (quantified as TEWL). These changes are specific to the aging epidermis. In our study, neither diabetes mellitus, nor DNP, were associated with TEWL values, but lower values of TEWL were associated with female gender. These results are similar to those described by Chilcott and Farrar [19] that reported significantly higher TEWL values ($P < 0.05$) for the forearm in eight male subjects compared to nine females.

Another finding of the present research is the inverse association observed between skin elasticity and age, association present both in diabetic patients and in non-diabetic subjects. Additionally, we observed that in patients with diabetes mellitus the elasticity measured at thigh level was associated with type of diabetes (lower elasticity was associated with

type 2 diabetes), and this association was independent of age (ß=–0.334, p=0.027). An explanation of this association could be the degradation of collagen fibers and reduced viscoelastic properties of skin induced by advanced glycation end products [20]. Although studies in the literature suggest that skin elasticity is low in diabetic patients [21], in our study we did not observe an association between skin elasticity and presence of diabetes (type 1 or 2).

Regarding the sebumetry, we observed that increased sebumetry results (increased sebum content) was negatively associated with gender (male sex in our research) in all patients and the presence of DNP negatively influenced the sebumetry results measured at leg level (ß=–0.510, p=0.018) but this association was mediated through age and sex (ß=–0.221, p=0.279 after adjustment for age and sex). These results are consistent with the findings previously reported [22, 23]. It is well known that sexual hormones influence sebum production [24, 25] and prior studies demonstrated that sebum production rates correlate positively with testosterone levels in both sexes, and with dehydroepiandrosterone in males and etiocholanolone in females [26, 27].

Conclusions

DNP presence, rather than diabetes itself, seems to lead to impaired SC hydration in patients with diabetes. Additionally, elasticity measured at tight level was associated with type of diabetes (lower elasticity was associated with type 2 diabetes), and this association was independent of age. Females, due to a different hormonal status, seem to have a reduced production of sebum, which affects SC hydration and TEWL.

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