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Association Between Self-reported Physical Activity and Skin Autofluorescence, a Marker of Tissue Accumulation of Advanced Glycation End Products in Adults With Type 1 Diabetes: A Cross-sectional Study

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ABSTRACT

Purpose: The accumulation of advanced glycation end products (AGEs) in local tissue is an important cause of low-grade inflammation and oxidative stress and is linked to late diabetic complications. Physical activity has various beneficial cardiometabolic effects in type 1 diabetes (T1D) and is associated with lower frequency of chronic complications of diabetes, although the specific mechanisms still remain unclear. The present study determines the association between self-reported physical activity and skin autofluorescence (AF), a marker of tissue accumulation of AGEs in adults with T1D.

Methods: We enrolled 119 patients (63 women), aged 34 years (interquartile range [IQR], 26–41 years), with T1D duration of 17 years (IQR, 12–25 years), glycosylated hemoglobin (HbA_{1c}) of 7.9% (IQR, 7.1%–8.9%) referred to an outpatient diabetes clinic. Patients with diabetes duration of <5 years, age >65 years, concomitant diabetic ketoacidosis, and severe complications that restrict physical activity (eg, diabetic foot, diabetic proliferative retinopathy, blindness) were excluded. Physical activity was measured with the short version of the International Physical Activity Questionnaire (IPAQ-SF), and raw scores were then log-transformed because of non-normality. The accumulation of AGEs in the skin was assessed on the basis of skin AF. Correlations between AF and various laboratory and clinical findings were assessed, and multivariate linear regression analysis was used to examine factors that influenced AGEs.

Findings: Skin AF correlated positively with age (Spearman's coefficient [Rs] = 0.47; $P < 0.0001$), HbA_{1c} ($Rs = 0.30$; $P = 0.001$), waist-to-hip ratio (WHR; $Rs = 0.23$; $P = 0.02$), and negatively with logIPAQ-SF ($Rs = -0.28$; $P = 0.002$). A stepwise multivariable linear regression analysis indicated age ($\beta = 0.46$; $P < 0.0001$), HbA_{1c} ($\beta = 0.21$; $P = 0.01$), and logIPAQ-SF score ($\beta = -0.17$; $P = 0.04$) as predictors of the skin AF after adjustment for sex and WHR ($R^2 = 0.36$; $P < 0.0001$).

Implications: Higher physical activity is related to lower accumulation of AGEs in patients with T1D. Our study provides new insight into the beneficial effects of physical activity in T1D according to tissue accumulation of AGEs. (*Clin Ther*. 2018;∎:∎∎∎–∎∎∎)

Key words: chronic complications, physical activity, skin autofluorescence, type 1 diabetes.

INTRODUCTION

Patients with type 1 diabetes mellitus (T1D) can encounter several barriers to stay active. Unfortunately, several studies found that children and adolescents with T1D are less active in comparison with healthy children.[1] Fear of hypoglycemia, problems with maintaining adequate glycemic control, and simply insufficient knowledge of exercise management can be a real obstacle to regular

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physical activity in this group of patients. However, with the advances in therapy and knowledge of the importance of safe physical activity in T1D, intentional physical exercise should no longer be frightening; instead, it has become widely recommended.[2]

The same numerous positive effects of physical activity have been observed both in the general population and in patients with diabetes. Peterson et al[3] found that the increase in energy expenditure of ≥336 calories per week in patients with depressive symptoms was associated with a significant decrease in cardiovascular mortality. Sport is associated with blood pressure reduction, improvement in levels of serum lipids, and the reduction of abdominal fat.[4] Moreover, physical activity is related to improved glycemic control as expressed by reduction of glycosylated hemoglobin (HbA_{1c}) values and reduced insulin requirement in patients with T1D.[5] Several biochemical pathways mediate the advantageous influence of physical activity. Those include the phosphorylation of adenosine monophosphate (AMP)-activated protein kinase and subsequent activation of the enzyme that elicits glucose transport and desirable lipid metabolism.[6] In addition, glucose transporter type 4 (GLUT4) plays an important role in this process because GLUT4 is exposed to the cell membrane with the participation of AMP-activated protein kinase.

One of the treatment goals in T1D is to prevent chronic neurovascular complications. There are several traditional risk factors for diabetic complications, such as chronic hyperglycemia, dyslipidemia, duration of the disease, smoking, and hypertension. The pathogenic pathways include, among others, tissue accumulation of advanced glycation end products (AGEs).[7] AGEs provide information on long-term glycemic control and reflect a phenomenon of glycemic memory. AGEs are formed as the result of a nonenzymatic reaction of glucose with proteins, lipids, and nucleic acids.[8] These modified molecules are responsible for increased stiffness of the protein matrix and blood vessels and for activation of inflammatory process and oxidative stress.[8] Because of the fluorescent properties of several AGEs, the indirect measurements of their concentration may be performed by evaluation of skin autofluorescence (AF) with the use of a noninvasive device. Now, it is proven that skin AF is higher in patients with T1D than in healthy control participants and is useful in the detection of late diabetic complications.[9–11]

It has not been examined yet if physical activity influences AGE concentration in the skin. Thus, the aim of the present study was to evaluate the association between physical activity and skin AF, a marker of skin AGE concentration.

PATIENTS AND METHODS

Study Population

The study was performed in the Department of Internal Medicine and Diabetology in a cohort of adults with T1D with at least 5 years' duration of the disease. The exclusion criteria were diabetic ketoacidosis at the time of enrollment to the study, diabetes duration of <5 years, age >65 years, and severe complications that restricted physical activity (eg, diabetic foot, diabetic proliferative retinopathy, blindness). Participants were enrolled in the outpatient clinic between years 2015 and 2017. Every participant was European Caucasian in origin. Bioethical Committee of Poznan University of Medical Sciences approved the study protocol. Every participant provided written informed consent. The study followed the Declaration of Helsinki guidelines about research conducted on human patients.

Diagnosis of diabetes was based on American Diabetes Association criteria that included classic symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose concentration of ≥11.1 mmol/L.[12] In addition, autoimmune cause was confirmed by a positive of at least 1 of 3 autoantibodies examined (against islet cells, glutamic acid decarboxylase, insulinoma-associated tyrosine phosphatase).

Examinations included standard proceedings conducted during the visit in the outpatient clinic with adjunctive skin AF and physical activity assessment. Anthropometric measurements such as body mass index [BMI] and waist-to-hip ratio [WHR] were performed with a set of blood tests. In addition, every patient completed a detailed questionnaire that requested information on smoking and T1D history.

Among 141 adults with T1D initially assessed, 18 were excluded because of missing data for covariates, 4 because of exclusion criteria. Finally, 119 participants, 56 men (47.1%), were included in the study. Median participant age was 34 years (interquartile