RESEARCH

Investigation of Lower Extremity Tissue Oxygen Saturation in Patients with Diabetes Mellitus

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Abstract: In the present study, we aimed to compare lower extremity tissue oxygen saturations in DM patients and healthy individuals. The study involved 22 patients with diabetes mellitus and 20 healthy subjects. StO_2 of all participants was measured with near-infrared spectroscopy on the dorsal side of the foot. First, stO_2 values between groups were compared, and then the DM group was divided into subgroups for further analysis. Median (IQR: 75th percentile-25th percentile) StO_2 levels were 83.6% (84.2-83.0) in the patient group, while this was 81.3% (82.4-80.4) in the control group. In the comparison between groups, the patient group had significantly higher StO_2 levels ($p < 0.0001$). In the subgroup analysis of the DM group, patients with neuropathy, nephropathy, or coronary artery disease have significantly higher StO_2 levels than patients without these complications or diseases. Our result showed that StO_2 values in DM patients were higher than in healthy subjects, and in the presence of some complications, this elevation was even more pronounced. We attribute this situation to the inability of the cells to sufficiently utilize the oxygen due to metabolic dysregulation, and thus the oxygen saturation in the veins returning from the tissue remains high. We may call this pathophysiological capillary shunting, which became more pronounced in the presence of DM complications.

INTRODUCTION

In recent years, diabetes mellitus (DM) has been a significant healthcare problem. The global prevalence of diabetes mellitus in adults was calculated as 9.3% in 2019, which corresponds to 463 million people worldwide[1]. Microcirculatory system abnormalities are quite severe complications of diabetes, and timely diagnosis of microvascular changes will make a significant contribution to healthcare. Clinical studies show that diabetes can damage blood vessels and nerves, and microvascular changes can occur in the preclinical stages of diabetes[2,3]. This situation crucially affects the quality of life of patients and may cause various disabilities[4].

It is a fact that microcirculation is impaired in patients with diabetes mellitus, and the mechanisms underlying this fact are gradually being understood[5-9]. However, there are still issues that need to be clarified in this regard. Several studies have been conducted on this topic, but further evidence is needed.

The evaluation of the microcirculation can be performed easily on the skin due to the accessibility. Cutaneous microcirculation is considered a valuable translation model to evaluate the general condition of the circulatory system[11]. Accordingly, it provides a suitable way for non-invasive diagnostic approaches aimed at evaluating diabetes-related vascular disorders. Various methods such as transcutaneous oximetry and laser Doppler flowmetry have been used to evaluate the peripheral circulation of patients with diabetes[12]. However, these methods are expensive and require experienced professional operators, and involve relatively little mobility in clinical practice. Therefore, new real-time and practical methods are needed to evaluate microcirculation.

Tissue oxygen saturation (StO_2) is one of the key parameters used in investigating homeostasis in human tissue. It provides information about the balance between oxygen delivery and utilization in the relevant tissue. StO_2 is included in the diagnosis and treatment evaluation process of many different pathologies due to its non-invasive and accessible nature[13–16]. There are several studies in the literature investigating StO_2 values in patients with DM[8,17]. A few studies have been conducted to investigate the success of StO_2 in predicting the prognosis of diabetic foot ulcers, and the results are promising[10,18]. In the relevant literature, a standard has not yet been achieved in terms of measurement protocol and location, reference values, and interpretation of results.

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Despite the clinical impact of microcirculation diseases, little is known about the oxygen saturation of the lower extremity and its relationship with diseases. The main objective of the present study was to compare lower extremity tissue oxygen saturations in DM patients and healthy individuals. Our secondary objective was to investigate how tissue oxygen saturation changes in the presence of DM complications and medical or demographic alterations. With these two objectives, we aimed to contribute to the knowledge about underlying pathophysiological mechanisms of diabetes mellitus and its complications.

MATERIALS and METHODS

Participants

The study involved 22 patients with diabetes mellitus from the Endocrine Department of Akdeniz University Hospital (Antalya, Turkey) and 20 healthy persons. Patients with DM (type 1 or 2) followed up by the Endocrine Department of Akdeniz University Medical Faculty Hospital and applied to the clinic for routine control examination were included in the study. Control group participants were selected from a University Medical Faculty Hospital staff on a voluntary basis. Approval was obtained from the Akdeniz University Local Ethics Committee for the study. In the DM group, persons with bilateral diabetic foot ulcers, unilateral or bilateral foot amputation, or any lung diseases that may affect blood oxygen saturation such as asthma or COPD were not included. Exclusion criteria for the control group were having diabetes mellitus, coronary artery disease (CAD), hypertension, peripheral artery disease, nephropathy, retinopathy, or neuropathy. Both groups were created regardless of gender and smoking status. Then the diabetes group was divided into subgroups, including neuropathy (+/-), nephropathy (+/-), retinopathy (+/-), hypertension (+/-), CAD (+/-), smoking (+/-) and diabetes type (I/II). The presence and the type of diabetes mellitus, diabetes-related complications, and other co-morbidities were evaluated by an experienced endocrinologist.

Tissue oxygen saturation measurements

A miniature spectrometer (Ocean Optics USB200, FL, USA), white light source (HL-2000; Ocean Optics, Dunedin, FL), and fiber-optic probe (Back reflection probe, Ocean Optics, FL, USA) were used in the StO_2 measurements. Detailed technical information on spectrometric measurement and calculation of StO_2 values was explained elsewhere[19].

The participants were taken to the patient examination room and rested in the supine position for 10 minutes to accommodate the room conditions. After the recording of vital parameters, StO_2 measurements were performed. During the measurement, the fiber-optic probe was gently placed on the relevant skin part, and participants were requested not to move. For all participants, measurements were obtained from the dorsal side of the foot. Ten consecutive measurements were taken serially at each point, and this was repeated three times in each measurement area. Then, a StO_2 value was calculated for each participant by taking the average of these 60 measurements.

Statistical analysis

Descriptive statistics such as frequency distribution, mean and standard deviations were used to describe data. Paired t-test was used to analyze normally distributed variables, and otherwise, the Mann-Whitney test was used. Chi-square test is used to compare categorical data. All tests were performed with a P-value of <0.05 considered statistically significant. Statistical analyzes were performed using GraphPad Prism software version 8 (GraphPad Software, USA).

RESULTS

The patient group consisted of 22 persons with a mean age of 50.8 ±15.3, and the control group consisted of 20 persons with a mean age of 43.6 ±14.8 (P=0.131). The number of male participants was 14 (64%) in the DM group and 13 (65%) in the control group (P=0.927). In the DM group, 8 (36%) were smokers, while six (30%) of control subjects were smokers (P=0.662). Eight (36%) patients had type 1 DM, and the other 14 (64%) had type 2 DM. Systolic blood pressure, diastolic blood pressure, and arterial pulse oxygen saturation levels were 129.4 ±13.5 mmHg, 76.5 ±7.1 mmHg and 98.5% ±1.0 in the DM patient group, and 116.1 ±10.5 mmHg (P=0.001), 75.7 ±8.2 mmHg (P=0.751) and 98.3% ±1.2 (P=0.599) in the control group, respectively. In the patient group, the number of cases with neuropathy, nephropathy, retinopathy, hypertension, and CAD was 9 (41%), 7 (32%), 6 (27%), 8 (36%), and 8 (36%), respectively. In Table 1, the demographic and other characteristics of both groups are presented in detail.

Table 1. Demographic data and baseline characteristics

	DM Group (n=22)	Control Group (n=20)	P
Gender, number of male (%)	14 (64%)	13 (65%)	0.927
Age	50.8 ±15.3	43.6 ±14.8	0.131
BMI (kg/m^2)	27.8 ±3.6	25.4 ±3.5	0.032
Systolic Blood Pressure (mmHg)	129.4 ±13.5	116.1 ±10.5	0.001
Diastolic Blood Pressure (mmHg)	76.5 ±7.1	75.7 ±8.2	0.751
Arterial Pulse Oxygen Saturation (%)	98.5 ±1.0	98.3 ±1.2	0.599

Quantitative data are expressed as mean ±standard deviation, and categorical data are expressed as frequencies (percentages). BMI: body mass index, DM: diabetes mellitus

StO_2 measurement results

Median (IQR: 75th percentile-25th percentile) StO_2 levels were 83.6% (84.2-83.0) in the patient group, while this was 81.3% (82.4-80.4) in the control group (Figure 1). In the comparison between groups, the patient group had significantly higher StO_2 levels (P<0.0001). The Median (IQR) StO_2 level of participants with Type I DM was 83.6% (84.3-82.7), while DM Type II group had 83.6% (84.5 -83.2). There was no significant difference between DM Type I and DM Type II group (P=0.534).

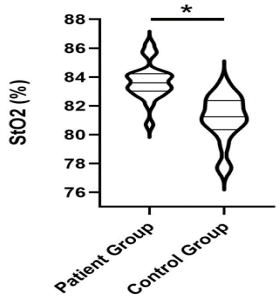

Figure 1. Violin plots of StO_2 level comparisons between groups. * indicates P<0.0001. Patient Group (n=22) had a median StO_2 level of % 83 (84.2-83.0), and control group (n=20) had a median StO_2 level of 81.3% (82.4-80.4).

In the subgroup analysis of the DM patients, neuropathy negative patients had a median StO_2 of 83.2% (83.8-82.7), while neuropathy positive patients had 84.2% (85.1-83.8). Neuropathy-positive patients had significantly higher StO_2 values than neuropathy-negative patients (P=0.013). Nephropathy-negative patients had a median StO_2 of 83.3% (83.9-82.7), while nephropathy-positive patients had 84.2% (85.6-83.9). StO_2 values of nephropathy-positive patients were significantly higher than negative patients (P=0.027). In the retinopathy groups, there was no significant difference between positive and negative patients (84.0% [84.2-83.0] vs 83.5% [84.3-82.8], P=0.891) (Figure 2 A, B, C).

Patients with CAD had a median StO_2 of 84.2% (85.8-83.4), while patients without CAD had 83.3% (84.0-82.7) (Figure 2 D). Patient with CAD had significantly higher StO_2 level than patient without CAD (84.2% [85.8-83.4] vs 83.3% [84.0-82.7], P=0.011). No significant differences were found in both hypertension (+/-) groups and in smoking (+/-) groups (P=0.255 and P=0.776, respectively), as seen in Figure 2.

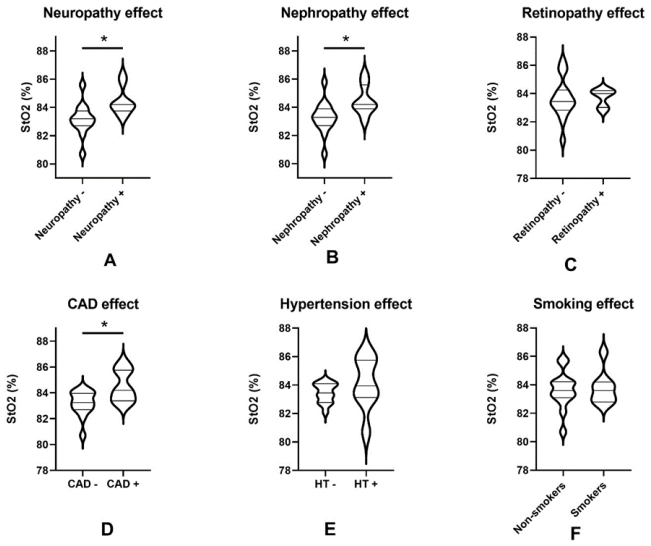

Figure 2. Comparison of diabetes patients subgroups. * indicates P<0.05. A: Neuropathy-negative group median StO_2 level was 83.2% (83.8 -82.7), and neuropathy-positive group median StO_2 level was 84.2% (85.1-83.8). B: Nephropathy-negative group median StO_2 level was 83.3% (83.9-82.7), and nephropathy-positive group median StO_2 level was 84.2% (85.6-83.9). C: Retinopathy-negative group median StO_2 level was 83.5% (84.3-82.8), and retinopathy-positive group median StO_2 level was 84.0% (84.2-83.0). D: CAD-negative group median StO_2 level was 83.3% (84.0-82.7), and CAD-positive group median StO_2 level was 84.2% (85.8-83.4). E: Hypertension-negative group median StO_2 level was 83.5% (84.1-82.8), and hypertension-positive group median StO_2 level was 84.0% (85.8-83.1). F: Non-smokers group median StO_2 level was 83.6% (84.2-83.1), and smoking group median StO_2 level was 83.6% (84.2-82.8). CAD: coronary artery disease, HT: hypertension.

DISCUSSION

Diabetes constitutes a significant and growing health problem worldwide. Diabetes can cause microvascular changes in the preclinical stages. Microcirculation disorders affect the functioning of many organs and systems such as the skin, kidneys, eyes, and cardiovascular system. Therefore, accurate diagnostic and monitoring methods are essential to provide timely and appropriate treatment planning and improve quality of life. Tissue oxygen saturation is one of the crucial parameters used in the evaluation of microcirculation in the tissue. The present study aimed to measure lower leg tissue oxygen saturation to evaluate microcirculatory circulation in patients with diabetes and healthy participants. Besides, we also aimed to evaluate the effect of neuropathy, nephropathy, retinopathy, hypertension, CAD, smoking, and diabetes types on tissue oxygen saturation in diabetic patients.

In the present study, StO_2 levels were 83.6% (84.2-83.0) in the DM group, compared to 81.3% (82.4-80.4) in the control group. StO_2 levels of the DM group were significantly higher than the control group (P<0.0001). Contrary to our results, there are also studies in the literature showing that tissue oxygen saturation is decreased in patients with diabetes mellitus compared to control[20,21]. However, physiological findings such as high local blood flow and high oxygen saturation in both tissue and collecting vessels accompanying cellular hypoxia are quite confusing[22]. According to the hypothesis of Gabbay et al., it is thought that the blood flow in diabetic foot tissue is redirected from the metarterioles main tract channel by bypassing the exchange capillaries. Thus, cells become hypoxic regardless of tissue blood flow, arterial oxygen is not consumed, and oxygen saturation in the veins remains high[23]. Therefore, increased tissue oxygen saturation in diabetes compared to control seems compatible with this hypothesis.

Tissue oxygen saturation level was significantly increased in patients with neuropathy positive group compared with neuropathy negative (84.2% (85.1-83.8) vs. 83.2% (83.8-82.7) P=0.013). Diabetic neuropathy is associated with endoneurial metabolism and microvascular abnormalities, but the roles of these factors in the etiopathogenesis of diabetic neuropathy have not been fully elucidated. The idea that microvascular changes cause diabetic neuropathy contradicts some reports of unaffected blood flow[24]. Considering this information, it is seen that our results do not contradict the literature. StO_2 values of nephropathy positive patients were significantly higher than negative patients. Some of the underlying causes of neuropathy, nephropathy, and retinopathy are cellular hypoxia and impaired oxygenation. Cellular hypoxia and circulatory impairment in diabetes may be due to mal-perfusion rather than hypo-perfusion. Patients with CAD had significantly higher StO_2 levels than patients without CAD. The pathophysiology underlying coronary artery disease is multifactorial and includes changes in the cardiac and regional microvasculature. Therefore, studies are needed in explaining the relationship between tissue oxygen saturation and CAD in diabetes.

The present study has some limitations. The major limitation is the small sample size. The second limitation is that the study was conducted in a single center. More extensive and multi-center studies are needed for the results to represent the entire population.

Conclusion

We concluded that oxygen saturation of foot skin differs between DM patients and healthy individuals. We think the present study will contribute to our understanding of microcirculation alterations in DM patients. Finally, this was a preliminary study, and we are aware that our results need to be confirmed by studies involving a larger patient population.

Conflict of interest

The authors declare that they have no conflict of interest.

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None.

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