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Impact of Sugar on the Mechanical Properties of Red Blood Cells Assessed by Optical Tweezers

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Abstract

The deformability of red blood cells is a mechanical property that is essential for effective blood microcirculation. Pathological metabolic conditions, particularly chronic hyperglycemia associated with diabetes, cause these cells to stiffen, contributing to microvascular complications. This study aims to quantify the impact of glucose exposure on the viscoelastic properties of human erythrocytes using an optical tweezers technique. Healthy erythrocytes were incubated under simulated hyperglycemia conditions for 2 hours. The microbead, trapped by a laser, was used to indent the red blood cell membrane and measure force relaxation over time. The results reveal an increase in relaxation time and a reduction in the viscous component of the membrane. The optical tweezers method is thus established as a sensitive and quantitative tool for assessing mechanical damage to erythrocytes, offering prospects for early diagnosis of the impact of diabetes on microcirculation.

Keywords

Red Blood Cell, Optical Tweezers, Hyperglycemia, Shear Modulus, Viscoelasticity, Relaxation Time

1. Introduction

The human Red Blood Cell (RBC) is an anucleated cell characterized by its unique biconcave shape and extreme deformability [1]. Their ability to deform and circulate through the finest capillaries is essential for ensuring adequate tissue oxygenation [2]. The mechanical properties of the RBC are governed primarily by the integrity of its membrane cytoskeleton, a network of proteins (spectrin, actin, ankyrin) that confers its shear resistance and elasticity [3]. An alteration of these rheological properties is directly linked to numerous hematological and circulatory pathologies [4]. Chronic hyperglycemia, a hallmark of diabetes mellitus, is associated with severe microvascular and macrovascular complications. A key mechanism in diabetic pathology is the non-enzymatic glycation (Maillard reaction) of proteins, leading to the progressive formation of Advanced Glycation End products (AGEs). Glycated hemoglobin (HbA1c) is the best-known clinical example [5]. Glycation is not limited to cytosolic proteins; it also affects the proteins of the RBC membrane cytoskeleton [6]. This modification is suspected to cause stiffening of the erythrocyte membrane, reducing the RBC's ability to deform and thereby contributing to microcirculatory obstruction and tissue hypoxia [7] [8]. Sugar, in particular, has been identified as a factor that can modify the mechanical properties of red blood cells, notably through glycation of membrane proteins [9]. Recent studies have shown that glycation of red blood cell membrane proteins can lead to changes in their deformability and viscosity, which can have significant implications for human health [10].

The Optical Tweezer is a non-contact, high-precision force manipulation and measurement technique, ideally suited for characterizing the rheology of single cells [11]. The specific approach used here employs a rigid microbead trapped by the laser to indent and probe the RBC membrane. This active microrheology technique enables high spatial and temporal resolution quantification of the membrane's viscoelastic response, providing precise values for the Shear Modulus (μ) and the Surface Viscosity (η) of the membrane [12].

The main objective of this work is to use a trapped microbead method to precisely and directly quantify the changes in the shear modulus and surface viscosity (η) of human RBCs following in vitro incubation with glucose concentration, simulating hyperglycemic conditions. These measurements will validate and characterize the biophysical mechanism of stiffening induced by glycation.

2. Material and Methods

2.1. Red Blood Cell and Microbead Samples Preparation

Blood was collected from healthy non-diabetic donors (with a normoglycemia to better characterize the sample) in anticoagulant (EDTA). RBC Separation and Washing: RBCs were separated by centrifugation and washed with an isotonic Phosphate-Buffered Saline (PBS).

Silica microbeads with a diameter of 3.5 µm were used. They were suspended in the isotonic buffer. To carry out the experiments, the sample was prepared as follows: 0.5 µl of blood was suspended in severe hyperglycemia of glucose at 25 mM for two hours, then this solution was incubated with a dilute solution of microbeads.

2.2. Optical Tweezers Setup

The optical tweezers experimental device is a complex system that allows measuring the mechanical properties of red blood cells with high precision. It consists of a diode laser emitting a light beam at a wavelength of 980 nm, a high numerical aperture microscope objective (NA = 1.4) that focuses the laser beam onto the measurement chamber, and a specially designed measurement chamber for optical tweezers experiments that contains the red blood cells and microbeads in suspension. The description of experimental setup has been well detailed in our previous articles [12].

2.3. Force Measurement and Calibration

This is a classic approach to characterizing the properties of an optical trap. Indeed, by trapping a microbead and measuring its displacements in the optical trap, we can use Boltzmann statistics to calculate the trap stiffness. Boltzmann statistics relate the probability of finding a microbead in a given energy state to the temperature and potential energy of the microbead. In the case of an optical trap, the potential energy is proportional to the distance from the center of the trap, and the trap stiffness is related to the curvature of the potential energy. By measuring the displacements of the trapped microbead, we can reconstruct the probability distribution of the microbead positions and thus determine the trap stiffness (κ, in pN/μm) [13] [14]. The trapped force (F) is calculated by the microbead displacement (Δx) from the trap center:

$$F = K \cdot \Delta x \tag{1}$$

2.4. Shear Modulus and Membrane Viscosity Calculation

Each time the contact between the trapped microbead and the RBC increases, the membrane deformation becomes significant. It is therefore possible to measure the indentation δ using this relationship [15].

$$\delta = \left(D - \sqrt{D^2 - d_i^2} \right) \tag{2}$$

where D is the microbead diameter and d_i is the touch diameter between microbead and RBC in micrometers.

The resultant membrane deformation (δ) was recorded by high-speed video microscopy as a function of time (t). The measured deformation-time curve, $\delta(t)$, was analyzed using a viscoelastic model to determine the mechanical parameters. Once the forces are calculated, we can use the Hertz model to analyze the data and determine the mechanical properties of the red blood cell.

The Hertz model is a theoretical model that describes the contact between two elastic spheres and can be used to describe the interaction between the microbead and the red blood cell. By fitting the experimental data to the Hertz model, we can extract the mechanical properties of the red blood cell, such as the elastic modulus and shear modulus. The elastic stiffness [15] [16]. Eh is given by

$$E_h = \left[\frac{3\left(1-\nu^2\right)}{4 \cdot \sqrt{\delta \cdot R}} \right] \cdot F_c \tag{3}$$

where R is the microbead radius, F_c the contact force between trapped microbead and cell, δ the indentation and ν the poisson ratio. $\nu = 0.5$ was used for these experiments [16]. In the literature, usually the cortical shear modulus μ_h is given, rather than the elastic stiffness E_h. The shear stiffnesses are related by:

$$\mu_h = \frac{E_h}{2\left(1+\nu\right)} \tag{4}$$

Membrane viscosity was calculated from the time-dependent deformation curve, $\delta(t)$, by fitting it to a simplified Kelvin-Voigt model [17] (or a similar viscoelastic representation):

$$\delta\left(t\right) = \delta_{eq} + \left(\delta_0 - \delta_{eq}\right) \cdot e^{-t/\tau} \tag{5}$$

The relaxation time (τ) was extracted from the fit. The surface siscosity (η) was then calculated as the product of the shear modulus and the relaxation time (τ) [18]:

$$\eta = \mu_h \cdot \tau \tag{6}$$

The membrane viscosity is reported in μN·s/m.

3. Results and Discussion

We worked on two RBCs: RBC$_1$ with diameter of 6 μm and RBC$_2$ with diameter of 6.5 μm. For the red blood cell with a diameter of 6 μm, a microbead with a diameter of 3.5 μm was optically trapped with a force of 24.52 pN and for the red blood cell with a diameter of 6.5 μm, the trapping force to trap the microbead was 31.79 pN. By translating the sample holder in horizontal direction, the contact diameter between microbead and RBC increases. Different images from the videos recorded during each measurement are shown in **Figure 1**.

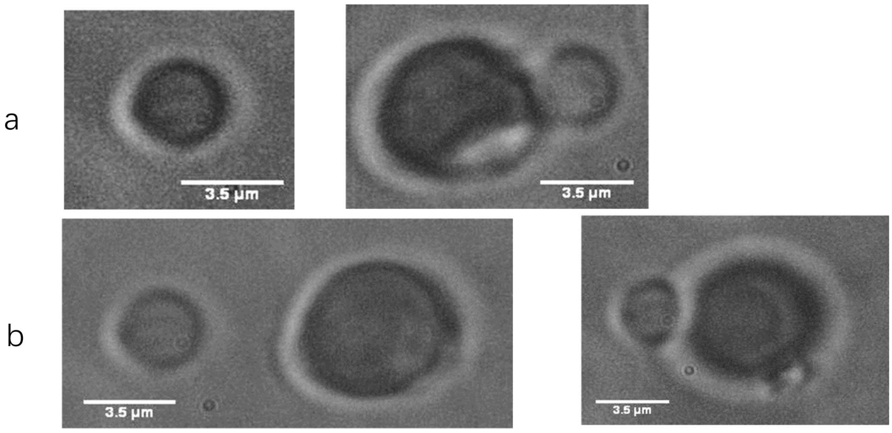

Figure 1. Images of RBCs indented at different contact forces: (a) RBC$_1$ with diameter of 6 μm and (b) RBC$_2$ with diameter of 6.5 μm.

Under the action of a contact force of 21.20 pN, an indentation of 0.55 μm was measured. We then used the Hertz model to obtain the mechanical properties of RBC$_1$: $\left(12.34 \pm 1.60\right)\ \mu\text{N/m}$ for the elastic modulus and $\left(4.11 \pm 0.83\right)\ \mu\text{N/m}$ for the shear modulus. The mean values of mechanical properties, in particular elastic modulus and shear modulus were $\left(12.44 \pm 1.43\right)\ \mu\text{N/m}$ and $\left(4.15 \pm 0.74\right)\ \mu\text{N/m}$ for RBC$_2$.

We also determined the relaxation time and membrane viscosity of red blood cells. From the time-dependent deformation curve, $\delta(t)$, by fitting it to a simplified Kelvin-Voigt model, the relaxation time (τ) was extracted from the fit (**Figure 2**).

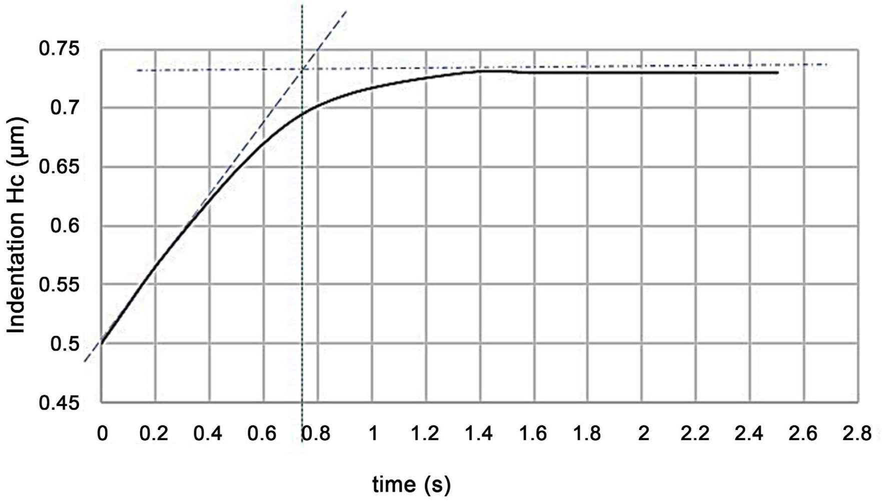

Figure 2. Time-dependent deformation curve, $\delta(t)$.

The relaxation time for the RBC$_1$ was $\approx 0.73\ \text{s}$ and the surface siscosity (η) calculated was $\eta = 3\ \mu\text{N}\cdot\text{s/m}$.

Measurements of contact force, indentation, shear modulus, relaxation time and membrane viscosity were presented in **Table 1**.

Table 1. Different values of measurements.

Parameters	RBC$_1$	RBC$_2$
Contact force (pN)	**21.20**	**25.00**
Indentation (μm)	**0.55**	**0.73**
Shear modulus (μN/m)	**4.11 ± 0.83**	**4.15 ± 0.74**
Relaxation time (s)	**0.73**	**0.70**
Meùbrane viscosity (μN·s/m)	**3.00 ± 0.60**	**2.90 ± 0.46**

The shear moduli obtained in this work are of the same order of magnitude as the values obtained using the optical tweezers technique, 1.233 μN/m [19] and (2.4 ± 0.4) μN/m [20], but they are higher. These shear moduli are of the same order of magnitude as those obtained using the micropipette suction method [21] (4 <

μ < 10 μN/m), but slightly higher than the lowest value.

Since the shear moduli are within the normal range (1.233 to 10 μN/m) [19]-[24], we can conclude that acute exposure to glucose for 2 hours does not significantly alter the elastic stiffness of the membrane. This shows that the permanent bonds (AGE cross-links) that stiffen the spectrin network and alter elasticity have not yet had time to form.

Despite normal shear moduli, relaxation times around 0.7 s are abnormally high, being 3 to 6 times longer than the relaxation time of healthy red blood cells [25] [26]. The increase in relaxation time and, consequently, membrane viscosity (up to 3.00 μN·s/m) means that deformation energy is dissipated much more slowly than in a healthy cell. This increase demonstrates that the early impact of hyperglycemia is a loss of dynamic fluidity, altering the ability of red blood cells to reorganize quickly under stress [26]. Exposure to glucose can induce rapid changes in surface charges or the arrangement of transmembrane proteins. These changes can slow down the lateral mobility of the membrane components necessary for the reorganization of red blood cells during relaxation.

According to previous studies, abnormal red blood cells often have altered mechanical properties, which can affect their function and survival in the bloodstream [22] [25]. For example, sickle red blood cells have increased stiffness due to the polymerization of hemoglobin S, which makes them more likely to accumulate in small blood vessels and cause vaso-occlusive crises [24]. The results obtained are in agreement with those of other studies that have shown that abnormal red blood cells have altered mechanical properties, such as increased stiffness and viscosity [26] [27]. For example, a study showed that red blood cells from patients with diabetes have increased stiffness and reduced deformability, which can contribute to the vascular complications associated with this disease [28].

4. Conclusion

In conclusion, the results obtained suggest that the mechanical properties of the studied red blood cells are altered, which could have implications for the function and survival of these cells in the bloodstream. Further studies are needed to understand the underlying mechanisms of these alterations and to develop new therapeutic approaches to treat diseases associated with red blood cells. We note that the small sample size (N = 2 RBCs) limits the scope of this study. In future work, we will analyze a large number of cells from several donors in order to validate these preliminary results.

Author Contributions

P. Yale, A. A.-B. N'Guessan, G.-O. Regnima conceived and designed the experiments; P. Yale, A. A.-B. N'Guessan performed the experiments; P. Yale analyzed the data; P. Yale wrote the paper. P. Yale, H. J. K. Loukou, J.-M. E. Konin, M. A. Kouacou and J. T. Zoueu revised the paper.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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