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MOBILE & WIRELESS HEALTH

Diabetic Macular Edema Screened by Handheld Smartphone-based Retinal Camera and Artificial Intelligence

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Abstract
Our aim was to assess the tomographic presence of diabetic macular edema in type 2 diabetes patients screened for diabetic retinopathy with color fundus photographs and an artificial intelligence algorithm. Color fundus photographs obtained with a low-cost smartphone-based handheld retinal camera were analyzed by the algorithm; patients with suspected macular lesions underwent ocular coherence tomography. A total of 366 patients were screened; diabetic macular edema was suspected in 34 and confirmed in 29 individuals, with average age 60.5 ± 10.9 years and glycated hemoglobin 9.8 ± 2.4%; use of insulin, statins, and aspirin were reported in 44.8%, 37.9%, and 34.5% of individuals, respectively; systemic blood hypertension, dyslipidemia, abdominal obesity, chronic kidney disease, and risk for diabetic foot ulcers were present in 100%, 58.6%, 62.1%, 48.3%, and 27.5% of individuals, respectively. Proliferative diabetic retinopathy was present in 31% of patients with macular edema; severity level was associated with albuminuria (p = 0.028). Eyes with macular edema had average central macular thickness 329.89 ± 80.98 mμ; intraretinal cysts, sub retinal fluid, hyper-reflective foci, epiretinal membrane, and vitreomacular traction were found in 87.2%, 6.4%, 85.1%, 10.6%, and 6.4% of eyes, respectively. Diabetic retinopathy screening overwhelms health systems and is typically based on color fundus photographs, with high false-positive rates for the detection of diabetic macular edema. The present, semi-automated strategy comprising artificial intelligence algorithms integrated with smartphone-based retinal cameras could improve screening in low-resource settings with limited availability of ocular coherence tomography, allowing increased access rates and ultimately contributing to tackle preventable blindness.

Keywords Diabetic retinopathy · Artificial intelligence · Mobile health · Public health

Introduction

Smartphone-based fundus imaging has become increasingly relevant for diabetic retinopathy (DR) screening strategies, in a cost-effective manner [1]. Diabetic macular edema (DME) is the most common cause of vision loss and referrals associated with DR [2]. Color fundus photographs (CFPs) are the basis of most DR screening programs, but they carry both poor positive predictive value and poor sensitivity for the detection of DME, which is ideally assessed by optical coherence tomography (OCT). However, adding OCTs to the screening process is too costly and logistically difficult to implement. Artificial intelligence (AI) algorithms could potentially predict DME from CFPs [3], particularly in underserved areas where optical coherence tomography (OCT) is not widely available.

Previously, we have described the high diagnostic accuracy of an AI algorithm embedded in a low-cost, portable retinal camera, for the detection of more than mild DR [4]; in the present study, we aimed to further evaluate the macular tomographic characteristics of referred patients with suspected DME.

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Methods

Study design and population

This was a retrospective study that assessed the tomographic presence of DME in a sample of 366 of individuals over 18 years old with a previous type 2 diabetes mellitus (T2DM) diagnosis and followed at primary health care units, who were screened for DR with CFPs of both eyes, obtained with a portable smartphone-based retinal camera and an assistive deep learning (DL) AI algorithm designed to detect fundus abnormalities, which was trained with a dataset of images exclusively obtained with a portable retinal camera (Phelcom Technologies, São Carlos, Brazil) [4]. The algorithm generates a heatmap that flags suspected retinal alterations with a color scale, from blue (low importance) to red (high importance) (Fig. 1). Besides algorithmic assessment, images were also remotely evaluated and classified by two retinal specialists, according to a previously published protocol.[4] The study protocol was approved by the local institutional ethics Committee (IPTAN – Faculdade de Medicina Santo

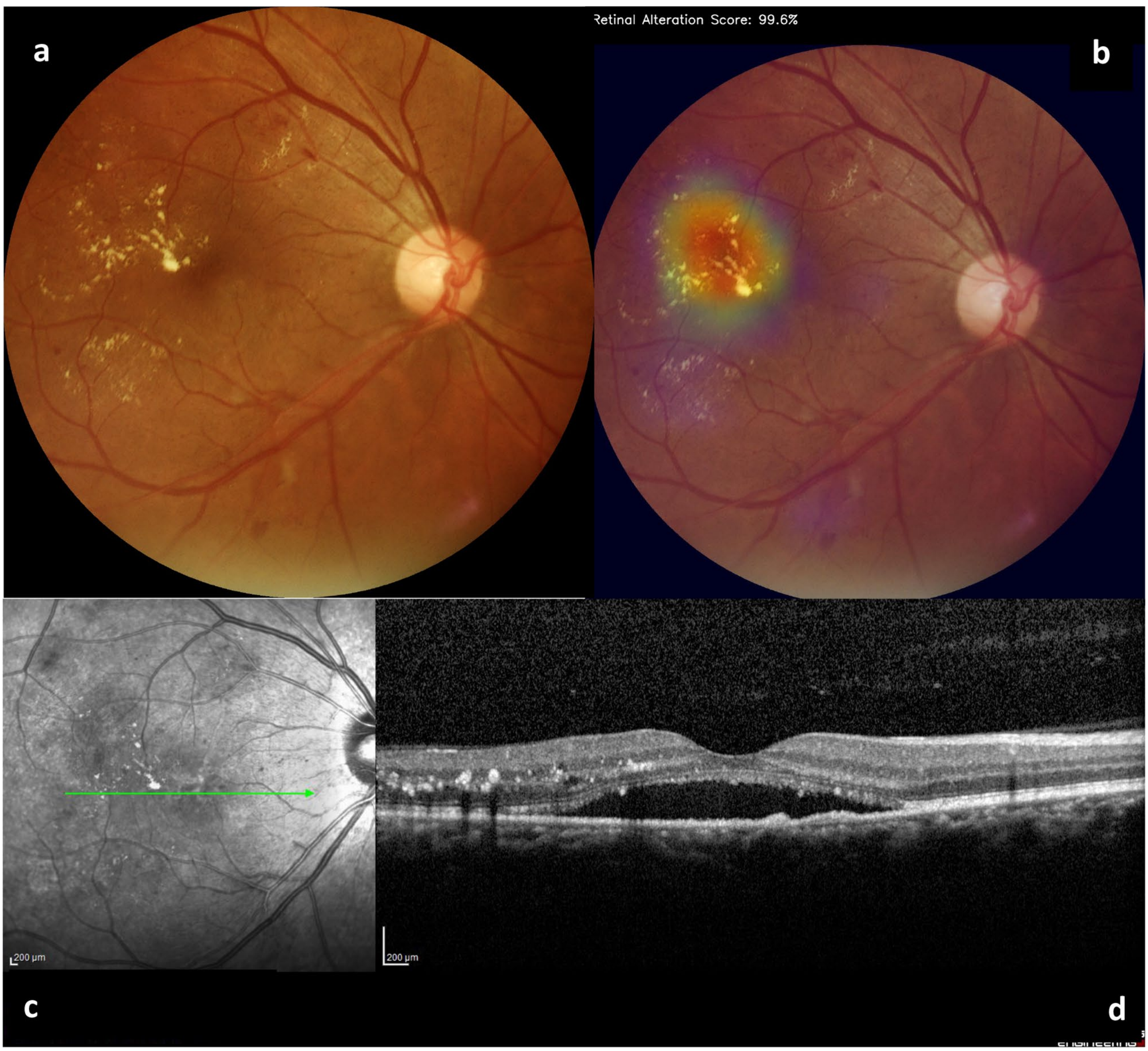

Fig. 1 Retinal images of Diabetic Macular Edema, algorithmic heatmap visualization and correspondent optical coherence tomography (OCT) scan (**a**) Color fundus photograph depicting hard exudates, hemorrhages and microaneurysms in the macular region, suggesting the possibility of diabetic macular edema (**b**) Overlay with the heatmap visualization can aid in making a diagnosis as the modifications are flagged in a color scale, from blue (low importance) to red (high importance) (**c**) En-face infrared reflectance image from Spectral Domain OCT (**d**) OCT scan showing hyper reflective foci, intraretinal cysts and sub retinal fluid

Agostinho – Itabuna, Brazil), Approval number 5.031.886 and was conducted in compliance with the Declaration of Helsinki. All clinical information was retrieved from electronic medical records designed in compliance to data privacy Brazilian legislation (General Person Data Protection Law). All ocular images, previously stored in data privacy compliant databases, were further anonymized and patients were de-identified for the analysis.

Optical coherence tomography

Sixty eyes of 34 patients with suspected DME as per the algorithm underwent macular spectral domain OCT (Spectralis OCT, Heidelberg, Germany) according to an acquisition protocol described elsewhere [2]. Quantitative assessment of DME included automatically calculated central macular thickness (CMT). Qualitative evaluation assessed the presence of sub retinal fluid (SRF), cystoid changes, hyper- reflective foci (HRF), epiretinal membranes and the status of the vitreomacular interface (detached, vitreomacular adhesion, vitreomacular traction). The listed features were evaluated on 3 horizontal OCT scans: 1 b-scan encompassing the fovea, 2 b-scans respectively 500 mm superior and 500 mm inferior to the fovea. Grading of OCT images was performed by a 3rd experienced retina specialist who was blinded to the other clinical results. Eyes with CMT $\geq$ 300 mμ and/or the presence of cystoid changes or SRF were considered to have DME [5]. Patients who presented with other macular diseases that prevented the detection of DME, such as macular scars, age-related macular disease or vascular occlusions, were excluded from the study.

Clinical and laboratory evaluation

Further clinical and laboratory evaluation for other diabetes complications was performed and included HbA1c (HPLC, Trinity Biotech, Ireland/Kansas City, MO, USA) and creatinine (CREA Slides, Vitros XT, Ortho Clinical Diagnostics, Rochester, NY, USA). Hypertension diagnosis was defined according to the WHO criteria and/or self-reported oral treatment with anti-hypertensive drugs [6]. Dyslipidemia was defined with low density lipoprotein cholesterol (LDL) and total cholesterol (TC) cut-of points $\geq$ 160 mg/dL and $\geq$ 200 mg/dL, respectively [7]. Abdominal obesity was defined with waist circumference cut-points of > 102 cm and > 88 cm for men and women, respectively [8]. Chronic kidney disease (CKD) was defined as low estimated glomerular filtration rate (GFR < 60 ml/min/1.73 m^2) or elevated urinary albumin excretion (albuminuria $\geq$ 30 mg/dl) [9]. Risk assessment of the diabetic foot was performed according to the international consensus [10].

Statistical analysis

Data were collected in MS Excel 2010 files (Microsoft Corporation, Redmond, WA, USA). Statistical analyses were performed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA). Individual's characteristics and quantitative variables are presented in terms of mean and standard deviation (SD). A paired two-tailed Student *t* test was used to compare continuous clinical variables and Fisher's exact or chi-square tests were used for unpaired variables. The 5% level of significance was used.

Results

The studied population comprised 366 individuals, mostly women (60.1%), with average age 62.9 $\pm$ 11.4 years; DR was present in 25.4%, and 6.8% had proliferative DR. OCT confirmed DME in 47 eyes of 29 patients, mostly women (51.7%) with average age 60.5 $\pm$ 10.9 years and HbA1C 9.8 $\pm$ 2.4%; use of insulin, statins, and aspirin were reported in 44.8%, 37.9%, and 34.5% of such individuals, respectively; systemic blood hypertension, dyslipidemia, and abdominal obesity were present in 100%, 58.6%, and 62.1% of individuals with confirmed DME, respectively. CKD was found in 48.3% of such individuals, 27.5% of whom were at moderate or high risk for diabetic foot ulcers. Proliferative DR was present in 31% of DME patients; DR severity level was associated with albuminuria ($p = 0.028$).

Eyes with confirmed DME had average CMT 329.89 $\pm$ 80.98 μ m; intraretinal cysts, SRF, hyper-reflective foci, epiretinal membrane, and vitreomacular traction were found in 87.2%, 6.4%, 85.1%, 10.6%, and 6.4% of eyes, respectively. The algorithm confirmation rate was 78.3%; among the 13 eyes (21.7%) with suspected DME as per the algorithm evaluation but not confirmed by OCT, macular hard exudates without macular thickening, pigment clumping, and image artifact that was misinterpreted by the algorithm as DME were found in 8, 4, and one, respectively (Fig. 2).

Discussion

The present study assessed the macular tomographic characteristics of T2DM patients with suspected DME as per the screening protocol that comprised a previously validated, high-sensitivity (97.8%) algorithmic tool for the detection of more than mild DR [4]; DME was confirmed by OCT in 85.3% of such patients. DR screening programs are a fundamental milestone for the prevention of blindness secondary to diabetes, but they overwhelm health systems, as hundreds of millions of individuals need periodical screening, with

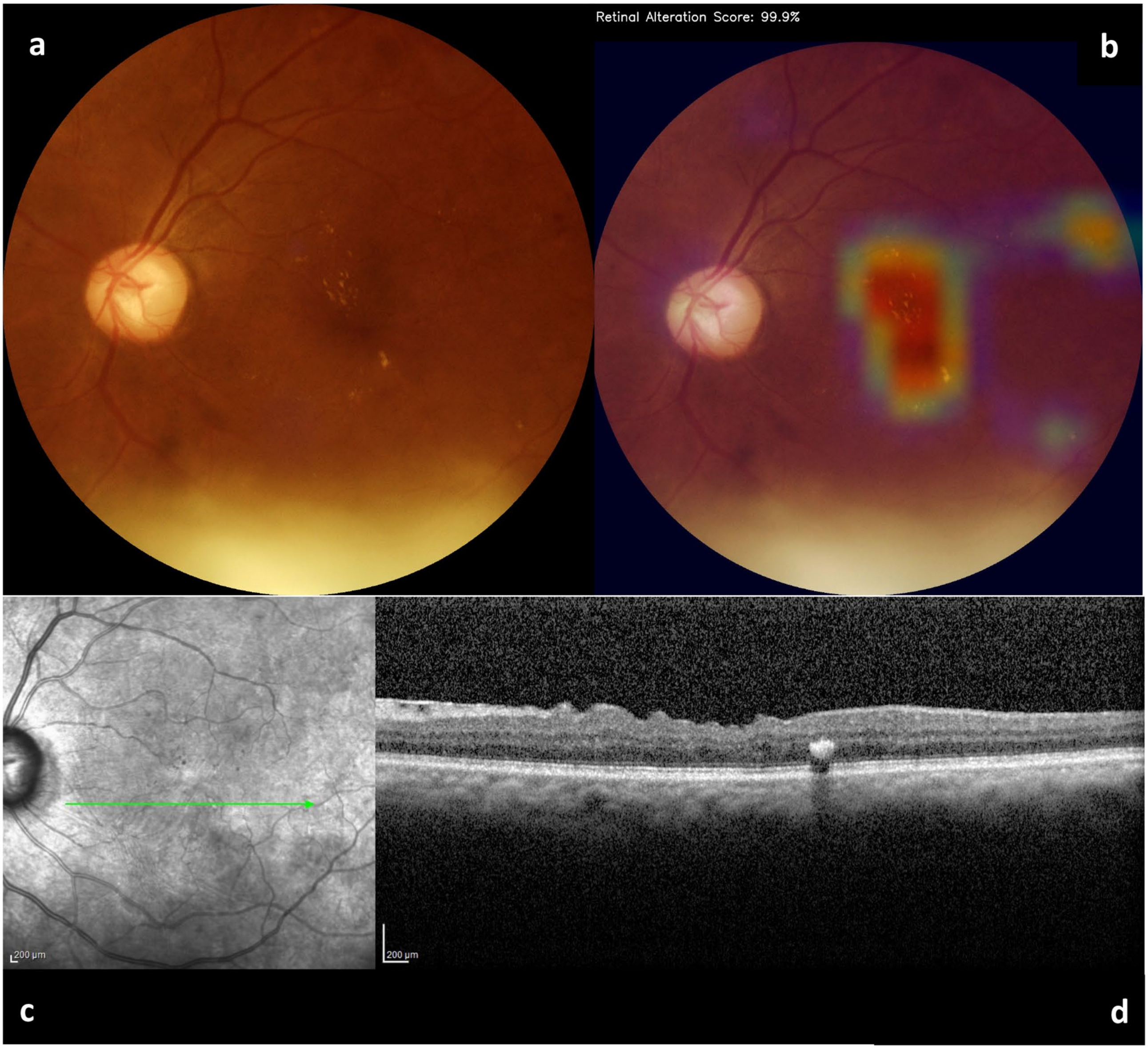

Fig. 2 Retinal images of a false-positive case of Diabetic Macular Edema, algorithmic heatmap visualization and correspondent optical coherence tomography (OCT) scan (**a**) Color fundus photograph depicting hard exudates in the macular region, suggesting the possibility of diabetic macular edema (**b**) Heatmap visualization suggesting changes in the macular region (**c**) En-face infrared reflectance image from Spectral Domain OCT (**d**) OCT scan showing hyper reflective foci, corresponding to hard exudates, without retinal thickening

increasing demands as diabetes prevalence grows globally [3]. Screening programs, typically based on CFPs, also face the challenge of diagnostic accuracy, with false-positive rates as high as 86.6% for the detection of DME, [3] leading to increased diagnostic burden and reduced cost-efficacy, as well as unnecessary displacement and exposure to particularly vulnerable patients, especially in the context of Covid-19 pandemic. Even though the evaluation of macular edema in two-dimensional retinal photographs is challenging, as it relies on surrogates rather than retinal thickening itself, we believe the reported semi-automated strategy is a valid alternative for CFP-based screening, especially in middle to low income countries, where OCT devices are not widely available. The algorithmic high sensitivity originally reported for more than mild DR translates into a very low risk of failure to refer a patient with sight-threatening DR, non-maleficence being a fundamental ethical principle of AI application [11].

In the present study, DME was confirmed by OCT in 7.9% of all screened patients, a rate that concurs with most population-based studies [12]. There is considerable variation in reported rates of DME, which may be related to the heterogeneity in methodology and to the imaging protocol employed [12]. Some exceptionally high prevalence rates of DME have been reported, making it difficult to ascertain if such abnormalities are due to genuinely high prevalence in some settings or due to inadequate methodology [4, 12]. Most patients with confirmed DME in our sample were obese, had poor metabolic control, systemic arterial hypertension, dyslipidemia, and almost half had CKD; we believe our sample adequately represents the Brazilian population with diabetes treated in the public primary care [4].

We believe the main strengths of the present descriptive study are reporting the performance of a low-cost DR screening strategy that comprises portable retinal cameras and an AI algorithm, while also reporting clinical characteristics of diabetes patients followed in a primary care setting of an underserved region; additionally, we present the tomographic characteristics of DME in this population: the presence of intraretinal fluid and HRF in our sample was compatible with previous reports; however, we have found a smaller rate of eyes with SRF [2].

Since the algorithm was previously validated, the present descriptive, non-controlled study was not designed to evaluate its diagnostic accuracy, but rather, to evaluate whether eyes with macular changes at CFPs detected by the algorithm corresponded to DME cases, according to quantitative or qualitative tomographic criteria. Due to its real-life design, only patients with suspected DME underwent OCT examination in the present study, as OCT devices were not available for every screened patient; hence, the study design did not allow tomographic evaluation of patients who may have had DME and were not flagged by the algorithmic evaluation, notwithstanding its high sensitivity originally reported for more than mild DR. [4] Other limitations of this study are the lack of follow-up and of functional parameters such as visual acuity, and the lack of external validity of the algorithm, exclusively trained with images from a single device and from the same population, carrying the risk of bias related to potential unbalanced datasets [13, 14]. Additionally, exclusion of other macular conditions may have decreased algorithmic performance for the desired outcome; of note, the algorithm has been proposed as an assistive tool, associated with human review of those cases considered altered. Further studies should contribute with more information on clinical variables and tomographic biomarkers of DME of patients treated in primary care settings, as there is scarcity of anatomic or prognostic data regarding such a prevalent disease in populations of different backgrounds; additionally, external algorithmic validation is mandatory in order to avoid poor performance in diverse settings.

In conclusion, a semi-automated strategy with low-cost retinal portable cameras, telemedicine and artificial intelligence achieved subsequent OCT confirmation of DME in the vast majority of suspected cases; such protocol offers an equitable option for low-resource areas and allows increased access rates, ultimately contributing to tackle preventable blindness. Furthermore, it is compatible with social distancing measures, avoiding unnecessary travel and exposure in the context of Covid-19 pandemic. Further studies should evaluate new perspectives for the detection of DME in primary care settings, including algorithms trained with OCT datasets as the ground truth for the prediction of macular thickness from CFPs, and portable, low-cost OCT devices [3, 15, 16].

Authors contribution Study conception and design: Fernando Korn Malerbi, Rafael Ernane Andrade. Material preparation, data collection and analysis: Fernando Korn Malerbi, Giovana Mendes, Nathan Barboza, Rafael Ernane Andrade. Reviewing and supervision: Fernando Korn Malerbi, Rafael Ernane Andrade, Paulo Henrique Morales, Roseanne Montargil. All authors read and approved the final manuscript.

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Declarations

The study followed the Declaration of Helsinki and was approved by the local Ethics Committee. All patients signed written informed consents for participation.

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

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