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ORIGINAL PAPER

Comparison of densitometric profile after deep lamellar keratoplasty with two different techniques for treatment of keratoconus

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Abstract
Purpose To compare densitometric outcome of two techniques of deep lamellar keratoplasty using Pentacam HR corneal densitometry software.
Methods Postoperative outcomes of 31 patients with big bubble (BB) and 28 patients with Melles (M) surgery for the treatment of keratoconus were evaluated. Data were gathered at least 3 months after the removal of all sutures including demographic data, uncorrected distance visual acuity (UCDVA), best spectacle-corrected visual acuity (BSCVA), refraction and endothelial cell count. Moreover, the Scheimpflug images were taken by Pentacam® HR to assess keratometric profile, densitometric outcomes in different depths and zones of the cornea and central corneal thickness. Anterior segment OCT was performed in ten cases of M group.
Results Thirty-one eyes with BB and 27 eyes M surgery were enrolled. Comparison of densitometric profile between groups revealed no statistical significance in zone 0–2 mm, zone 2–6 mm and zone 10–12 mm in all depths (all P values $>$ 0.05). Zone 6–10 mm of M group had lower densitometric readings (more transparent) in anterior, central and posterior layers of the cornea in comparison with BB group (all $P <$ 0.05). Also no statistical difference was found in UCDVA, BSCVA, spherical or cylindrical refractive error, and spherical equivalent, keratometric readings, endothelial cell count and central corneal thickness in two groups (all P values $>$ 0.05).
Conclusion Densitometric profiles were identical in both methods in visually important zones so as visual and refractive outcomes.

Keywords Densitometric profile · Deep lamellar keratoplasty

Introduction

It was shown that lamellar keratoplasty has advantages over penetrating keratoplasty for the treatment of corneal stromal pathologies including keratoconus [1, 2]. Newer lamellar keratoplasty techniques with thinner residual stroma of recipient cornea known as deep lamellar keratoplasty (DALK) brought more favorable results [1, 3]. Melles technique and Anwar big bubble technique are two cardinal methods of DALK [3–5]. Big bubble technique has theoretical

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advantage of baring Descemet membrane, and it has been widely used by corneal surgeons [5, 6]. On the other hand, Melles procedure is used by some other surgeons as their routine technique. Both methods have promising results, with some advantages and disadvantages [7], but there is no report compared corneal transparency after these procedures.

Pentacam HR can noninvasively create quantitative maps of backscattered light known as corneal densitometry map. Corneal densitometry has been already applied to show density of normal cornea [8, 9], during different corneal pathologies [9–18] and dry eye [19]. It was also used to determine corneal density after refractive surgeries [20–24], corneal cross-linking [9, 25–28], various types of corneal transplantation [29–33] and pterygium excision [34].

To our knowledge, no study has compared postoperative corneal density between planned Melles and big bubble techniques. Main object of this study is to determine corneal backscatter light status after these two types of procedures using Pentacam HR add-on densitometric software. Alternatively, it may compare outcomes of visual function, refraction, keratometry, endothelial cell density and corneal thickness.

Methods and materials

In this retrospective nonrandomized comparative study, postoperative results of 31 eyes that underwent deep anterior lamellar keratoplasty (DALK) with big bubble technique were compared with a cohort of 27 eyes that underwent DALK with Melles technique. The study was conducted according to the tenets of Helsinki Declaration. Eligible participants had a significant keratoconus without deep corneal scar. They were contact lens intolerant. Exclusion criteria were any systemic disease, pregnancy or breast feeding, any corneal pathology rather than keratoconus, the presence of vernal keratoconjunctivitis, glaucoma, retinal pathologies and dry eye. Patients with any previous intraocular operation or corneal cross-linking and those patients using systemic medicines with known effects on cornea or tear quality were excluded too. Data were gathered at least 1 year after operation when all sutures had been removed.

Surgery

All patient underwent DALK in Aban Eye Clinic by two expert cornea surgeons (SMG and SH) under general anesthesia.

In Melles group, after marking center of cornea, aqueous was replaced with air through a self-sealing paracentesis. A 5-mm-length superior scleral tunnel created 1 mm posterior to the limbus; then, a Melles dissector was introduced through the tunnel to the corneal stroma in depth of 90% corneal thickness; then, it was extended bluntly toward peripheral cornea using Melles dissector to build a full-corneal diameter pre-Descemet membrane pocket. (The air–endothelium interface acts as a mirror, and the less the distance between dissector tip and its image, the closer the dissection plan to the Descemet membrane has been achieved.) The air in the AC was replaced with BSS thereafter, and the space between anterior and posterior lamellae was filled with an ophthalmic viscosurgical device (OcuCoat, Bausch & Lomb, USA) and the anterior lamella was cut and removed using Barron trephine (Katena Products, Denville, NJ, USA); then, viscoelastic was washed out completely.

In big bubble group, cornea was cut with Barron trephine approximately 75% of thinnest preoperative corneal thickness at 8 mm perimeter. To make big bubble, air was injected forcefully within the corneal stroma at the 90% depth with a 27-gage, bevel-down needle attached to a 2-ml air-filled syringe when the needle reached 4 mm from the entry point in the trephination groove. After debulking of the anterior lamella with a crescent knife, a self-sealing paracentesis was made with 15° knife to lower the pressure. Anterior wall of the bubble was ruptured with 15° knife, and the reminded stromal tissue was incised and removed using Castroviejo keratoplasty scissors to bare Descemet membrane.

In both groups, Descemet membrane of donated cornea was stained with trypan blue and it was removed; then, the cornea was punched with Barron punch (Katena Products Inc., NJ, USA). In all cases, the donor was sutured to host cornea with eight separate and one running 10–0 nylon sutures. Based on recipient corneal size, 7.75- to 8.25-mm trephines were selected for each individual patient and the same size Barron punches were employed for donated corneas. All donated cornea were obtained from eye

bank of Islamic Republic of Iran (Tehran, Iran) in preservation storage media (Optisol).

Postoperative follow-up and measurements

All patients received ciprofloxacin drop four times a day for 10 days and betamethasone drop every 4 h for 1 month. Betamethasone was tapered and ceased during two next months. Artelac eye drops that are containing the active ingredient hypromellose (Bausch & Lomb Incorporated, Rochester, NY, USA) were applied per need in those with foreign body sensation. Some sutures were removed selectively to manage astigmatism in some patients after month 3. At the end of the first year, all reminded sutures were removed. At least 3 months after all sutures were removed, eligible participants were summoned and examined. Postoperative collected data were gathered including demographic data, uncorrected distance visual acuity (UCDVA), best spectacle-corrected visual acuity (BSCVA), refraction and endothelial cell count. Ambient light that is lowered to the minimum and kept constant used in the room during examinations. Endothelial cell count was measured with Tomey EM 3000 specular microscope (Tomey Corporation, Nagoya, Japan). Moreover, the Scheimpflug images were taken by Pentacam® HR (Oculus Optikgeräte GmbH, Wetzlar, Germany) to assess keratometric profile, densitometric outcomes and central corneal thickness. Corneal densitometry is an add-on module for main software of Pentacam devices. This function noninvasively provides objective and reproducible information about the transparency of the cornea. To have densitometric map, the device captures several images along different meridians from corneal backscattered light. The corneal apex is automatically registered as center, and a circular area with diameter of 12 mm around this central point is analyzed. The output is reported as grayscale units (GSU). GSU = 0 means minimum light backscatter (maximum transparency), while GSU = 100 represents maximum light backscatter (minimum transparency). The analyzed area is subdivided into four areas by the software: Central zone is 2 mm in diameter and centered on then apex. The second zone is a ring extending from 2-mm to a 6-mm-diameter circle. The third zone is a ring extending from 6 to 10 mm with the final zone extending from 10-mm to a 12-mm-diameter circle. The outcome is also subdivided into three depth zones, anterior layer which is the most anterior 120 μm of the cornea, posterior layer which is the most posterior 60 μm of the cornea and the central layer corresponds to the layer between anterior and posterior corneal layers, regardless of the corneal thickness. Anterior segment OCT was performed for ten cases in Melles group using Optovue OCT (Optovue Inc., Fremont, CA, USA) to demonstrate thickness of residual posterior layer of recipient cornea.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 19.0., Armonk, NY: IBM Corp. Data were presented as a mean ± SD for the groups. Independent t tests and nonparametric Mann–Whitney U test were used as statistical tests. Normality was tested with the Kolmogorov–Smirnov test with the Lilliefors correction. ($P > 0.05$ was considered for a normal distribution.) Correlations were analyzed with the use of Spearman's rank correlation coefficient test. $P < 0.05$ was regarded as significant.

Results

Fifty-eight eyes of 40 patients who met inclusion criteria and completed follow-ups were enrolled in this study. Out of this, 31 eyes (18 males and 13 females) were listed under big bubble and 27 eyes (17 males and 10 females) under Melles group. No statistical difference was found in mean duration of follow-up in either group (2.53 ± 1.03 years in big bubble group and 2.62 ± 1.23 years in MELLES group, independent t test, $P = 0.7$). Mean age was 38.03 ± 7.88 and 34.37 ± 10.86 years in big bubble group and Melles group, respectively, that was statistically insignificant ($P = 0.14$). There was no significant difference between white and white corneal diameter between two groups (11.65 ± 0.50 mm in big bubble group versus 11.87 +/0.45 mm, $P = 0.18$, two independent sample t test).

Visual acuity and refractive outcomes

There was no statistically significant difference between two groups in uncorrected distance visual acuity (UCDVA) that was 0.87 ± 0.78 logMAR in big bubble group and 1.00 ± 0.73 logMAR in Melles group (Mann–Whitney U test, $P = 0.63$). Best spectacle-corrected visual acuity (BSCVA) was 0.10 ± 0.10 and 0.12 ± 0.14 logMAR in big bubble and Melles group, respectively, that was not significantly different (Mann–Whitney U test, $P = 0.81$).

Also no statistical difference was found in spherical and cylindrical refractive error and also spherical equivalent in two groups (Table 1).

There was no significant difference between two groups in minimal keratometric readings (42.95 ± 2.58 in big bubble and 43.42 ± 2.18 in Melles group) and maximal keratometric readings (46.87 ± 3.06 in big bubble and 47.08 ± 2.12 in Melles group (T test, $P = 0.3$ and $P = 0.8$, respectively).

Endothelial cell density and corneal thickness

At the end of follow-up, endothelial cell density (ECD) was 2064.35 ± 563.35 in big bubble and 2080.91 ± 380.88 in Melles group. The difference between two groups was not statistically significant (Mann–Whitney U test, $P = 0.59$). No statistical difference was noted in the coefficient of variation (42.12 ± 7.49 in big bubble and 39.92 ± 6.71 in MELLES group, $P = 0.2$) and hexagonality (46.93 ± 12.83 in big bubble and 47.44 ± 8.95 in MELLES group, $P = 0.8$) between two groups.

There was no significant difference in central corneal thickness (CCT) between two groups (big bubble group: 528.86 ± 44.67 µm and Melles: 550.80 ± 89.53 µm, Mann–Whitney U test $P = 0.25$). Residual posterior cornea in ten patients of Melles group was measured with anterior segment OCT, and mean thickness of this section in this subgroup was 45.8 ± 18.48 µm. The CCT of this subset was 544.22 ± 44.78 µm that was not statistically different from rest of Melles group so was big bubble group ($P = 0.934$ and 0.836, respectively).

Densitometry

Densitometric outcomes for different depth and zones of the cornea are shown in Table 2.

Gray rows indicate layers and zones with significantly different densitometry.

There was a significant correlation between UCVA and density in 0–2-mm zone in anterior (Spearman's rho: 0.29 and $P = 0.02$), central (Spearman's rho: 0.26 and $P = 0.04$) and posterior (Spearman's rho: 0.36 and $P = 0.005$). There was a significant correlation between total density of cornea and UCVA (Spearman's rho = 0.32 and $P = 0.01$) although this correlation was not statistically significant with CDVA ($P = 0.1$).

In the big bubble group, there was a significant correlation between UDVA and density of cornea in central 2 mm of cornea in anterior, central and posterior zone (Spearman's rho 0.46, 0.33 and 0.35 and $P = 009$, 0.05 and 0.48, respectively) that was stronger in anterior zone, while in the Melles group, in the central 2-mm area, posterior zone had a significant correlation with UDVA (Spearman's rho = 0.41 and $P = 0.03$), while there was no significant correlation between UDVA and anterior and central zone (Spearman's rho = 16 and 0.27, $P = 0.42$ and $P = 17$, respectively).

In the MELLES group, there was a reverse significant correlation between stromal thickness and total posterior thickness (Spearmen's rho = − 0.75, $P = 0.02$). There was no significant correlation

Table 1 Postoperative refractive error comparison between two groups

	Big bubble mean ± SD	Melles mean ± SD	P value
Spherical (D)	− 1.65 ± 3.24	− 1.86 ± 2.78	0.796
Cylindrical (D)	− 3.61 ± 2.024	− 4.35 ± 2.07	0.175
Spherical equivalent (D)	− 3.45 ± 3.35	− 4.02 ± 3.32	0.515

Table 2 Densitometric outcomes for different depth and zones of the cornea in Melles and big bubble groups in standardized grayscale (SGU)

Corneal layer	Zone	Big bubble	Melles	*P* value
Anterior	0–2 mm	24.30 ± 5.02	23.02 ± 5.59	0.36
	2–6 mm	23.48 ± 4.72	21.28 ± 3.93	0.06
	6–10 mm	27.30 ± 8.92	22.62 ± 4.85	0.01
	10–12	28.98 ± 11.56	25.98 ± 8.50	0.27
	Total	28.83 ± 6.01	22.52 ± 3.42	0.01
Center	0–2 mm	15.56 ± 2.77	15.23 ± 3.37	0.68
	2–6 mm	14.71 ± 2.46	14.10 ± 2.89	0.38
	6–10 mm	19.51 ± 5.20	16.36 ± 3.49	0.01
	10–12	19.86 ± 7.30	17.78 ± 4.95	0.22
	Total	17.17 ± 3.35	15.50 ± 2.73	0.04
Posterior	0–2 mm	13.83 ± 4.22	14.05 ± 2.86	0.82
	2–6 mm	13.44 ± 3.74	12.91 ± 3.30	0.58
	6–10 mm	15.18 ± 3.97	12.83 ± 2.24	0.01
	10–12	14.58 ± 5.61	14.12 ± 5.19	0.75
	Total	14.30 ± 3.47	13.27 ± 2.65	0.21
Total	0–2 mm	17.90 ± 3.68	17.03 ± 4.60	0.42
	2–6 mm	17.21 ± 3.32	16.10 ± 3.20	0.20
	6–10 mm	20.64 ± 5.70	17.28 ± 3.19	0.01
	10–12	20.80 ± 7.93	19.27 ± 5.51	0.41
	Total	19.06 ± 4.05	17.10 ± 2.79	0.04

between residual stromal thickness and visual acuity (Spearman's rho:− 0.41, $P = 0.24$).

There was no significant correlation between endothelial cell density/hexagonality and densitometric value in different zones and layers of cornea ($P > 0.05$ in all cases).

Discussion

Few studies have compared the outcomes of Melles and big bubble techniques for the treatment of keratoconus [5, 6, 35, 36]. To our knowledge, this is the first study that quantitatively assessed corneal densitometric profile in multiple layers and zones after Melles and big bubble techniques using Pentacam HR densitometric software.

In this study, the most peripheral zone (10–12 mm) which was located out of the transplanted area showed similar densitometric values in all depths as well as total densitometry of peripheral cornea in both groups. On the other hand, 6–10-mm zone in all different depths of the cornea was more transparent in Melles group than in DALK group. This zone was the site of already removed stitches in the graft–host interface. Bhatt et al. [6] compared successful big bubble DALK with manually performed DALK following failed big bubble, and they stated comparable interface densitometry in two groups. However, they calculated average of manually measured densitometry of rectangular areas within the stromal interface in only four major axes; moreover, they did not used the add-on Pentacam HR densitometric software. We did not assess structural or densitometric properties of exact host–donor junction which might discuss dissimilarity of corneal densitometry in all depth of this zone. One previous study has been showed weak repeatability and reproducibility of densitometric reading in 6–10- and 10–12-mm zones in keratoconus and post-collagen cross-linking [9], so it could be a possible confounding factor in the current study too.

In this study, densitometric values of all corneal layers in central 2-mm zone were statistically the same in Melles and DALK groups as well as all layers in 2–6-mm annulus. Accordingly, overall corneal clarity was equivalent in the optically important central 6-mm area of the grafted cornea after Melles or big bubble DALK.

It has been found that anterior layer of both keratoconic and normal virgin cornea has highest

backscatter light than the other corneal layers [8, 15]. Our study also demonstrated after lamellar keratoplasty, the anterior corneal layer had highest densitometric values with both techniques. It might be related to more cellularity of subepithelial portion of the cornea [37].

When whole-hog 12 mm is considered, Melles technique was superior to big bubble in terms of corneal densitometry, and it should be because of better densitometric profile of 6–10-mm zone in Melles group. Normative values of Pentacam HR corneal densitometry were obtained by Ni Dhubhghaill et al. [8] from a large Caucasian population. Our study showed higher numerical densitometric values in SGU for most of the corneal layers and zones comparing to normative values of the same age group (Table 3 and Fig. 1). However, meta-analytic studies are necessary for more comprehensive deductions. It should be emphasized while we did not evaluate preoperative densitometry of participant, some authors have revealed central 6 mm of the cornea with keratoconus has higher densitometric values in comparison with normal cornea [15, 16]; in our study, the age of donors was not took into account, given the fact the host graft diameters used in this study range from 7.75 to 8.25 mm, and the eye banks currently tend to exclude corneas affected by clinically relevant peripheral degenerations, and the lack of donors age is not relevant in the visually important zones (0–6 mm) [8].

Previous studies have shown that remaining a thin layer of posterior cornea after lamellar keratoplasty did not have adverse effect on visual function [1, 5, 6, 35, 36, 38]. Ardjomand et al. [6, 38] considered thickness less than 20 μ ideal and more than 80 μ unacceptable. Others suggested remaining stromal thickness less than 65 μ was satisfactory. Difference in ultrastructure of posterior cornea and anterior cornea can explain poor clarity of graft when the remaining posterior lamella is not thin. Scanning electron microscopy has shown that collagen fibrils are densely interwoven in anterior lamella, while they are forming loose fibrillar networks in the innermost stromal region adjacent to Descemet membrane [39]. In addition, biochemical measurements of the DNA content of different regions of cornea have shown 30% lower cellularity in the subendothelial region compared to the subepithelial stroma [37].

We assessed remaining stromal layer after Melles lamellar keratoplasty with OCT in 10 participants; the average was within acceptable range and CCT of this subgroup was neither different with the rest of Melles patients nor big bubble ones. These findings in addition that central corneal thickness (CCT) and thinnest point of cornea were not statistically significant between Melles and big bubble DALK, can be assumed a thin residual stromal layer in Melles group.

Comparable postoperative corneal curvatures, refractive outcomes and corneal thickness with acceptable residual stroma in Melles group discuss why densitometric profile of grafted cornea was

Table 3 Mean ± SD of densitometry in different zones and layers of cornea in two techniques versus normative values of corresponding age group

	Normative densitometric values in SGU (30–40 years) [8]	Big bubble densitometric values in SGU 38.03 ± 7.88 years	Melles densitometric values in SGU 34.37 ± 10.86 years
Anterior layer	23.8 ± 4.06	28.83 ± 6.01	22.52 ± 3.42
Center layer	15.8 ± 2.50	17.17 ± 3.35	15.50 ± 2.73
Posterior layer	13.9 ± 2.09	14.30 ± 3.47	13.27 ± 2.65
Total anterior to posterior	17.9 ± 2.77	19.06 ± 4.05	17.10 ± 2.79
0–2-mm zone	16.9 ± 1.87	17.90 ± 3.68	17.03 ± 4.60
2–6-mm zone	15.4 ± 1.78	17.21 ± 3.32	16.10 ± 3.20
6–10-mm zone	17.5 ± 1.79	20.64 ± 5.70	17.28 ± 3.19
10–12-mm zone	24.6 ± 6.06	20.80 ± 7.93	19.27 ± 5.51

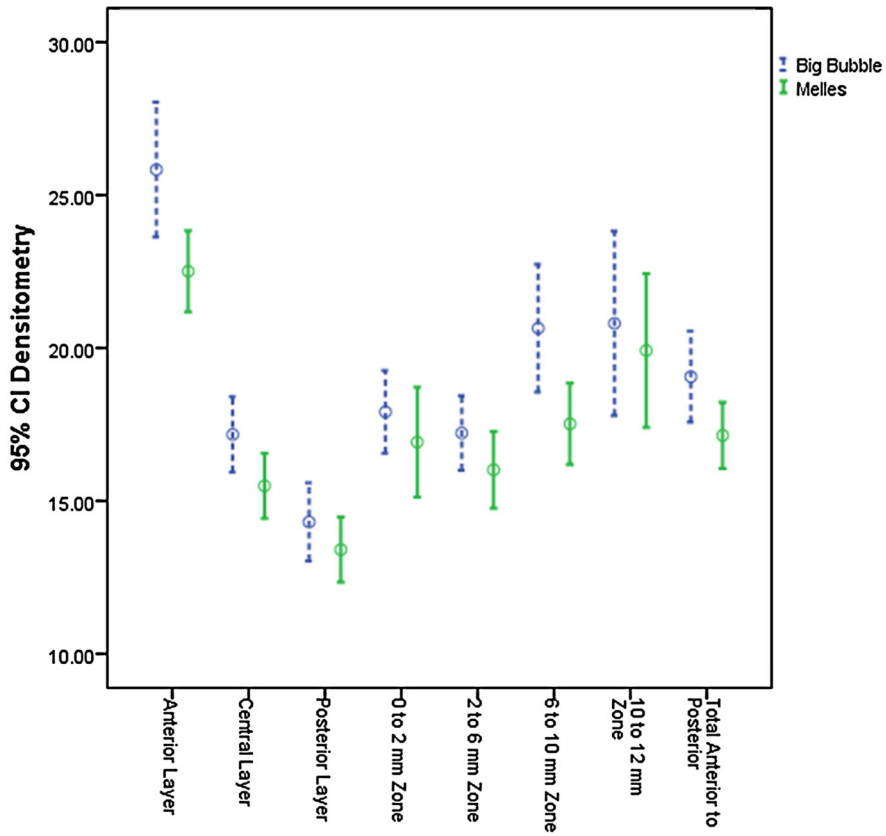

Fig. 1 Densitometric value in different zones and layers of cornea in two techniques

almost the same for both techniques; consequently, it was expected the same visual outcomes. In this study, at the end of follow-up, acceptable corrected distance visual acuity was achieved without statistically significant difference between two techniques. This is similar to results of most other comparative studies that had been published [5, 6, 36, 40]. In contrast, in another study, the visual outcome of Melles was inferior to that of big bubble in spite of similar refractive outcomes [35]. Deep anterior lamellar keratoplasty has been already compared with penetrating keratoplasty, and according to American Academy of Ophthalmology (AAO), visual outcomes of DALK will be the same as PK when residual stromal bed is less than 65 μ [1].

Our current study showed at the end of follow-up time endothelial cell density (ECD) and endothelial shape factors were statistically insignificantly different in both groups. This is in accordance with that published previously [36, 41]. Stable postoperative ECD is expected because endothelium and Descemet membrane of donated cornea are usually peel off during big bubble or Melles and it eliminates the major antigenic load for subclinical immune-mediated endothelial cell loss. Some investigators have shown an early decrease in endothelial cell density after lamellar keratoplasty [5, 7, 42]. In contrast, Salouti et al. [43] had observed a significant increase in ECD three months after Melles operation; they suggested that it was due to surgical-induced flattening of the corneal and subsequent endothelial cell crowding rather than absolute increase in number of endothelial cells. We only considered postoperative endothelial status though.

Retrospective nonrandom nature is the major limitation of the current research. The absence of data about age of donated corneas is another major pitfall too.

Conclusion

This study pointed out that densitometric status is similar in optically noteworthy zones of cornea after

lamellar keratoplasty with big bubble or Melles techniques which is in accordance with postoperative refractive and visual outcome as well as endothelial cell density and thickness. Therefore, they can be used interchangeably.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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