Color Doppler Ultrasound Pattern of Cutaneous Exosomes at High and Ultra-High Frequency

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Exosomes are extracellular vesicles that play a crucial role in intercellular communication and are becoming an increasingly popular worldwide aesthetic procedure. To date, the ultrasound changes in the cutaneous layers generated by exosomes have not been reported. We present 3 cases that were ultrasonographically studied before and 3 months after the last exosome procedure, using high (24 MHz) and ultra-high (71 MHz) frequencies. The exosome regions were compared with the contralateral (non-treated) areas and adjacent tissues before and after application. Hyperechoic islets in the upper hypodermis and an increase in dermal vascularity were detected in these cases, forming a consistent pattern in the 3 cases at the exosome regions. This may be related to a mild degree of inflammation and neoangiogenesis in the treated regions. In 1 patient with alopecia, there was evidence of hair follicle growth at the exosome area. Further investigations are needed to examine the persistence of these changes over time and the impact of local trauma on the ultrasonographic abnormalities resulting from the application of these agents. The capability to identify ultrasonographic patterns in cutaneous exosomes may help discriminate them from abnormalities present in dermatologic diseases, particularly when patients do not provide a clear history, and monitor anatomical changes more objectively.

Key Words—aesthetic; dermatologic ultrasound; dermatology; exosomes; ultrasound

Exosomes are extracellular vesicles that play an essential role in intercellular communication. These small membrane-bound vesicles secreted by cells have gained significant attention for their therapeutic potential. They measure between 30 and 160 nm in diameter, with an average of 100 nm, and are derived from various cell types. Exosomes play a crucial role in intercellular communication by transferring proteins, lipids, and RNA between cells.[1]

Exosomes participate in various steps of the wound repair mechanism, including coagulation, migration, stem cell mobilization, angiogenesis, extracellular matrix remodeling, and immunoregulation. Exosomes can be derived from saliva, platelets, and mononuclear macrophages.[2–4]

They have a plasma-membrane-derived phospholipid bilayer structure and contain cytosolic components from their cell of origin. For dermatologic use, several types of exosomes are available, including human mesenchymal stem cell-derived exosomes, lactobacillus plantarum-derived exosomes, and rose stem cell exosomes. The application of cutaneous exosomes requires the creation of

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Abbreviation
RNA, ribonucleic acid

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delivery channels, such as fractional CO_2 laser, radiofrequency, microneedling, or electroporation.

There is emerging evidence for the usefulness of exosomes in dermatology and aesthetics, particularly for anti-aging, reducing inflammation, cutaneous repair (wound healing), and hair regeneration. Exosomes also have a demonstrated ability to enhance angiogenesis, thereby optimizing healing.[1–5]

Color Doppler ultrasound has been increasingly used for studying dermatologic diseases and aesthetic procedures.[6–13] However, to date, there are no reports on the ultrasonographic pattern of changes in the cutaneous layers resulting from exosome application.

Methods and Materials

We studied 3 cases before and 3 months after the last exosome procedure using ultrasound at 24 MHz (compact linear probe at high frequency) and 71 MHz (linear probe at ultra-high frequency). The devices used were Logiq E10 (General Electric Health Systems, Waukesha, WI) and Vevo MD (VisualSonics, Toronto, Canada).

The scans followed the protocol outlined in the published guidelines for performing dermatologic ultrasound examinations,[6,11] and all cases signed an informed consent form to participate and publish their data.

The application area was selected on ultrasound and marked on the skin according to the region with the highest chances to be standardized to scan the exact same site before and after the application. Three exosome delivery procedures were scheduled, 1 per month. The selected patients and delivery of exosome procedures in the first month were:

Patient 1

A 25-year-old man with Norwood III androgenetic alopecia of 4 years duration without previous treatment was cutaneously marked in the left frontal region of the scalp, and then underwent microneedling with a 1.5-mm Dermapen on the scalp.

Patient 2

A 69-year-old woman with severe photodamage and wrinkling without previous treatments. The ultrasonographically marked cutaneous area for exosome application was the right malar region. Then, she underwent Jeisys Edge One fractional CO_2 laser with 30 w spot 120, 20 joules, 1 procedure on the entire face.

Patient 3

A 49-year-old woman with long-standing segmental vitiligo without previous treatments was ultrasound marked in the right frontal region for the application of exosomes and then underwent full-face Dermapen microneedling with a 1.5 mm penetration.

In the 3 cases, the exosome application was performed 15 minutes after the drug delivery procedure. In the second and third months, the drug delivery procedure was performed through electroporation in all cases.

The application was made as a split face in all cases using Exosomes ExoCobio® 2.5 mL on one-half of the face (in 2 cases) and one-half of the alopecia area of the frontal region of the scalp. In the

Figure 1. Alopecia patient (left, before; right, after 3 months of application of exosomes in the left frontal region at 71 MHz). Notice the growth of hair follicles and hair tracts in the follow-up. There are several islets of hyperechogenicity of the hypodermis (*) at the follow-up.

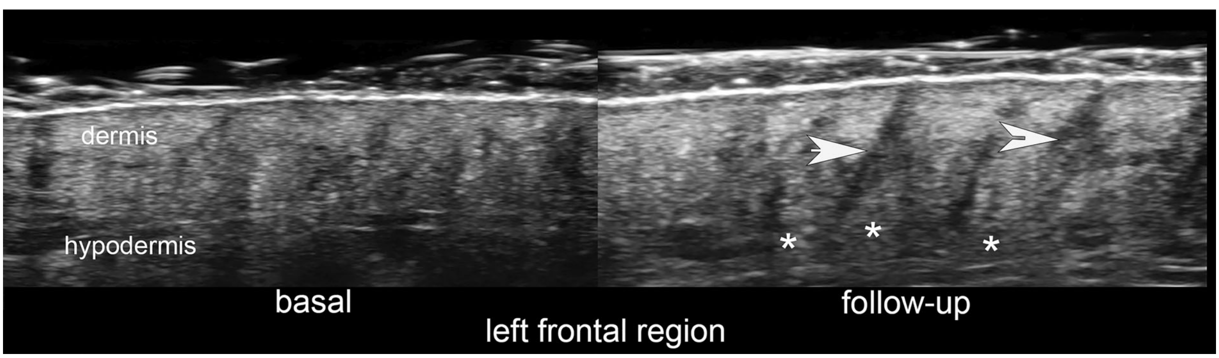


Figure 2. Alopecia patient (left, before, color Doppler; right, after 3 months of application of exosomes in the left frontal region, power Doppler at 24 MHz). At the follow-up, there is an increase in the vascularity of the dermal layer in the exosome region after application.

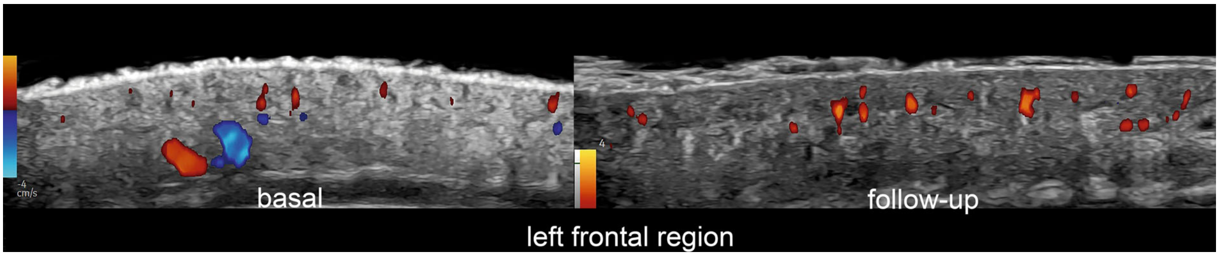
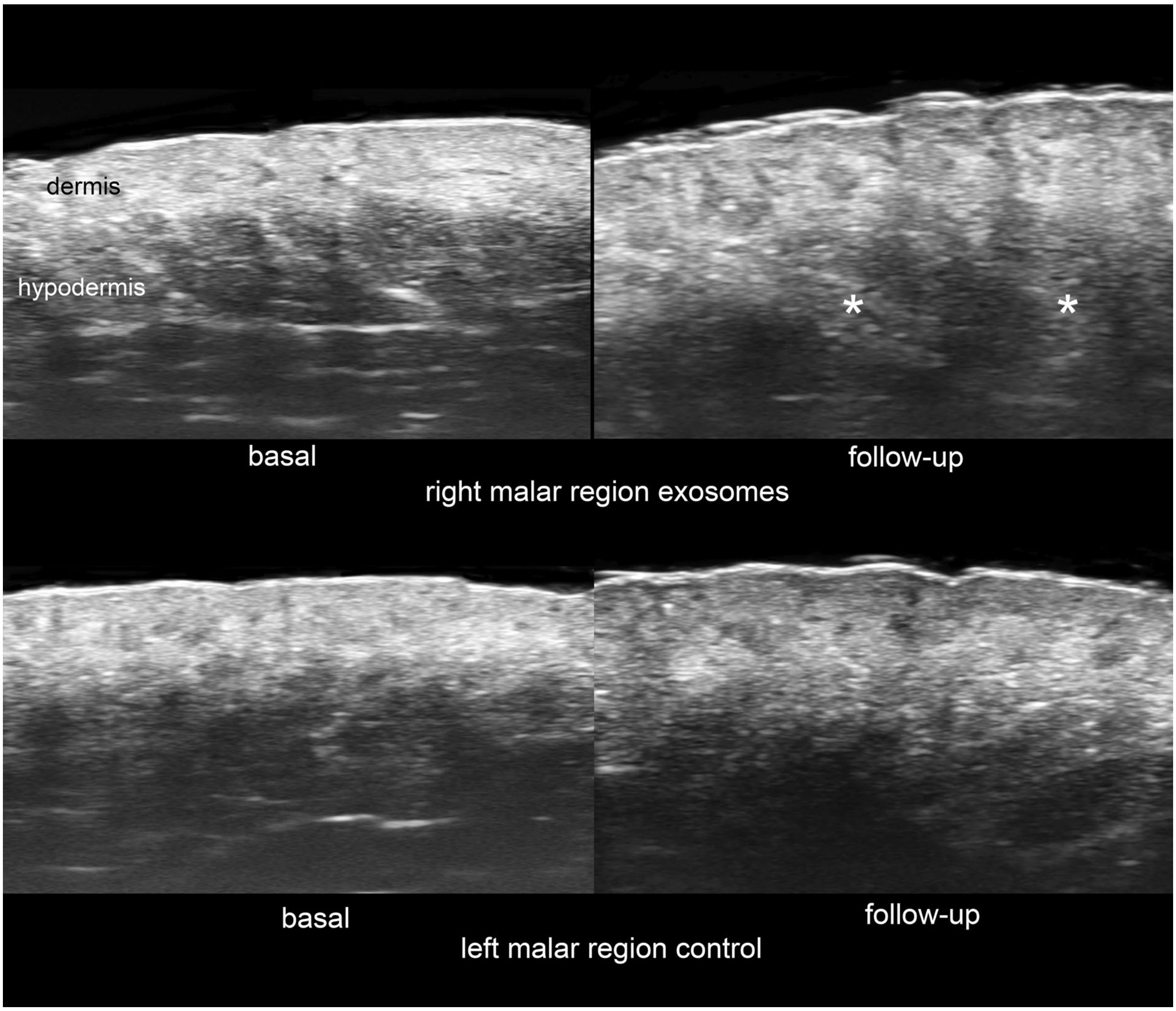


Figure 3. Wrinkled skin patient. (upper and lower left, before application; upper and lower right, 3 months after application of exosomes at 71 MHz; upper images correspond to the right malar region where the exosome treatment took place; lower images present the contralateral left malar region, which was the control area). Notice the presence of hyperechoic islets (*) in the follow-up of the exosome application area and no such alteration in the control region. A mild dermal thickening and hypoechogenicity were observed in the exosome and follow-up regions, which may be related to post-traumatic and/or photoaging changes.



remaining halves of the face and scalp, 2.5 mL saline solution was applied (control areas).

We examined the echogenicity of the cutaneous layers and the regional vascularity before and after 3 months of the procedures, comparing the lesional, perilesional, and contralateral tissue.

Results

In the 3 cases, focal islets of increased echogenicity in the upper hypodermis were observed at ultra-high frequency, and dermal hypervascularity was noted at high frequency in the areas corresponding to the regions of exosome application, compared with the pre-application images, contralateral zones, and peri-application zones.

In the alopecia patient, the hair follicles of the affected region became more prominent, and some new hairs were detected, which clinically corresponded to the appearance of some hair growth in the area. In the vitiligo patient, mild dermal hypervascularity was observed before injection, which increased after the application of exosomes (Figures 1–6).

Figure 4. Wrinkled skin patient (color Doppler before [left] and after exosome [right] at 24 MHz). There is dermal hypervascularity in the malar region at the basal phase, which increases after exosome application (follow-up).

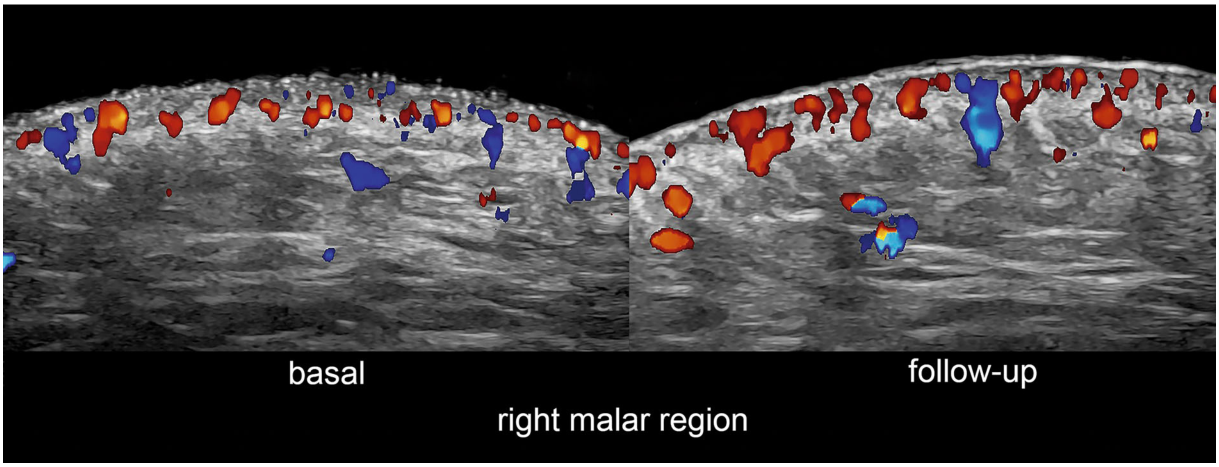


Figure 5. Vitiligo patient. Before and after exosome application at 71 MHz (left: basal, right: follow-up). Notice the presence of hyperechoic islets (*) in the upper hypodermis at the follow-up.

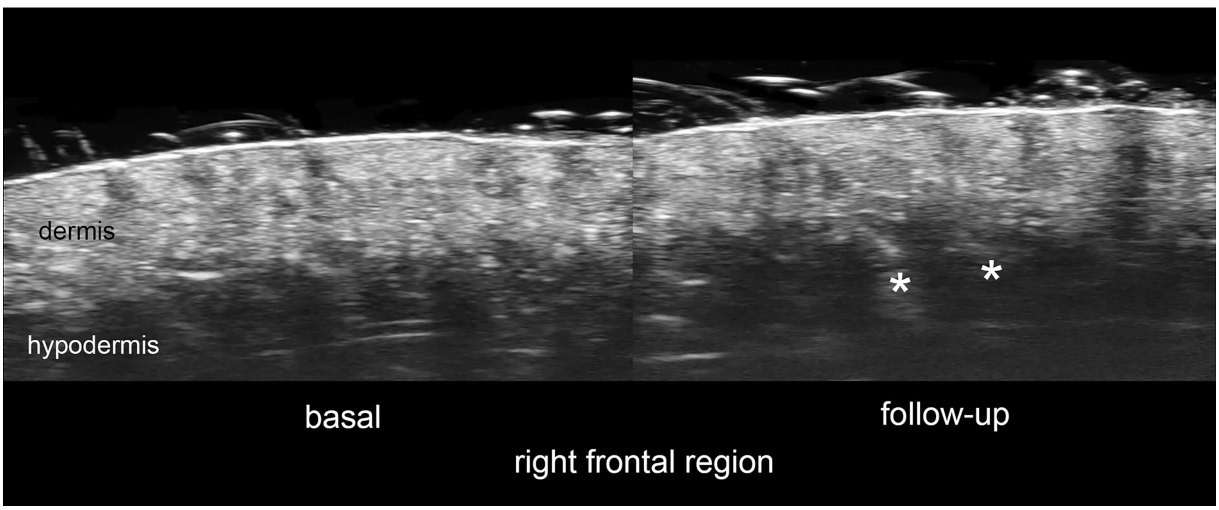
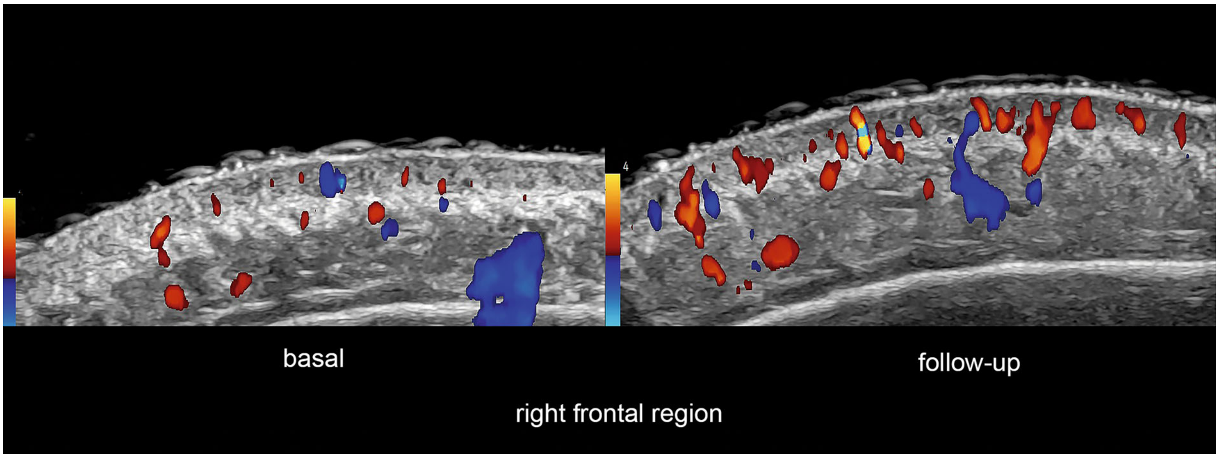


Figure 6. Vitiligo patient. Color Doppler ultrasound before and after exosome application (left, basal; right, follow-up). There is a mild increase in dermal vascularity during the basal phase, which becomes even higher at the follow-up phase.



Discussion

Interestingly, despite the growing use of exosomes worldwide, this is the first report on the ultrasonographic pattern of cutaneous exosomes. Further investigation is required to probe these changes in larger, multicenter studies.

These alterations in the echostructure and vascularity of the cutaneous layers may indicate the presence of slight inflammation; however, it is unclear whether these changes will persist over time, which would require a much longer observation period.

Even though the trauma of the applications can cause these ultrasonographic abnormalities, the persistence of these anatomical changes after 3 months of the procedures may lower the possibility of just a traumatic origin and will require further investigation.

In the vitiligo patient, there was a basal (before procedure) mild dermal hypervascularity that increased after the exosomes. The presence of subclinical dermal inflammation in vitiligo has been reported in the literature.[14] However, the ultrasonographic increase in hypervascularity after exosome treatment has not been described, and is consistent with the development of neoangiogenesis for repair and/or a higher degree of inflammation in the region.

In the patient with wrinkled skin, there was mild thickening and hypoechogenicity of the dermis in both the exosome and control areas, which may be indicative of post-traumatic and/or photoaging changes.

The identification of ultrasonographic patterns in cutaneous exosomes may help discriminate against abnormalities present in dermatologic diseases, particularly when patients do not provide a clear history, and also support the monitoring of changes over time in a more objective manner.

In summary, hyperechoic islets in the upper hypodermis and increased dermal hypervascularity were observed 3 months after the application of cutaneous exosomes in all 3 cases. The meaning and duration of these changes need a larger series investigation; nevertheless, this is the first report of the detection of anatomical changes using these agents.

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