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Adenosine washing improves the retention rate of fat grafts under conditions of obesity

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Background Fat grafting is a commonly employed aesthetic procedure for contour enhancement. However, outcome prediction is challenging due to the complex regeneration and remodeling processes involved. We investigated whether adenosine improves engraftment and fat graft survival under conditions of obesity.

Methods Fat was harvested from mice fed a high-fat diet. This fat was washed with either Krebs-Ringer bicarbonate HEPES buffer (the vehicle group) or a buffer containing 500 nM adenosine (the adenosine wash group). Subsequently, the fat was transplanted into normal mice at 0.2 mL per mouse. In both groups, 50% of the mice were sacrificed at 1 week and the remainder at 4 weeks post-transplantation. Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analysis was conducted during week 1. In week 4, micro-computed tomography, immunofluorescence staining, and RT-qPCR were performed. A sample of the initially harvested fat was set aside for lipolysis assay.

Results Adenosine washing improved fat graft retention volumes by up to 50%. One week post-transplantation, the expression of adipogenic and angiogenic genes was found to be upregulated in the adenosine wash group. After 4 weeks, immunofluorescence staining revealed greater adipocyte integrity and an increased number of vessels. Furthermore, adenosine appeared to modulate inflammation by stabilizing the lipolysis rate.

Conclusions Adenosine washing increased the fat graft survival rate under conditions of obesity. Clinically, this suggests a simple, cost-effective adjuvant method for improving fat graft survival in individuals with obesity. Further research is warranted to elucidate the underlying mechanisms and explore the applicability of this technique for autologous transplantation.

Keywords Adenosine / Obesity / Graft survival / Adipose tissue / Transplantation

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INTRODUCTION

Fat grafting is a highly effective technique for contour improvement. However, the survival rate of the transplanted fat is inconsistent, as the adipose tissue can be damaged during the remodeling process. This damage can lead to apoptosis and absorption of the graft [1]. Initially, the grafted fat must rely on the diffusion of nutrients and oxygen from the surrounding tissues, since it lacks adequate blood supply from the recipient site until revascularization occurs [2]. During this period of acute ischemia and hypoxia, the adipocytes are subjected to oxidative stress [2]. The resulting inflammation and lipolysis can adversely impact the regeneration of the adipose tissue, leading to low survival rates [1].

Numerous studies have been conducted to address this challenge, focusing on methods such as fat harvesting, fat processing, injection techniques, or bed preconditioning. Although pharmacological strategies involving hormones or cytokines have been ex-

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plored, their safety and efficacy remain unconfirmed. In contrast, adenosine—an endogenous substance—increases its own production under hypoxic conditions, interacting with adenosine receptors to regulate inflammation and protect cells from diverse stressors [3]. Our research team has demonstrated that prefabrication, as opposed to direct injection, increases angiogenesis and improves graft survival [4].

Considering the rising global prevalence of obesity, the proportion of fat graft recipients who have obesity is likely also increasing. Moreover, given the autologous nature of the procedure, it is probable in such cases that both the graft bed and the donor adipocytes exist under conditions of obesity. Unlike normal fat, obese adipose tissue undergoes a remodeling process, becomes hypertrophic, and triggers a subclinical, chronic inflammatory state [5]. Building on our previous research, we aimed to explore the impact of adenosine on fat graft engraftment in the context of obesity.

METHODS

Animals and diet intervention

As shown in Fig. 1, we designed a study where obesity was induced in mice by feeding them a high-fat diet. Four-week-old male C57BL/6 mice (Orient Bio Inc.) were housed under controlled conditions with a 12-hour light/dark cycle, constant humidity (50%±5%), and constant temperature (25±2 °C). Ten donor mice were randomly selected and fed a high-fat diet (60% kcal from fat; D12492, Research Diets, Inc.) for 6 weeks. Meanwhile, 20 recipient mice were fed a standard diet (4.5% kcal from fat; PicoLab Rodent Diet 20 5053, LabDiet) for the same duration. Of the recipient mice, 10 were randomly assigned to the adenosine wash group and the remaining 10 to the vehicle group.

All harvest and transplant procedures were performed under anesthesia with isoflurane. Fat tissue was harvested from the bilateral epididymal fat pads of donor mice. The tissue was then manually minced using a blade and rinsed with either Krebs-Ringer bicarbonate buffer (n=10, termed the vehicle group) or a buffer containing 500 nM adenosine (n=10, designated the adenosine wash group). The procedures are shown in Supplementary Video 1. The harvested fat was injected subcutaneously in volumes of 0.2 mL between the ears of recipient mice, utilizing a Luer-lock syringe and an 18-gauge needle.

Both groups were provided with a regular diet following the procedure. Planned tests were conducted on 50% of the animals (five mice from each group) at weeks 1 and 4.

Micro-computed tomography

The volume of the fat graft was measured using high-resolution micro-computed tomography (micro-CT) 4 weeks after the procedure. The mice were anesthetized with isoflurane and subjected to CT at settings of 90 kV and 88 μA, utilizing the Quantum GX2 micro-CT imaging system (PerkinElmer). Image analysis was performed with Caliper Analyze 12.0 (AnalyzeDirect Inc.) at the Soonchunhyang Biomedical Research Core Facility.

Histological analysis

The grafted fat was fixed after excision, embedded in paraffin, and sectioned to a thickness of 0.5 μm. For immunohistochemistry, the tissue slices were blocked with phosphate-buffered saline containing 5% bovine serum albumin and 0.1% Triton X-100. These slices were then incubated with primary antibodies: anti-mouse perilipin (ab61682; Abcam, dilution 1:100) to stain intact adipocytes; anti-mouse F4/80 (14480182; eBioscience, dilution 1:100) to stain macrophages; anti-tyrosine hydroxylase (ab152; Millipore, dilution 1:100); to stain catecholamine-containing neurons; and anti-mouse *Pecam1* (553370; BD Biosciences, dilution 1:100) to stain capillaries. Fluorescent dye-conjugated secondary antibodies (Thermo Fisher Scientific, 1:200) were applied for visualization. The stained samples were imaged using a fluorescent microscope (DMi8, Leica) or a confocal microscope (LSM 710, Carl Zeiss).

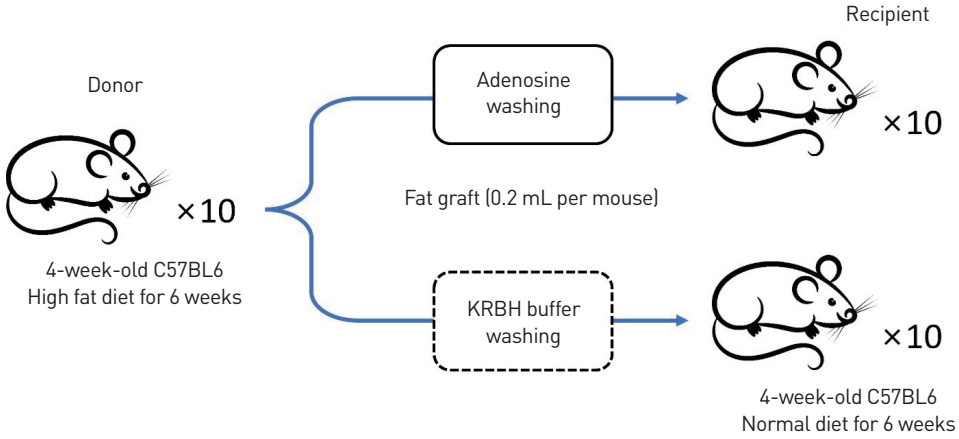

Fig. 1. Schematic illustration of the experimental design.

Reverse transcription-quantitative polymerase chain reaction

RNA was isolated using RiboEx reagent (GeneAll Biotechnology). The integrity of the RNA was assessed with a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific). Subsequently, complementary DNA was synthesized from the RNA using a high-capacity reverse transcription kit (Applied Biosystems). Reverse transcription-quantitative polymerase chain reaction (RT-qPCR) was conducted using SYBR green PCR master mix (Toyobo) on the QuantStudio 1 Real-Time PCR system (Applied Biosystems). *Arbp* served as the internal control gene for normalization purposes. Each sample was tested in duplicate, and relative gene expression levels were calculated using the $2^{-\Delta\Delta CT}$ method. The primers employed in this study are listed in Table 1. All assays were performed in accordance with manufacturer protocols.

Lipolysis assay

Before the grafting procedure, small samples of the harvested epididymal fat tissue were sectioned off for a lipolysis assay. For this assay, 20 mg of the tissue was finely chopped and allocated into wells on a plate. We prepared a total of 40 wells, each containing Dulbecco modified Eagle medium with 2% bovine serum albumin. To 20 wells, chosen at random, we added 500 nM adenosine. These wells were designated as the adenosine group, while the remainder served as the control group. All samples were incubated at 37 °C in an environment with 5% carbon dioxide and 95% humidity for durations of 0, 15, 30, and 60 minutes. Each time-point group consisted of five wells. Following incubation, the samples were processed using the EZ-Free Glycerol Assay kit (DoGenBio), adhering to the manufacturer's instructions. Subsequently, we quantified the amount of free glycerol present for each group.

Table 1. Primers used for reverse transcription-quantitative polymerase chain reaction

Target gene	Sequence (5′-3′)
Arbp	For: AGATTCGGGATATGCTGTTGGC
	Rev: TCGGGTCCTAGACCAGTGTTC
Pparg2	For: TCGCTGATGCACTGCCTATG
	Rev: GAGAGGTCCACAGAGCTGATT
Fabp4	For: AAGGTGAAGAGCATCATAACCCT
	Rev: TCACGCCTTTCATAACACATTCC
Vegfa	For: GCACATAGAGAGAATGAGCTTCC
	Rev: CTCCGCTCTGAACAAGGCT
Pecam1	For: GAGCCCAATCACGTTTCAGTTT
	Rev: TCCTTCCTGCTTCTTGCTAGCT
Il6	For: TAGTCCTTCCTACCCCAATTTCC
	Rev: TTGGTCCTTAGCCACTCCTTC
iNos	For: CCAAGCCCTCACCTACTTCC
	Rev: CTCTGAGGGCTGACACAAGG
Tnfa	For: CCCTCACACTCAGATCATCTTCT
	Rev: GCTACGACGTGGGCTACAG

For, forward; Rev, reverse; *Arbp*, attachment region binding protein; *Pparg2*, peroxisome proliferator-activated receptor gamma 2; *Fabp4*, fatty acid-binding protein 4; *Vegfa*, vascular endothelial growth factor A; *Pecam1*, platelet and endothelial cell adhesion molecule 1; *Il6*, interleukin 6; *iNos*, inducible nitric oxide synthase; *Tnfa*, tumor necrosis factor alpha.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software Inc.). The results were expressed as mean ± standard error of the mean. Statistical significance was determined using an unpaired two-tailed Student t-test for comparisons between groups. A P-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Adenosine washing improved volume retention in fat grafts from obese rats

On the CT image, the transplanted fat retained its round shape and displayed homogeneous integrity. Radiologic investigations did not suggest fat necrosis (Fig. 2A). The average volume of the transplanted fat was approximately 50% greater in the adenosine wash group compared to the vehicle group (Fig. 2B). A visual comparison of the transplanted fat revealed that the samples from the adenosine wash group were larger and had a greater number of small vessels on their surface. However, we observed no noticeable difference in color between the groups (Fig. 2C).

Adenosine washing increased adipogenesis in fat grafts from obese rats

Cross-sections stained with perilipin, visible in green, indicated that the adenosine wash group displayed a greater number of viable adipocytes, which were relatively uniform in both size and shape (Fig. 3A). RT-qPCR performed at 1 week revealed significant upregulation in the expression levels of *Pparg2* and *Fabp4* (Fig. 4A), genes associated with adipogenesis. These findings aligned with the histological results. However, we observed no significant difference in the expression of adipogenesis-related genes at 4 weeks post-grafting, as determined by RT-qPCR analysis (Fig. 4B).

Adenosine washing promoted angiogenesis in fat grafts from obese rats

Pecam1 staining (visible in red) revealed a marginally higher number of *Pecam1*-positive cells in the adenosine wash group compared to the vehicle group (Fig. 3B). This may suggest an elevation in endothelial cell numbers, which could be interpreted as neovascularization. RT-qPCR analysis conducted 1 week post-transplantation demonstrated significant differences in the expression levels

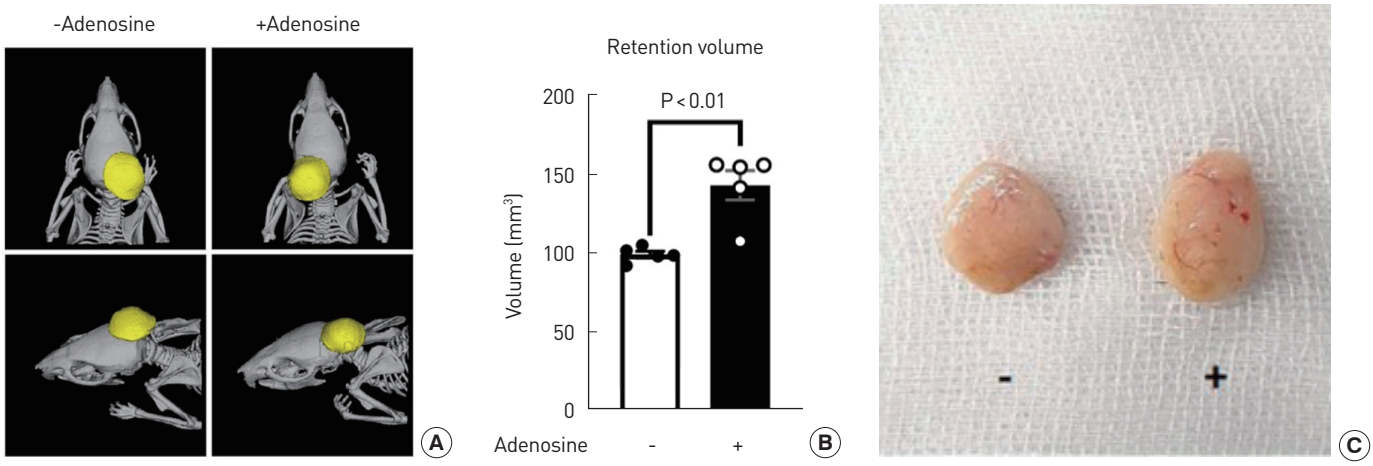

Fig. 2. Adenosine washing was shown to improve volume retention. (A) Example of micro-computed tomography. (B) Difference in average volume at 4 weeks post-transplantation. (C) Gross photograph. The adenosine wash group exhibited a larger size and an increased number of vessels on the surface.

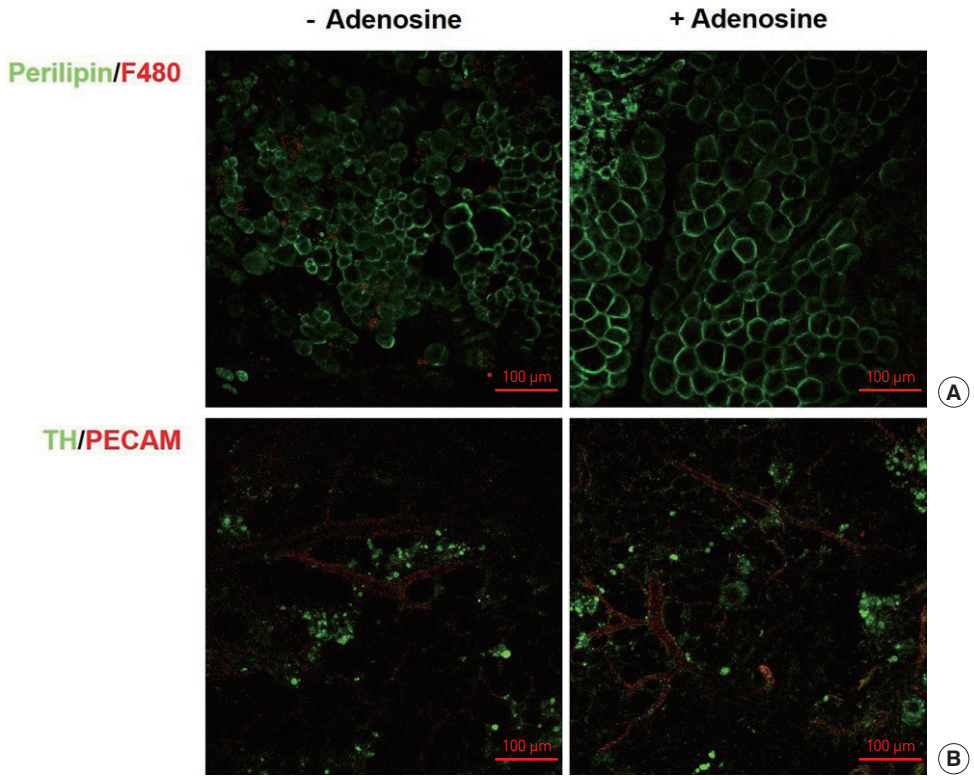

Fig. 3. Representative immunofluorescence images. (A) Stained for perilipin (green) and F4/80 (red). (B) Stained for tyrosine hydroxylase (TH; green) and *Pecam1* (red). In the adenosine wash group, we noted a higher number of perilipin-positive cells (adipocytes), which were more uniform in shape and size (A). *Pecam1*-positive cells (endothelial cells) appeared to form vascular structures (B).

of the *Vegfa* and *Pecam1* genes (Fig. 4A). However, the expression increase did not reach statistical significance in the RT-qPCR assay performed at 4 weeks (Fig. 4B).

Adenosine washing modulated inflammation by stabilizing lipolysis in fat grafts from obese rats

We measured the amount of free glycerol produced by lipolysis in fat tissue samples collected immediately after harvest (Fig. 5). At the final time point (60 minutes), the glycerol levels in the adenos-

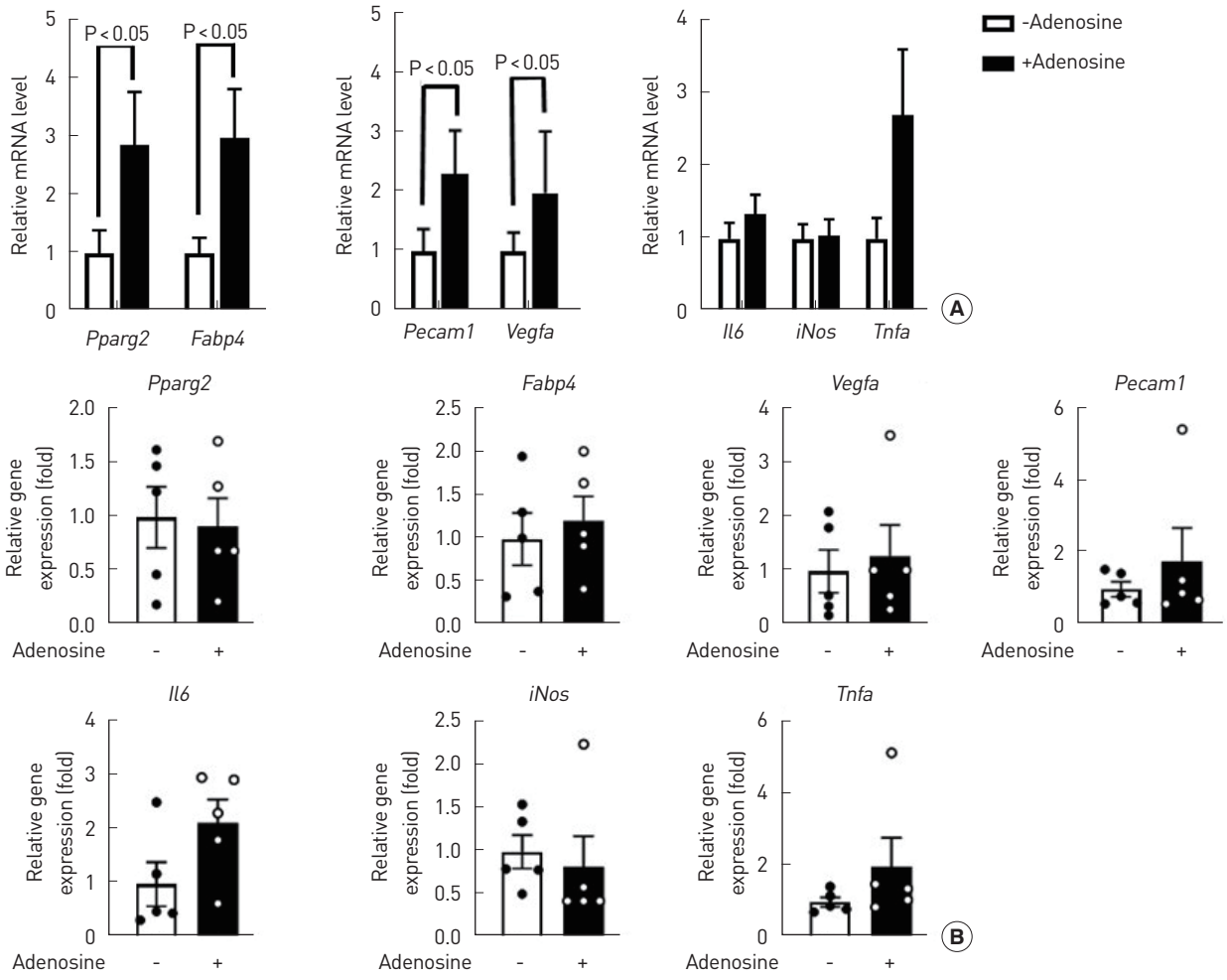

Fig. 4. Relative gene expression was compared through normalization to the *Arbp* gene. (A) One week after transplantation, increased expression of adipogenesis- and angiogenesis-related genes was observed. (B) Four weeks after transplantation, no significant difference in gene expression was evident between the adenosine wash group and the vehicle group.

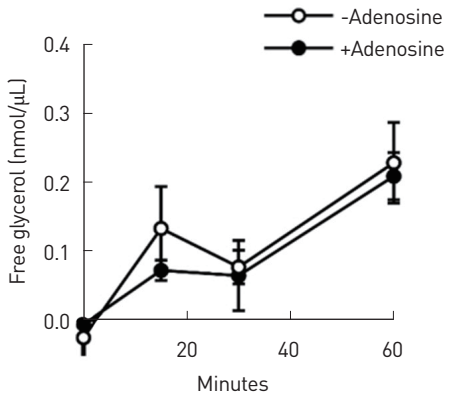

Fig. 5. Lipolysis assay. The harvested fat was divided into two groups (adenosine wash and vehicle), with samples from each group incubated for 0, 15, 30, and 60 minutes. With adenosine treatment, the steep slope evident in the control group between 0 and 15 minutes was attenuated.

ine and vehicle groups were nearly identical. However, the control group exhibited a rapid increase in glycerol levels between 0 and 15 minutes, whereas the rate of lipolysis remained constant in the tissue washed with adenosine. Four weeks after transplantation, only a few F4/80-positive macrophages were observed in both the adenosine wash and vehicle groups (Fig. 3A). This may be attributable to stabilization of the initial remodeling process after 4 weeks. However, the vehicle group displayed more dark areas without staining, which are likely to be regions filled with oil droplets and dead adipocytes. No significant differences were found in the expression of the inflammation-related genes *Il6*, *iNos*, and *Tnfa* at 1 and 4 weeks after transplantation (Fig. 4).

DISCUSSION

Adenosine is an endogenous molecule that plays a key role in various aspects of cellular physiology, including neuronal activity, vas-

cular function, and the regulation of blood cells [6]. Intracellularly, adenosine regulates energy consumption and cellular activities, while providing protection against cellular stress [6]. Under normal physiological conditions, extracellular adenosine concentrations are between 20 and 300 nM [7]. These levels can increase under conditions of cellular stress or pathology; for instance, adenosine concentrations can reach approximately 30 μM during ischemia [8,9].

Adenosine primarily acts through four G protein-coupled receptors: the A1, A2A, A2B, and A3 adenosine receptors [6]. These receptors are distributed across a variety of tissues, including those of the nervous, cardiovascular, respiratory, gastrointestinal, urogenital, and immune systems and bone, joint, eye, and skin tissue [6]. Each receptor type is associated with distinct secondary signaling transducers and physiological effects [6]. For instance, the A1 adenosine receptor (A1AR) inhibits lipolysis and insulin secretion in adipose tissue [10]. The A2A adenosine receptor (A2AAR) reduces the secretion of proinflammatory cytokines, suppresses immune responses in lymphocytes and macrophages, and induces vasodilation [11]. The A2B adenosine receptor (A2BAR) has functions resembling those of A2AAR, including the suppression of immune responses, induction of mast cell degranulation, and promotion of angiogenesis [6]. The A3 adenosine receptor (A3AR) diminishes neutrophil chemotaxis and helps regulate anti-inflammatory effects [6]. The expression levels of adenosine receptors vary across cell types; adipocytes exhibit high levels of A1AR, while preadipocytes and microvascular endothelial cells strongly express A2BAR [12-14].

Adenosine plays a critical role in adipocytes, essential for the regulation of metabolite and endocrine functions. When adenosine binds to A1AR, it modulates intracellular processes by suppressing lipolysis and augmenting the lipogenic and antilipolytic effects of insulin [15]. Studies have indicated that in the context of obesity, disrupted A1AR signaling leads to heightened adipocyte A1AR activity [16-17]. Notably, A1AR activation can decrease insulin resistance and may represent a promising therapeutic target for the treatment of type 2 diabetes [18]. Additionally, adipocytes express A2A, A2B, and A3 adenosine receptors, which can be activated under cellular stress and elevated adenosine levels to promote energy expenditure through thermogenesis or to modulate inflammation [19].

Adipose tissue stores excess energy as either hypertrophy or hyperplasia, contributing to maintaining energy homeostasis [20]. In obesity, pathological adipose tissue remodeling is expedited, characterized by diminished angiogenic remodeling, heightened extracellular matrix production, infiltration by immune cells, and amplified proinflammatory responses [20]. Hypoxia during adipocyte hypertrophy is a principal driver of inflammation, resulting in the secretion of proinflammatory interleukins, growth factors, and inflammatory modulators [19].

Our previous study demonstrated the effect of adenosine on engraftment using normal adipose tissue [4]. We chose to use epididymal visceral adipose tissue due to its ease of access and the larger quantity available compared to inguinal subcutaneous fat. Additionally, because visceral fat is relatively sensitive to obesity, we selected it for this study [21]. We hypothesized that transplanting adipose tissue from obese donors, as opposed to that from normal-weight donors, would yield different results due to subclinical and chronic inflammation. Therefore, in this study, we analyzed fat grafts from obese donors at 1 and 4 weeks after transplantation to assess differences during the early phase after adenosine washing and throughout the most active period of remodeling [22].

One week after grafting, we observed elevated expression levels of both adipogenesis-related genes (*Pparg2* and *Fabp4*) and angiogenesis-related genes (*Vegfa* and *Pecam1*). At the 4-week mark, CT imaging revealed that the adenosine wash group retained over 50% greater fat volume compared to the vehicle group. Additionally, the fat cells in the treated group exhibited higher viability, appeared visually larger, and displayed a greater number of small surface vessels. These findings indicate that the adenosine washing method improves the quality of the transplanted fat by promoting adipogenesis and angiogenesis in the early stages, thereby facilitating the survival of the grafted tissue. The impact of the adenosine washing process on lipolysis was assessed by measuring free glycerol levels. The results indicated that adenosine significantly decreased the slope of the graph between 0 and 15 minutes, suggesting an initial regulatory effect of adenosine on lipolysis.

Adenosine functions as a modulator of inflammation and exhibits anti-inflammatory effects. Adenosine receptors are present in a range of cell lineages, from monocytes to macrophages, with the expression of these receptors varying according to the level of differentiation [23]. The anti-inflammatory effects in macrophages are supported by the activation of A2A, A2B, and A3 receptors, as well as by extracellular adenosine [23]. Additionally, adenosine plays a role in regulating neutrophil activation and is known to facilitate neutrophil chemotaxis via A1AR [24].

In the early stages of fat grafting, the transplanted tissue undergoes acute ischemia and hypoxia, relying on the diffusion of oxygen and nutrients from the adjacent tissues until revascularization occurs [25]. Prior research has indicated that adenosine helps regulate inflammation in macrophages [20,23]. Consequently, we anticipated that washing with adenosine would reduce the expression of genes associated with inflammation. However, our findings revealed no significant differences in the expression of these genes between the adenosine wash and control groups. Drawing from the results of the lipolysis assay, we suggest that adenosine washing may modulate the early inflammatory response induced by lipolysis rather than exerting a direct effect on overall inflammation.

Nevertheless, several limitations of this study should be acknowledged. First, the investigation was based on an allograft model, meaning the donor and recipient mice existed under different conditions. Our objective was to investigate the impact of adenosine on

obese fat, so we used a simplified experimental model that minimized the influence of the recipient bed. However, since clinical fat grafting procedures involve the harvesting and transplantation of autologous tissue, the direct applicability of our findings to clinical practice may be limited. Further research is required for translation to human applications. Second, our structural evaluation was confined to immunofluorescence staining, without the use of hematoxylin and eosin. With structural evaluation limited to perilipin staining, only indirect evaluation of aspects such as cell wall viability was possible. Third, although the efficacy of adenosine was demonstrated, we did not elucidate the role of adenosine receptors. For a deeper understanding of the underlying mechanisms, cellular-level studies, such as the examination of receptor expression, are necessary.

In conclusion, our study demonstrated that adenosine washing can improve the survival of fat grafts under conditions of obesity. This technique promoted adipogenesis and angiogenesis while concurrently reducing inflammation by stabilizing the rate of lipolysis. Adenosine washing represents a promising approach to improving fat graft survival in patients with obesity, offering a relatively straightforward method that can be readily implemented in clinical practice.

NOTES

Conflict of interest

Han Gyu Cha and Eun Soo Park are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

Ethical approval

All experiments were performed in compliance with the ethical approval and guidelines set forth by the Institutional Animal Care and Use Committee of Soonchunhyang University Hospital (Approval No. SCH20-U-104).

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Supplemental material

Supplementary materials can be found via https://doi.org/https://doi.org/10.14730/aaps.2023.01046.

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