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ORIGINAL ARTICLE

Pharmacological Preconditioning of Stem Cells with Dapagliflozin for Diabetic Wound Healing: A Physiology-Based Community KAP Study and Experimental Study in Karachi

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ABSTRACT

Background & Objective: Pakistan faces a severe epidemic of Type 2 Diabetes Mellitus, affecting approximately 30.8% of adults, with 15–25% developing diabetic foot ulcers (DFUs) and up to 60% of uncontrolled diabetic cases suffering from impaired, delayed wound healing. The metropolitan population of Karachi bears a disproportionately high burden of non healing diabetic wounds, driven by socio economic challenges, delayed presentation, and chronic metabolic dysregulation.

Methodology: This dual phase investigation integrated a community based Knowledge, Attitudes, and Practices (KAP) survey (Phase I, n = 384 diabetic patients and caregivers in Karachi) with a translationally aligned ex vivo experimental preconditioning trial (Phase II). Human adipose derived stem cells (ADSCs) isolated from diabetic donors were subjected to ex vivo pharmacological preconditioning with dapagliflozin (10 μM) under high glucose (25 mM) stress conditions. Physiological assays evaluated glucose homeostasis, reactive oxygen species (ROS) production, pro inflammatory cytokine expression (TNF α, IL 6), VEGF secretion, tube formation, and cellular migration scratch rates.

Results: Phase I survey revealed widespread gaps in community KAP: while 78.1% of respondents recognized diabetes as a chronic illness, only 28.4% demonstrated adequate knowledge regarding diabetic foot care, and 61.2% engaged in unsafe home wound management practices. Phase II experimental results demonstrated that dapagliflozin preconditioning significantly restored ADSC survival and physiological function despite high glucose oxidative stress. Dapagliflozin preconditioned diabetic ADSCs exhibited a 58.4% reduction in intracellular ROS ($p < 0.001$), significant down regulation of TNF α and IL 6 ($p < 0.001$), a 2.4 fold increase in VEGF secretion ($p < 0.001$), and an accelerated in vitro wound closure rate (88.6 ± 4.2% vs. 41.2 ± 5.1% in unconditioned diabetic ADSCs, $p < 0.001$).

Conclusion: Pharmacological preconditioning with dapagliflozin rescues diabetic stem cell exhaustion by modulating glucose toxicity, attenuating oxidative stress, suppressing inflammation, and enhancing pro angiogenic capacity. Integrating community level foot care education with novel preconditioned stem cell therapeutics offers a robust physiological strategy to address non healing diabetic ulcers in Karachi.

Keywords: Dapagliflozin; Stem Cell Preconditioning; Diabetic Foot Ulcers; Oxidative Stress; Angiogenesis; KAP Survey; Karachi; Tissue Regeneration.

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has reached catastrophic epidemic proportions in Pakistan, with contemporary national epidemiological surveys indicating an adult prevalence of approximately 30.8%. This alarming disease burden places Pakistan among the countries most severely impacted by metabolic disorders globally[1]. Among the chronic vascular and neuropathic complications of diabetes, diabetic foot ulcers (DFUs) represent a primary cause of morbidity, prolonged hospitalization, and non traumatic lower extremity amputations. Clinically, 15% to 25% of individuals diagnosed with T2DM will develop a diabetic foot ulcer during their lifetime[2]. Furthermore, impaired and delayed wound healing is observed in nearly 60% of patients with uncontrolled diabetes, creating a massive public health challenge. Within the densely populated urban metropolis of Karachi, the burden of non healing diabetic wounds is exceptionally high. Socio economic disparities, limited healthcare access, low literacy levels, self treatment habits, and late presentation to tertiary care facilities compound the physiological vulnerability of these patients. Understanding the socio behavioral dynamics surrounding foot care practices alongside the molecular pathophysiology of impaired healing is essential to formulate effective, multi tiered healthcare interventions in this region[3,4].

From a physiological perspective, cutaneous wound healing relies on an intricate, highly coordinated cascade of overlapping phases: inflammation, granulation tissue formation, re epithelialization, angiogenesis, and matrix remodeling. In the diabetic microenvironment, persistent hyperglycemia disrupts systemic glucose homeostasis, leading to the accumulation of advanced glycation end products (AGEs), excessive intracellular reactive oxygen species (ROS) generation, and sustained activation of pro inflammatory signaling pathways (specifically NF κB, TNF α, and IL 6)[5]. This state of chronic oxidative stress and hyper inflammation impairs endogenous stem cell populations particularly mesenchymal and adipose derived stem cells (ADSCs) inducing premature senescence, apoptosis, and functional exhaustion. Diabetic stem cells exhibit severely diminished migratory capacity and blunted secretion of crucial pro angiogenic growth factors, most notably vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)[6]. Consequently, microvascular network formation is severely restricted, preventing adequate tissue oxygenation and nutrient delivery to the healing wound bed. To overcome this systemic regenerative blockade, novel pharmacological strategies capable of restoring stem cell functionality within diabetic microenvironments are urgently required[7].

Sodium glucose cotransporter 2 (SGLT2) inhibitors, such as dapagliflozin, have revolutionized clinical endocrinology by promoting urinary glucose excretion and lowering systemic glycemic load. Beyond their established renal and metabolic actions, emerging physiological evidence suggests that SGLT2 inhibitors exert direct pleiotropic, cell protective effects independent of systemic glucose clearance[8]. These include anti oxidative, anti inflammatory, and mitochondrial stabilizing properties. However, whether ex vivo pharmacological preconditioning of functionally exhausted diabetic stem cells with dapagliflozin can rescue their cellular survival, attenuate

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glucotoxicity induced ROS overproduction, suppress inflammatory cytokine release, and reactivate pro angiogenic paracrine signaling remains uncharacterized[9]. Furthermore, existing regional literature lacks integrated studies connecting community level Knowledge, Attitudes, and Practices (KAP) regarding diabetic foot care in Karachi with laboratory based translational cellular therapeutics. Therefore, the primary objective of this study was to evaluate community KAP regarding diabetic wound prevention among diabetic patients in Karachi, and to experimentally investigate the physiological impact of dapagliflozin preconditioning on stem cell survival, oxidative stress, inflammatory expression, angiogenesis, and tissue regeneration in an ex vivo high glucose wound model.

METHODOLOGY

It was a a dual phase, mixed methods research design combining a community-based cross-sectional Knowledge, Attitudes, and Practices (KAP) survey (Phase I) with a translationally aligned ex vivo experimental preconditioning trial (Phase II). The investigation was carried out by the Department of Physiology in collaboration with tertiary care clinical diabetic centres and basic research laboratories in Karachi over a 14 month period from June 2022 to July 2023. The target population for Phase I comprised adult patients with diagnosed T2DM (N = 384) attending outpatient diabetic clinics across Karachi. Sample size was determined using OpenEpi software based on an estimated 50% baseline community foot care awareness, a 95% confidence interval (Z = 1.96), and a 5% margin of error (d = 0.05). Data were collected via a pre validated, structured interviewer administered questionnaire evaluating: (a) Demographic variables (age, gender, duration of diabetes, literacy, income); (b) Knowledge regarding diabetic foot complications and glycemic control; (c) Attitudes toward foot inspection and professional medical care; and (d) Practices concerning foot hygiene, footwear selection, and home wound management. KAP scores were categorized as Good (\ge 75\%), Moderate (50–74\%), or Poor (< 50\%). Phase II: Ex Vivo ADSC Isolation and Dapagliflozin Preconditioning was performed from adipose derived stem cells (ADSCs) that were isolated from lipoaspirate tissue obtained from diabetic donors (n = 6) undergoing elective procedures, following informed consent. Tissues were enzymatically digested with 0.1% collagenase Type I, centrifuged to isolate the stromal vascular fraction (SVF), and cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin streptomycin at 37°C in a 5% CO2 humidified incubator. Surface marker expression (CD90+, CD105+, CD34 , CD45) was verified using flow cytometry. To simulate diabetic pathophysiology in vitro, passaged ADSCs (P3–P5) were assigned to four experimental treatment groups: Control Group (Normal Glucose, NG): ADSCs cultured in 5.5 mM D glucose. High Glucose Group (HG): ADSCs cultured in 25 mM D glucose for 48 hours to induce glucotoxicity and oxidative stress. Osmotic Control Group (OC): ADSCs cultured in 5.5 mM D glucose + 19.5 mM L mannitol. Dapagliflozin Preconditioned Group (HG + DAPA): ADSCs exposed to 25 mM D glucose and preconditioned with 10 µM dapagliflozin for 24 hours.

Experimental outcomes were evaluated across key physiological parameters: Intracellular ROS and Oxidative Stress: Intracellular reactive oxygen species generation was quantified using 2',7' dichlorofluorescin diacetate (DCFH DA) fluorescent microplate assays. Superoxide dismutase (SOD) and malondialdehyde (MDA) levels were measured using commercial colorimetric kits. Pro inflammatory Cytokine Expression: Gene and protein expression of tumor necrosis factor alpha (TNF α) and interleukin 6 (IL 6) were quantified using quantitative real time PCR (qRT PCR) and enzyme linked immunosorbent assay (ELISA). Angiogenic Secretory Profile: Vascular endothelial growth factor (VEGF) concentration in cell culture conditioned media was measured via ELISA. In vitro capillary like tube formation was evaluated by seeding human umbilical vein endothelial cells (HUVECs) in Matrigel matrix conditioned with ADSC media. In Vitro Re Epithelialization Scratch Assay: ADSC migration rates were determined using a standardized wound scratch assay. ImageJ software quantified percent wound closure at 0, 12, 24, and 36 hours post scratch. Statistical computations were executed using IBM SPSS Version 27.0. Survey data were summarized as frequencies, percentages, means, and standard deviations. Chi square (\chi^2) tests analyzed associations between demographic parameters and KAP scores. Experimental data were evaluated for normality using the Shapiro Wilk test and analyzed using one way Analysis of Variance (ANOVA) followed by Tukey's post hoc tests for pairwise group comparisons. Data were presented as mean ± SD. A two tailed p value < 0.05 was considered statistically significant. The protocol was formally reviewed and approved by the Institutional Ethics Review Committee. Written informed consent was obtained from all survey respondents and tissue donors. Guidelines of the Declaration of Helsinki were strictly observed.

RESULTS

Community KAP Survey Demographic Profile and Score Distribution: Phase I evaluated 384 diabetic participants in Karachi (mean age: 54.2 ± 9.8 years; 58.3% male, 41.7% female). The overall community assessment revealed significant deficits in foot care knowledge and self-care practices. While 78.1% (n = 300) recognized that diabetes increases wound risk, only 28.4% (n = 109) possessed adequate knowledge regarding specific warning signs of DFUs. Poor overall KAP scores were documented in 54.7% (n = 210) of participants, moderate scores in 31.3% (n = 120), and good scores in only 14.1% (n = 54). Unsafe home management (e.g., walking barefoot, applying unsterilized home remedies to active ulcers) was reported by 61.2% (n = 235) of respondents.

KAP Parameter	Overall Cohort (n=384)	Controlled HbA1c < 7.0% (n=128)	Uncontrolled HbA1c ≥ 7.0% (n=256)	p value
Adequate Foot Care Knowledge (n, %)	109 (28.4%)	58 (45.3%)	51 (19.9%)	< 0.001*
Daily Self Foot Inspection (n, %)	82 (21.4%)	46 (35.9%)	36 (14.1%)	< 0.001*
Proper Diabetic Footwear Usage (n, %)	96 (25.0%)	48 (37.5%)	48 (18.8%)	< 0.001*
Unsafe Home Remedies Practice (n, %)	235 (61.2%)	52 (40.6%)	183 (71.5%)	< 0.001*
History of Active / Healed DFU (n, %)	88 (22.9%)	14 (10.9%)	74 (28.9%)	< 0.001*

Effect of Dapagliflozin Preconditioning on ADSC Survival and ROS Production: Exposure of diabetic ADSCs to high glucose (25 mM) stress induced severe cellular toxicity, increasing intracellular ROS accumulation by 2.8-fold relative to normal glucose controls ($p < 0.001$). Preconditioning with 10 µM dapagliflozin significantly mitigated glucotoxicity, reducing intracellular ROS formation by 58.4% ($p < 0.001$). Furthermore, dapagliflozin restored antioxidant enzyme activity, elevating SOD levels (38.5 ± 4.2 vs. 16.2 ± 2.8{ U/mg protein}, $p < 0.001$) and markedly reducing lipid peroxidation (MDA: 1.82 ± 0.25 vs. 4.15 ± 0.48{nmol/mg}, $p < 0.001$).

Oxidative Stress Parameter	Normal Glucose (5.5 mM)	High Glucose (25 mM)	HG + Dapagliflozin (10 µM)	p value
Relative ROS Fluorescence (AU)	1.00 ± 0.08	2.84 ± 0.22	1.18 ± 0.12	< 0.001*
Superoxide Dismutase (U/mg protein)	45.2 ± 3.8	16.2 ± 2.8	38.5 ± 4.2	< 0.001*
Malondialdehyde (nmol/mg protein)	1.25 ± 0.18	4.15 ± 0.48	1.82 ± 0.25	< 0.001*
Cell Viability at 48 h (% of Control)	100.0 ± 4.2%	52.4 ± 5.1%	89.6 ± 4.8%	< 0.001*

Modulation of Pro-inflammatory Cytokine Secretion: High glucose culture stimulated a robust pro-inflammatory response in diabetic ADSCs, characterised by marked upregulation of TNF α (145.2 ± 12.8{ pg/mL}) and IL 6 (210.5 ± 18.4{ pg/mL}) in culture supernatants. Dapagliflozin preconditioning effectively blunted this inflammatory activation, reducing TNF α secretion to 48.6 ± 5.2{ pg/mL} ($p < 0.001$) and IL6 to 72.4 ± 7.8{ pg/mL} ($p < 0.001$), thereby re-establishing a pro-regenerative paracrine profile.

Inflammatory Biomarker	Normal Glucose	High Glucose	HG + Dapagliflozin	p value
TNF α Secretion (pg/mL)	32.4 ± 4.1	145.2 ± 12.8	48.6 ± 5.2	< 0.001*
IL 6 Secretion (pg/mL)	52.1 ± 6.2	210.5 ± 18.4	72.4 ± 7.8	< 0.001*
TNF α mRNA Relative Fold Change	1.00 ± 0.05	4.52 ± 0.38	1.42 ± 0.15	< 0.001*
IL 6 mRNA Relative Fold Change	1.00 ± 0.06	5.18 ± 0.42	1.65 ± 0.18	< 0.001*

Enhancement of Angiogenic Secretory Profile and Endothelial Tube Formation: High glucose severely suppressed ADSC VEGF secretion (112.4 ±14.5{ pg/mL} vs. 345.8 ± 22.1{ pg/mL} in normal controls, $p < 0.001$). Preconditioning with dapagliflozin rescued VEGF production, increasing secretion to 285.4 ± 18.2{ pg/mL} ($p < 0.001$). In HUVEC Matrigel capillary formation assays, conditioned media from dapagliflozin preconditioned ADSCs increased total capillary mesh length and branch point formation by 2.2 fold compared to unconditioned high glucose media ($p < 0.001$).

Angiogenic Assay Parameter	Normal Glucose	High Glucose	HG + Dapagliflozin	p value
VEGF Concentration (pg/mL)	345.8 ± 22.1	112.4 ± 14.5	285.4 ± 18.2	< 0.001*
HUVEC Tube Length (µm/field)	1250 ± 85	420 ± 45	1080 ± 72	< 0.001*
Capillary Branch Points / Field	28.4 ± 3.2	8.2 ± 1.5	23.6 ± 2.8	< 0.001*

In Vitro Wound Scratch Migration and Closure Kinetics: In vitro scratch assays demonstrated severely impaired cell migration in high glucose cultured ADSCs, achieving only 41.2 ± 5.1\% wound closure at 24 hours. Preconditioning with dapagliflozin significantly accelerated stem cell migration, achieving 88.6 ± 4.2\% scratch closure at 24 hours ($p < 0.001$), restoring wound closure kinetics to levels comparable to non diabetic controls (92.4 ± 3.8\%).

DISCUSSION

Diabetic foot ulcers (DFUs) represent a growing medical emergency in Pakistan, where an adult diabetes prevalence of 30.8% fuels high rates of non healing chronic wounds, microvascular complications, and lower extremity amputations. The present study provides a unique dual-perspective evaluation of this problem in Karachi, combining a community-based KAP survey with basic physiological investigations into stem cell preconditioning. Our Phase I findings highlight severe community-level gaps in diabetic foot care knowledge and self-management practices[10]. Over 54% of surveyed diabetic patients possessed poor overall KAP scores, and over 61% engaged in unsafe home wound practices. These widespread behavioural deficiencies directly contribute to delayed clinical presentation, high rates of advanced ulceration, and secondary bacterial superinfections. This socio-behavioural vulnerability reinforces the necessity of combining community educational interventions with advanced physiological research aimed at accelerating tissue repair[11,12].

At the cellular level, impaired diabetic wound healing is driven by stem cell dysfunction resulting from persistent hyperglycemia. Adipose derived stem cells (ADSCs) resident within cutaneous tissues play a crucial role in normal wound repair by releasing pro angiogenic cytokines, coordinating extracellular matrix deposition, and recruiting endothelial progenitor cells[13]. However, under high glucose conditions, excessive intracellular glucose flux accelerates mitochondrial electron transport chain overload, generating massive amounts of reactive oxygen species (ROS). In our study, high glucose exposure induced a 2.8 fold surge in intracellular ROS and severely depleted endogenous superoxide dismutase (SOD) activity in diabetic ADSCs. This oxidative stress triggers premature cellular senescence, lipid peroxidation, and apoptosis, effectively exhausting the endogenous stem cell pool necessary for cutaneous regeneration[12,14].

A central finding of this investigation is that ex vivo pharmacological preconditioning with dapagliflozin effectively rescues diabetic ADSCs from glucotoxicity induced oxidative collapse. Preconditioning with 10 µM dapagliflozin reduced intracellular ROS accumulation by 58.4%, restored SOD activity, and suppressed malondialdehyde formation[15]. Although dapagliflozin was originally developed as an oral anti-hyperglycemic agent targeting renal tubular SGLT2 co transporters, accumulating physiological evidence indicates that SGLT2 inhibitors exert direct cell protective effects on extra renal tissues[16]. By modulating intracellular sodium and calcium dynamics, stabilizing mitochondrial membrane potential, and activating the Nrf2/HO 1 antioxidant pathway, dapagliflozin protects stem cells from glucose induced metabolic stress, preserving their viability and physiological function[17].

Sustained inflammatory activation represents another major pathophysiological barrier in diabetic wounds[18]. In non diabetic wound healing, the initial inflammatory phase resolves rapidly, transitioning into granulation and tissue repair. In contrast, diabetic wounds remain trapped in a self perpetuating pro inflammatory state mediated by sustained activation of the NF κB signaling pathway. Our experimental results showed that high glucose exposure caused a massive release of pro inflammatory cytokines (TNF α and IL 6) from diabetic ADSCs[19,20]. Pharmacological preconditioning with dapagliflozin markedly blunted this cytokine response, downregulating TNF α and IL 6 gene and protein expression. By shifting the secretory profile of diabetic ADSCs from a pro inflammatory to an anti inflammatory state, dapagliflozin preconditioning creates a microenvironment conducive to tissue repair and extracellular matrix remodelling[21].

Angiogenesis is essential for successful wound repair, as newly formed capillary networks supply oxygen, nutrients, and systemic signaling molecules to the regenerating tissue bed[22]. In diabetic ulcers, impaired VEGF production by dysfunctional stromal cells results in microvascular regression and tissue hypoxia[23]. Our study demonstrated that dapagliflozin preconditioning rescued VEGF secretion in diabetic ADSCs (285.4 pg/mL vs. 112.4 pg/mL in unconditioned high glucose cells), driving a 2.2 fold increase in endothelial tube formation. Furthermore, in vitro scratch assays showed an accelerated cell migration rate (88.6% closure at 24 hours). These findings confirm that dapagliflozin preconditioning enhances both the intrinsic migratory capability of stem cells and their extrinsic paracrine capacity to stimulate endothelial capillary assembly[24].

CONCLUSION

This study confirms that diabetic foot ulceration in Karachi is driven by a combination of low community foot care knowledge, unsafe self-management practices, and underlying stem cell dysfunction caused by glucotoxicity. Pharmacological preconditioning of human adipose derived stem cells with dapagliflozin (10 µM) effectively reverses glucose induced cellular exhaustion by

suppressing oxidative stress, downregulating TNF α and IL 6 inflammation, rescuing VEGF secretion, and accelerating cell migration and endothelial capillary tube formation.

These findings highlight the therapeutic potential of dapagliflozin preconditioned stem cell transplantation as a viable strategy to enhance tissue regeneration in non healing diabetic wounds. Integrating community wide diabetic foot care education with translationally advanced cell based therapies provides a comprehensive framework to reduce amputation rates and improve clinical outcomes in Pakistan.

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