Preservation of Skin Thickness and Area by Metformin in X-Ray-Irradiated Ex Vivo Skin Model

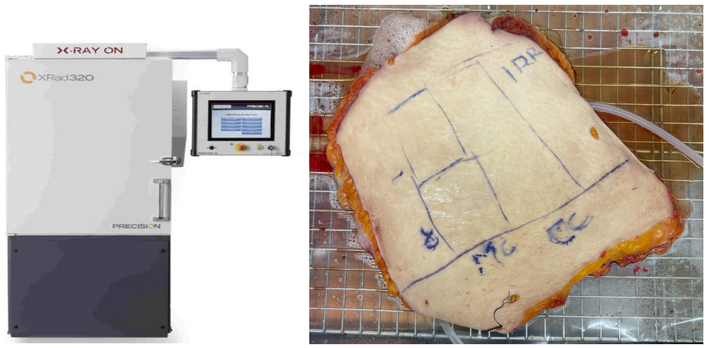
Alexa Rivera del Rio Hernandez, MD[1], Naresh Mahajan, PhD[1], Juan J. Andrade Rojas, MD[2], Samantha Lee Bosco, BS[1], Jeffrey A. Gusenoff, MD[1], Francesco M. Egro, MBChB, MSc, MRCS[1], J. Peter Rubin, MD, FACS, MBA[1], Asim Ejaz, PhD[1].
1University of Pittsburgh, Pittsburgh, PA, USA, [2]Hospital Santa Inés, Cuenca, Ecuador.

INTRODUCTION

Radiation-induced skin atrophy, characterized by reduced thickness, compromised barrier function, and loss of surface area, is a well-documented consequence of high-dose ionizing radiation exposure. These morphological changes weaken the skin's structural integrity, hinder wound healing, and increase susceptibility to secondary injuries and infections. Developing effective interventions to preserve skin morphology and function post-radiation exposure is crucial for maintaining tissue viability and promoting recovery. Metformin, primarily known for its role in managing type 2 diabetes, has demonstrated anti-inflammatory and tissue-preserving properties, making it a promising candidate for mitigating radiation-induced skin atrophy.

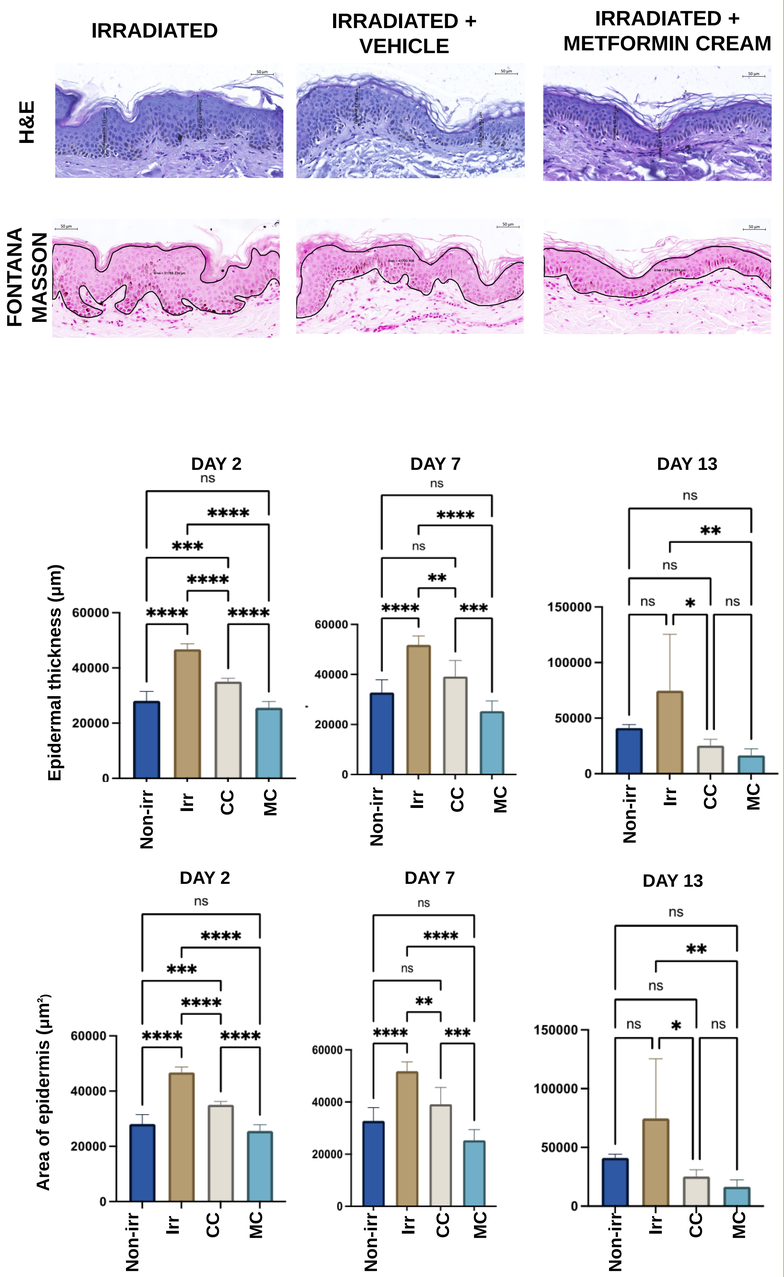
MATERIALS & METHODS

This study aimed to assess the protective effects of topical metformin on skin morphology following X-ray exposure. Human skin flaps maintained on an ex vivo perfusion system were exposed to 10 Gy of X-ray radiation and divided into three groups: irradiation only, irradiation with a control cream, and irradiation with metformin cream. Biopsies were collected at days 2, 7, 11, and 13 post-irradiation, and skin thickness and surface area were measured through histological analysis and image quantification.



XRad320 for X-ray exposure and gross section of the *Ex-vivo* human skin flap showing the various study groups

RESULTS



Metformin-treated skin maintained greater thickness and structural integrity, countering radiation-induced thinning, contraction, and atrophy, likely through its anti-inflammatory effects and extracellular matrix stabilization.

- **Preservation of Skin Thickness and Surface Area:** Metformin-treated skin exhibited significantly greater thickness and surface area compared to untreated irradiated skin, with notable differences observed at later time points.
- **Reduction in Progressive Thinning and Contraction:** Untreated skin showed continuous thinning and contraction over time due to radiation exposure, while metformin treatment mitigated these effects.
- **Maintenance of Epidermal and Dermal Integrity:** Metformin preserved the structural integrity of both the epidermis and dermis, preventing radiation-induced atrophy and degradation.
- **Anti-Inflammatory Effects:** Metformin's anti-inflammatory properties likely contributed to reduced tissue degradation and supported the stability of the extracellular matrix.
- **Enhanced Protection Against Radiation Damage:** The overall protective effects of metformin helped minimize the adverse impact of radiation on skin structure and function.

CONCLUSIONS

- Topical metformin effectively prevents radiation-induced thinning and contraction, preserving both skin thickness and surface area over time.
- Metformin plays a significant role in maintaining the structural integrity of epidermal and dermal layers, reducing radiation-induced atrophy.
- Metformin's anti-inflammatory properties minimize tissue degradation and support extracellular matrix stability, critical for preventing skin damage.
- By reducing apoptosis and supporting DNA repair processes, metformin aids the skin's natural healing and recovery mechanisms post-radiation.
- Metformin shows promise as a therapeutic agent in clinical settings to safeguard skin integrity for patients undergoing radiotherapy or accidental radiation exposure.

Topical metformin is a valuable therapeutic intervention for protecting and maintaining skin integrity post-radiation, offering significant potential in clinical and accidental exposure scenarios.