

The Effect of Conditioned Medium Derived *Wharton's* Jelly Mesenchymal Stem Cell for Diabetic Foot Ulcer: Preliminary Study – Case Series

Ferry Arrochman, Eva Niamuzisilawati, Nurrachmat Muliando, Indah Julianto
*Dermatovenereology Departement Dr. Moewardi General Hospital/Faculty of Medicine Sebelas Maret University,
Surakarta*

Keywords: Wharton's jelly, diabetic foot ulcer.

Abstract: Diabetic foot ulcer (DFU) is the one of long term complications of diabetes melitus with the life time risk up to 25%. The patogenesis of DFU is complicated and multifactorial, resulting from the combined effects of both local and systemic abnormalities. It is a chronic inflammation condition that diabetes melitus it self can increase vascular complications like perifer neuropathy, vascular permeability cause high compartment and triger tissue hypoxia. The failure of diabetic fibroblast to produce VEGF disturb neovascularization then DFU can not recover easily. Topical conditioned medium derived wharton's jelly as the therapeutic strategies in regenerative medicine of diabetic foot ulcer. It is an evolution for DFU regeneration.

1 INTRODUCTION

Chronic ulcers are defined as spontaneous or traumatic lesions, typically in lower extremities that are unresponsive to initial therapy or that persist despite appropriate care and do not proceed towards healing in a defined time period with an underlying etiology that may be related to systemic disease or local disorders (Suthar et al., 2017).

Diabetic foot ulcer are the most common medical complication of patients with diabetes melitus, with an estimated prevalence of 12-15% in diabetes melitus patients (American Diabetes Association). Diabetes mellitus type II (DM2) is a metabolic disorder defined by hyperglycemia due to insulin resistance. In diabetes, chronic skin ulcerations are common on the lower extremities, particularly the foot (Okonkwo & Dipetro, 2017). The diabetic patient with foot ulcer require long-term hospitalization and cary the risk of limb amputation (Mariam et al., 2017).

Diabetes mellitus-associated impaired wound healing severely affects life quality of patients (Dangwal et al., 2015). The hunt for effective therapies to treat the sizable patient population affected by the chronic, non-healing wounds brought on by diabetes has been elusive. While there has been research that has progressed from laboratory, to

clinical trials, and finally to clinical practice, these treatments have failed to be the silver bullet that will heal chronic diabetic wounds (Dangwal et al., 2015).

Wound healing requires a coordinated interplay among cells, growth factors, and extracellular matrix proteins. Central to this process is the endogenous mesenchymal stem cell (MSC), which coordinates the repair response by recruiting other host cells and secreting growth factors and matrix proteins (Julianto & Dindiausti, 2016). This study use messenchimal conditioned media from messenchimal punca cell wharton's jelly. Wharton's Jelly is the primitive mucous, connective tissue of the umbilical cord lying between the amniotic epithelium and the umbilical vessels. First observed by Thomas Wharton in 1656, this gelatinous substance is comprised of proteoglycans and various isoforms of collagen. The main role of the Wharton's Jelly is to prevent the compression, torsion, and bending of the umbilical vessels which provide the bi-directions flow of oxygen, glucose and amino acids to the developing fetus, while also depleting the fetus and placenta of carbon dioxide and other waste products (Taghizadeh et al., 2011).

Mesenchimal punca cell has a specific character that is improve and transdiferensiasi it self to become some cell strain like bone cell, tendo and myosit. On the other hand messenchimal punca cell

can regulate human immunity and inflammation responses. It is very important for wound healing by repair and make inflammation process be faster then there is no chronic healing (Julianto & Rindiastuti, 2016).



Figure 1: Before treatment.

2 CASE

We reported a preeliminary study - case series taken from dermatology outpatient clinic Moewardi hospital Surakarta. The patient is a male 58 years old who is consulted from an orthopedics with DFU. He suffered from diabetes melitus since he was 42 year old. He got DFU for a year. His foot fingers, digiti 2 and 3 has been amputated 6 month ago by orthopedics. We started treated this patient by applicated topical conditioned medium derived *wharton's* jelly mesenchymal stem cell while the ortopedics did debridement.

Photographic documentation was performed by the same investigator and with the same digital camera immediately before (Figure 1) the procedure and after (Figure 2) therapy session

3 DISCUSSION

Chronic wounds (CWs) are by definition 'wounds that have failed to progress through the normal stages of wound healing and therefore enter a pathological state of inflammation. As a result, the healing process is delayed, or incomplete, and does not proceed in a coordinated manner, subsequently

resulting in a poor anatomical and functional outcome (Abbott et al., 2005).

With respect to diabetes, patients with the disease have a 12-25 % lifetime risk of developing a diabetic foot ulcer (DFU) (Singh et al., 2005; Johansson et al., 2008). and 5-8 % require amputation within 1 year (Johansson et al., 2008; Pompers et al., 2008). In fact complications of DFUs are the primary cause of non-traumatic lower extremity amputations with DFUs preceding approximately 85 % of such amputations. Furthermore amputation secondary to DFUs is associated with a high morbidity and mortality rate, with a survival rate as low as 31 % for major limb amputees (Larsson et al., 1998; Miyajima et al., 2006).

SC-CM has a wide range of cytokines and GF related directly to the wound healing process (Table 1). The next phase of recovery involves angiogenesis, whereby molecules such as VEGF, bFGF, EGF and TGF- β promote new blood vessel, sustain the newly formed granulation tissues and help in the survival of endogenous keratinocytes. In the late phase of the wound healing process, GFs such as EGF, GM-CSF and hepatocyte GF (HGF) prompt keratinocytes to migrate from the basal population around the wound edge to cover the lesion and differentiate into squamous keratinizing epidermal cells (Metcalf & Ferguson, 2007).

4 CONCLUSION

Then after treatment we can report that Topical conditioned medium derived wharton's jelly mesenchymal stem cel is an evolution which can regenerate diabetic foot ulcer very well.



Figure 2: After treatment.

REFERENCES

- Abbott, C.A., Garrow, A.P., Carrington, A.L., Morris, J., Van Ross, E.R., Boulton, A.J., 2005. Foot ulcer risk is lower in South-Asian and African-Caribbean

- compared with European diabetic patients in the U.K.: The North-West diabetes foot care study. *Diabetes Care* 28, 1869–1875. doi:10.2337/diacare.28.8.1869
- American Diabetes Association: Diabetes Statistics. Available at: www.diabetes.org/diabetes-statistics.jsp
- Cetrulo, C.L., 2011. Wharton's Jelly stem cells: Future clinical applications. *Placenta* 32. doi:10.1016/j.placenta.2011.06.010
- Dangwal, S., Stratmann, B., Bang, C., Lorenzen, J.M., Kumarswamy, R., Fiedler, J., Falk, C.S., Scholz, C.J., Thum, T., Tschoepe, D., 2015. Impairment of Wound Healing in Patients with Type 2 Diabetes Mellitus Influences Circulating MicroRNA Patterns via Inflammatory Cytokines. *Arteriosclerosis, Thrombosis, and Vascular Biology* 35, 1480–1488. doi:10.1161/ATVBAHA.114.305048
- Jonasson, J.M., Ye, W., Sparén, P., Apelqvist, J., Nyrén, O., Brismar, K., 2008. Risks of nontraumatic lower-extremity amputations in patients with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care* 31, 1536–1540. doi:10.2337/dc08-0344
- Julianto, I., Rindiasuti, Y. 2016. Pengobatan topikal dengan “sekretome” sel punca mesenkim pada penyembuhan luka, Laporan kasus. *Acta. Med. Indones-Indones. J. Intern. Med.* 48(3): 217-220.
- Larsson, J., Agardh, C.-D., Apelqvist, J., Stenstrom, A., 1998. Long Term Prognosis After Healed Amputation in Patients With Diabetes. *Clinical Orthopaedics and Related Research* 350, 149-158. doi:10.1097/00003086-199805000-00021
- Lazarus, G.S., Cooper, D.M., Knighton, D.R., Margolis, D.J., Percoraro, R.E., Rodeheaver, G., Robson, M.C., 1994. Definitions and guidelines for assessment of wounds and evaluation of healing. *Wound Repair and Regeneration* 2, 165–170. doi:10.1046/j.1524-475X.1994.20305.x
- Mariam, T.G. 2017. Prevalence of diabetic foot ulcer and associated factors among adult diabetic patients who attend the diabetic follow-up clinic at the university of gondar referral hospital, north west ethiopia, 2016: institutional-based cross-sectional study. *J Diabetes Res*, 1-6.
- Metcalfe, A.D., Ferguson, M.W.J., 2007. Tissue engineering of replacement skin: the crossroads of biomaterials, wound healing, embryonic development, stem cells and regeneration. *Journal of The Royal Society Interface* 4, 413–437. doi:10.1098/rsif.2006.0179
- Miyajima, S., Shirai, A., Yamamoto, S., Okada, N., Matsushita, T., 2006. Risk factors for major limb amputations in diabetic foot gangrene patients. *Diabetes Research and Clinical Practice* 71, 272–279. doi:10.1016/j.diabres.2005.07.005
- Okonkwo, U.A., Dipietro, L.A., 2017. Diabetes and wound angiogenesis. *International Journal of Molecular Sciences*. doi:10.3390/ijms18071419
- Prompers, L., Schaper, N., Apelqvist, J., Edmonds, M., Jude, E., Mauricio, D., Uccioli, L., Urbancic, V., Bakker, K., Holstein, P., Jirkovska, A., Piaggese, A., Ragnarson-Tennvall, G., Reike, H., Spraul, M., Van Acker, K., Van Baal, J., Van Merode, F., Ferreira, I., Huijberts, M., 2008. Prediction of outcome in individuals with diabetic foot ulcers: Focus on the differences between individuals with and without peripheral arterial disease. *The EURODIALE Study. Diabetologia* 51, 747–755. doi:10.1007/s00125-008-0940-0
- Singh, N., Armstrong, D.G., Lipsky, B. a, 2005. Preventing foot ulcers in patients with diabetes. *JAMA: the journal of the American Medical Association* 293, 217–228. doi:10.1001/jama.293.2.217
- Suthar, M., Gupta, S., Bukhari, S., Ponemone, V., 2017. Treatment of chronic non-healing ulcers using autologous platelet rich plasma: a case series. *Journal of Biomedical Science* 24. doi:10.1186/s12929-017-0324-1