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A Review
The Role of Maggot Debridement Therapy in Wound Healing

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Abstract
The upward trend of diabetes and its complications had taken a big toll on developing countries where big budgets are allocated to manage it. Diabetes-based foot ulcerations have become a nightmare for patients and equally clinicians due to their chronicity and devastating complications. Diabetic foot ulcers (DFU) take a long time to heal and are generally resistant to conventional methods. DFU is commonly associated with high numbers of foot complications such as infection, gangrene, and lower-limb amputations. Despite the technological advancement in chronic wound management, the numbers of preventable foot complications especially amputations of toes and limbs are still on the upward trend as the number of diabetics increases across the globe. Alternative method using sterile maggots of *Lucilia spp* has been much talked about for the past few decades to improve wound healing outcomes and ultimately reduce foot complications. Maggot debridement therapy, commonly known as MDT has been widely used as an alternative tool in the debridement of chronic wounds to remove slough, necrotic tissue from the wound bed. The usage of MDT has produced significant debridement and healing outcomes in diabetic foot ulcers and has been shown to reduce infections and stimulate healing. Despite numerous findings pointing to the relevance of MDT in the treatment protocol of chronic wounds especially DFU, MDT remains the last resort in the process of salvaging limbs.

Introduction
Lower limb amputation has been a devastating impact on diabetics with chronic foot complications. It was reported that a person with diabetes has a 10–30 times greater risk of undergoing lower limb amputation as compared to non-diabetics (Cho et al., 2018). The prevalence of lower limb amputation is escalating across the globe and continues to be a healthcare burden and contributing to morbidity and mortality (Lavery et al., 2016). Since the number of diabetes is increasing globally, incidences of diabetic foot ulcers were on the upward trend too (Hussein, 2015; Tallis et al., 2013). As mentioned by Pedras, Carvalho, & Pereira. (2016), the risk of a patient with diabetes developing a foot ulcer throughout life can reach up to 25%. It was reported that every 30 seconds a lower limb is being amputated somewhere in the world due to diabetes-based foot complications. Therefore, diabetic foot ulcers pose a great threat to morbidity and mortality (Hoogeveen., 2015; Nube et al., 2016). Therefore, urgent interventions are required to manage and prevent foot complications which could lead to lower limb amputations. The impact of amputation not only affects the patient but also burdens healthcare finance in developing countries especially (Arifin et al., 2017). The majority of the foot complications and amputations can be avoided if diabetic foot ulcer is treated with an effective wound healing strategy since chronicity of diabetic foot ulcer delays wound closure (Cazander, Gottrup, & Jukema, 2009). The resistance of diabetic foot ulcers to conventional methods contributes greatly to massive foot complications, amputation, and mortality. Hence, looking back into the past has given much light in addressing the current foot complications such as infection, antibiotic resistance, gangrene, and amputations. One of the modalities which have produced positive healing outcomes in chronic wounds since World War II is maggot therapy or maggot debridement therapy, commonly known as MDT (Raposio, Director, Bortolini, Maistrello, & Grasso, 2017; Sherman, 2014; Shi & Shofler, 2014).

Background: Maggot Debridement Therapy

Alternative method using biological agents such as maggot is commonly known as biosurgery, maggot therapy, or MDT. This type of debridement method is referring to the application of medical-grade sterile larvae on wounds to expedite the debridement process and stimulate healing (Jordan et al., 2018). MDT had been indicated for sloughy, necrotic, non-exposed bones, abscess, non-profusely bleeding, and infected but non-life-threatening infected wounds that require urgent surgical debridement (Cazander et al., 2009; Gottrup & Apelqvist, 2012; Sherman, 2009). Clinical observations in previous studies had concluded that MDT is a promising alternative method to debride, disinfect, and stimulate the healing of chronic wounds (Choudhary et al., 2016). Furthermore, MDT had been successful in cases where conventional debridement methods failed to yield a positive result in chronic wounds (Bazaliński et al., 2019; Naik & Harding, 2017; Mudge et al., 2014). Over the years, MDT had been reported to have a success rate of 80-90% in the treatment of chronic wounds since the introduction of maggots decades ago (Linger et al., 2016). Some studies had shown MDT to be mostly used as the last option in limb salvaging in DFU which is a matter of concern (Opletalová et al., 2012; Paul et al., 2009; Steenvoorde et al., 2007).

Wound infestations with maggots are not new and had been observed for centuries. Maggots or larvae of certain flies are known to feed on the dead tissue of animals and humans. Some maggots ingest the tissue of live animals or humans to cause myiasis. However, there 18 are maggots of flies *Lucilia sericata,* belonging to the family of Calliphoridae which were proven to produce positive wound healing outcomes (Gupta, 2008; R A Sherman, Sherman, Gilead, Lipo, & Mumcuoglu, 2001). *Lucilia sericata,* a common green bottle fly is a blowfly, and its sister species *Lucilia cuprina* had shown to be useful in debriding slough and necrotic tissue from chronic wounds (Sherman, Hall, & Thomas, 2000). The life cycle of *Lucilia sericata* goes into four stages; egg, larva (3 instars), pupa, and adult fly. A female green bottle fly could lay almost 200eggs at one time and 1000 eggs within a week. The eggs are yellowish and slightly pale and they normally hatch in 8 to 24 hours after being deposited onto a moist host. They hatch into larva of 2mm size which go through three instar stages. The instar could grow up to 1cm in length before entering into the pupa stage in a dry environment and changing into the adult stage (imago) (Cowan, Stechmiller, Phillips, Yang, & Schultz, 2013). *Lucilia sericata* is found throughout the world with a temperate climate such as in America and Europe whereas *Lucilia cuprina* is found in tropical countries such as Malaysia. Similar appearance and morphological characteristics are observed in *Lucilia sericata* and *Lucilia cuprina*. The adult fly is about 810mm and usually in metallic green and copper green whereas the mouth is yellowish. The morphology of the fly includes three cross-grooves on the thorax with short, sparse black bristles. Light brown veins are prominent on the wings whereas the legs and antennae are black (Williams et al., 2014). The application of sterile larvae of these green bottle fly species, known as maggot therapy was able to remove slough and dead tissue from the wounds due to the nature of feeding by the larvae. Maggot debridement therapy or MDT has been used for medical and forensic sciences for decades (Čičková, Čambal, Kozánek, & Takáč,

History of Sterile Maggots

The utilization of insects for treatment purposes in wound healing started hundreds of years ago across different cultures. Observations on the effect of maggots in promoting wound healing were dated back to World War 1. It was reported that maggots accelerated the granulation of tissues in the wounds of soldiers (Mumcuoglu, 2001; Sherman, Hall & Thomas, 2000). There was also a historical perspective of MDT dating back to the aborigines in Australia and Maya tribes in Central America. Evidence of the usage of maggots for wound healing was also demonstrated in the ancient old paintings of Mayans, Burmese, Chinese, and aborigines of Australia ((Beasley & Hirst, 2004; Wollina et al., 2002; Karte, Herold, & Looks, 2000). In the 19th century, the clinical usage of sterile larvae of the greenbottle blowfly, *Lucilia sericata* was reported in the treatment of children with osteomyelitis. The clinical outcome showed complete debridement, reduction of pathogenic organisms, reduced odor, and increased rates of healing within 2 months (Baer, 1931). The clinical finding was the first to be published on the effectiveness of maggots in the treatment of osteomyelitis and was the initiator for many other successful studies with sterile maggots of Lucilia sericata (Beasley & Hirst, 2004; Wolff & Hansson, 2003; Sherman et al., 2000). Maggots were widely used for chronic wound management until 1940 across the United States of America and Europe. However, the utilization of maggots for wound healing started to decline with the discovery of antibiotics to control numerous infections (Wollina et al., 2002b; Courtenay, Church & Ryan, 2000). Nevertheless, maggots made a comeback due to the emergence of antibiotic resistance in chronic wounds in the late 1990s

(Fleischmann, Grassberger & Sherman, 2004). It was mentioned that the resurgence of maggots can be attributed to the methicillin-resistant *Staphylococcus aureus* towards penicillin in the late 1990s which also contributed to the increased number of non-healing wounds. In the late 1980s, the United States of America and Europe started using sterile maggots of *Lucilia sericata* which was available in a temperate climate to counter the effect of bacterial resistance for the treatment of infected chronic wounds (Sherman, 2002). Based on the scientific evidence and reports published on MDT, the United States Food & Drug Authority (USFDA) (2004) approved the registration of Lucilia sericata as a medical device in 2004 (Cazander, Gottrup, & Jukema, 2009). MDT was approved to be used for pressure ulcers, venous stasis ulcers, neuropathic foot ulcers, and non-healing traumatic postsurgical wounds (Cambal, 2006; Lipsky, 2004). According to published articles in recent times, MDT had created much interest among clinicians with the rise of hard-to-heal chronic wounds such as foot complications, and lower-limb amputations (Gottrup et al., 2014; Marineau, Herrington, Swenor & Eron, 2011; Sherman, 2009). However, not all species of flies are safe and effective to be used for wound debridement. Greenbottle flies *Lucilia sericata* were mainly found in temperate countries and most commonly used in the majority of studies. Research on *Lucilia cuprina* which is largely found in tropical countries has also been forthcoming, especially in Malaysia which indicated that MDT could play a pivotal role in the debridement of sloughy DFU and enhance healing (Azad, Wan Azizi, Adham, & Yee, 2016; Marimuthu & Makhtar, 2020; Paul et al., 2009). Despite MDT consistently demonstrating prominent and promising positive outcomes for the past two decades in the treatment of chronic wounds, MDT is not considered as the first line of debridement modality in the majority of healthcare settings (Narres et al., 2017; Linger et al., 2016; Andrews, Houdek, & Kiemele, 2015).

The striking effect of maggots is based on their three major modes of action which include debridement, disinfection, and stimulation of wound healing (Bazaliński et al., 2019).

Debridement

Past evidence showed that one of the reasons for the delay in chronic wound healing was the failure of debridement. The sooner the debridement is done, the faster the healing takes place (Gray & M., 2008). Removal of devitalized tissue in the debridement process stimulates angiogenesis, granulation, epithelialization, and ultimately wound closure (Lim et al., 2017). It was mentioned in previous studies that the absolute reason behind the usage of maggots was because they only consumed slough, necrotic tissue, and non-viable tissue while leaving healthy structures intact (Borst, Goettler, Kachare, & Sherman, 2014; Tantawi, Williams, & Villet, 2010). It was reported that maggots used mechanical mechanisms to remove slough from the wound bed. The maggot’s body is covered with tiny spines that indirectly scrape the wound base as it crawls and loosens the slough or necrotic tissue. The mandibles are also known as mouth hooks of the maggot that were used to move, crawl, and probe every corner of the wound in search of slough or non-viable tissue to feed on (Vilcinskas, 2011; Chan et al., 2007; Chambers et al., 2003). Recent clinical findings reported that the secretion of maggots produced three proteolytic enzymes that are responsible for degrading the extracellular matrix, breaking down the slough, necrotic tissue into semi-solid form, and ingested with minimal trauma. These enzymes were responsible for the efficient debridement effect of maggots to prepare the wound bed for further treatment and closure (Abdolmaleki, Razi, Moghaddam, & Farahani, 2015; Valachova, Majtan, Takac, & Majtan, 2014). A body of evidence had concluded MDT is a safe, highly effective debridement tool and is highly recommended for maintenance debridement till wound closure (Leaper et al., 2012; Muldoon, 2013).

Disinfection

The majority of clinical studies had reported infections as common in almost all chronic wounds and tended to slow the healing process and impede wound closure (Mavrogenis et al., 2018; Uçkay, Aragón-Sánchez, Lew, & Lipsky, 2015; Musa & Ahmed, 2012). Few studies had reported maggot to be a potent disinfection tool (Daeschlein et al., 2017; Gilead, Mumcuoglu, & Ingber, 2012; Hall, 2010). Maggots’ secretion is demonstrated to contain deoxyribonuclease (DNAse) which is indicated for the degradation of human microbial DNA in the non-viable tissue on the wound bed and gets ingested by the maggot (Brown et al., 2012). Clinical evidence had emerged that DNAse also inhibits the growth of microbial and biofilm. Earlier reports showed the secretion of maggots contained ammonia with a broad spectrum of bactericidal effects to increase wound pH and inhibit bacterial growth (Choudhary et al., 2016; Čičková et al., 2013). The investigation also revealed that the secretion of ammonia by maggots impedes bacterial growth of methicillin-resistant *Staphylococcus aureus* (MRSA), Streptococci, and Pseudomonas (Margolin & Gialanella, 2010). Thus, the efficacy of MDT is further enhanced with the ability of MDT to disinfect chronic wounds. Recent studies had shown maggots' ability to remove biofilm from the wound bed (Bohova et al., 2014). Biofilm is a big problem in the treatment of chronic wounds whereby it is made up of one or more species of bacterial cells which creates a polymeric matrix and is very difficult to be penetrated (Gomes, Teixeira, Ferraz, Prudencio, & Gomes, 2017). The secretion and excretion had been reported to act against the biofilm of Staphylococcus aureus and *Pseudomonas aeruginosa* (Yan et al., 2018; Cazander et al., 2012; Zhang et al., 2009). Previous clinical observations had shown antibiotic-free days were observed in foot ulcers treated with MDT as compared to the conventional debridement method (Armstrong et al., 2005; Paul et al., 2009; Tian, Liang, Song, Zhao, & Yang, 2013). Clinical observations on the disinfection factor of MDT are forthcoming and are being researched currently for managing bacterial resistance and biofilm (Jordan et al., 2018).

Healing Enhancement

Complementing the role of maggots in the debridement and disinfection of chronic wounds is the stimulation of wound healing. One study indicated that the enhancement of wound healing by MDT was due to growth factors & growth stimulating factors contained in the excretion & secretion of the maggots (Stadler et al., 2015). Tissue growth stimulation by maggots was investigated, and it was reported that secretion & excretion of maggots increased fibroblast proliferation which contained a wide array of matrix metalloproteinase (MMP). These MMPs are crucial for tissue regeneration, remodeling, and wound healing. Secretion and excretion of maggots also enhanced vascular perfusion and tissue oxygenation (Yan et al., 2018). In addition, secretions of maggots also increase the pH of the wound bed and make the environment less conducive for bacteria in the elimination of bacteria from the wound bed. Resolving chronic wound healing with continuous debridement and disinfection with MDT until wound closure could stimulate positive wound healing outcomes (Marineau et al., 2011).

There were isolated reports of tingling sensation, pain, itch, and bleeding in patients treated with MDT (Gilead, Mumcuoglu, & Ingber, 2012). Arguably, other studies on MDT were shown to reduce pain (Tanyuksel et al., 2005; Kitching, 2004). Pain had always been a subjective and controversial subject related to MDT since other underlying causes could contribute to the presence of pain such as ischemia. (Steenvoorde et al., 2005; Jones, Green, & Lillie, 2011; Mccaughan, Cullum, & Dumville, 2015; Mirabzadeh et al., 2017).

Conclusion

Recent findings have shown that wounds achieve faster healing when debrided with MDT compared to conventional methods (Petherick et al., 2006). The poor window of usage in clinical settings is a matter of concern. Nevertheless, clinical experiences with MDT were abundant and maggots had been effective in saving limbs (Davydov, 2011; Steenvoorde & van Doorn, 2008; Steenvoorde et al., 2007). The effectiveness of MDT in the treatment of diabetic foot ulcers had been quite promising. Pieces of evidence on MDT are present but it remains a question mark why it is yet to be used by clinicians on a larger scale in clinical settings. It is still far-fetched to be integrated into the treatment protocol for diabetic foot ulcers in healthcare settings (Gottrup & Jorgensen, 2011). It is a known fact based on previous findings that delayed wound healing increases the risk for foot complications in diabetics (Thomas et al., 2005). Diabetic foot ulcers could not achieve optimal debridement effect with non-surgical conventional methods (Pritchard & Nigam, 2013; Yazdanpanah et al., 2015). With the increasing trend of foot complications and lower limb amputations, exploration of MDT in the treatment of diabetic foot ulcers is very much needed (Ahmed Hassan Fawzi El-tawdy., 2016; Ousey et al., 2018). The majority of the patients with diabetic foot ulcer has a lot to lose when the conventional debridement method fails to produce positive healing outcomes. To achieve the optimal benefit of MDT, sloughy wounds should be considered to be debrided with MDT in the early process of managing chronic wounds and not only consider it as the last option, especially in Malaysia where sterile maggots of *Lucilia cuprina* is readily available.

There may be a few factors that make MDT take a back seat and one of them is less exposure to the effectiveness of MDT from the clinician and also patient perspective. Secondly, the preference of clinicians to proceed with surgical debridement as the result of debridement is immediate; despite many failing to stop the recurrence of slough and necrotic tissue on the wound bed. Thirdly, could be a cost factor since maggots needs to be purchased by the patient. Hence, it is recommended that healthcare policy makers integrate MDT in the treatment protocol for chronic wounds such as diabetic foot ulcer and subsidize the MDT for the patients in the public healthcare settings. On another note, research on cost-effectiveness of using MDT versus other debridement modalities needs to be performed to ascertain the practicality of prescribing MDT for patients to bring a more convincing potency of MDT from the clinicians' perspective. The healing of diabetic foot ulcers is very much dependent on wound bed preparation to stimulate the healing process. Debridement is an essential part of wound bed preparation in chronic wounds to remove slough and non-viable tissue which could impede the wound healing process. MDT had stood the test of time and shown promising results in the debridement of chronic wounds at large. Hence, MDT's window of usage should be expanded to the best medical advantage to reduce foot complications and prevent amputations.

References

1. Ahmed Hassan Fawzi El-tawdy, B., Abdel Hamed Ibrahim, E., Shokryabdallah, E., Mahmoud Aly Sakhawy, E. AL, & Morsy, T. A. (2016). MAGGOT DEBRIDEMENT THERAPY (MDT): IT IS SAFE AND ECONOMIC FOR TREATING A DIABETIC FOOT ULCER. In *Journal of the Egyptian Society of Parasitology* (Vol. 46).
2. Arifin, N., Hasbollah, H. R., Hanafi, M. H., Ibrahim, A. H., Wan Abdul Rahman, W. A., & Che Aziz, R. (2017). Provision of prosthetic services following lower limb amputation in Malaysia. *Malaysian Journal of Medical Sciences*, *24*(5), 106–111. https://doi.org/10.21315/mjms2017.24.5.12
3. Azad, A. K., Wan Azizi, W. S., Adham, S. A., & Yee, B. L. (2016). Maggot debridement therapy for diabetic foot ulcer : Experience from Maggot treatment Centers. *Asian Journal of Pharmacy and Pharmacology*, *2*(1), 23–25.
4. Cazander, G., Gottrup, F., & Jukema, G. N. (2009). Maggot therapy for wound healing: clinical relevance, mechanisms of action and future prospects. *Journal of Wound Technology*, *5*(July), 18–23.
5. Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*. https://doi.org/10.1016/j.diabres.2018.02.023
6. Davydov, L. (2011). Maggot therapy in wound management in modern era and a review of published literature. *Journal of Pharmacy Practice*, *24*(1), 89–93. https://doi.org/10.1177/0897190010366938
7. Hoogeveen, R. C., Dorresteijn, J. A. N., Kriegsman, D. M. W., & Valk, G. D. (2015). Complex interventions for preventing diabetic foot ulceration. *Cochrane Database of Systematic Reviews*, Vol. 2015. https://doi.org/10.1002/14651858.CD007610.pub3
8. Hussein, Z., Taher, S. W., Gilcharan Singh, H. K., & Chee Siew Swee, W. (2015). Diabetes Care in Malaysia: Problems, New Models, and Solutions. *Annals of Global Health*, *81*(6), 851–862. https://doi.org/10.1016/J.AOGH.2015.12.016
9. Lavery, L. A., Davis, K. E., Berriman, S. J., Braun, L., Nichols, A., Kim, P. J., … Attinger, C. (2016). WHS guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair and Regeneration : Official Publication of the Wound Healing Society [and] the European Tissue Repair Society*, *24*(1). https://doi.org/10.1111/wrr.12391
10. Marimuthu, P., & Makhtar, A. (n.d.). *Effectiveness of Maggot Debridement Therapy (Luciliacuprina) In the Treatment of Diabetic Foot Ulcer*. *9*(2), 50–56. https://doi.org/10.9790/1959-0902025056
11. Ousey, K., Chadwick, P., Jawien, A., Tariq, G., Nair, H. K. R., Lázaro-Martínez, J. L., … Moore, Z. (2018). Identifying and treating foot ulcers in patients with diabetes: saving feet, legs and lives. *Journal of Wound Care*, *27*, S1–S52. https://doi.org/10.12968/jowc.2018.27.Sup5.S1
12. Paul, A. G., Ahmad, N. W., Lee, H., Ariff, A. M., Saranum, M., Naicker, A. S., & Osman, Z. (2009). Maggot debridement therapy with Lucilia cuprina: A comparison with conventional debridement in diabetic foot ulcers. *International Wound Journal*, *6*(1), 39–46. https://doi.org/10.1111/j.1742-

481X.2008.00564.x
13. Paul, A. G., Ahmad, N. W., Lee, H. L., Ariff, A. M., Saranum, M., Naicker, A. S., … Dompmartin, A. (2010). Maggot therapy for wound debridement: A randomized multicenter trial. *Archives of Dermatology*, *148*(3), 43–51. https://doi.org/10.1111/wrr.12127
14. Pedras, S., Carvalho, R., & Pereira, M. da G. (2016). Sociodemographic and clinical characteristics of patients with diabetic foot ulcer. *Revista Da Associacao Medica Brasileira (1992)*, *62*(2), 171–178. https://doi.org/10.1590/1806-9282.62.02.171
15. Petherick, E., O'Meara, S., Spilsbury, K., Iglesias, C., Nelson, E., & Torgerson, D. (2006). Patient acceptability of larval therapy for leg ulcer treatment: a randomised survey to inform the sample size calculation of a randomised trial. *BMC Medical Research Methodology*, *6*(1), 43. https://doi.org/10.1186/1471-2288-6-43
16. Pritchard, D. I., & Nigam, Y. (2013). Maximising the secondary beneficial effects of larval debridement therapy. *Journal of Wound Care*, *22*(11), 610–616. https://doi.org/10.12968/jowc.2013.22.11.610
17. Raposio, E., Director, F., Bortolini, S., Maistrello, L., & Grasso, D. A. (2017). Larval Therapy for Chronic Cutaneous Ulcers: Historical Review and Future Perspectives. *REVIEW Wounds*, *2929*(1212).
18. Sherman, R. A. (2014). Mechanisms of maggot-induced wound healing: what do we know, and where do we go from here? *Evidence-Based Complementary and Alternative Medicine : ECAM*, *2014*, 592419. https://doi.org/10.1155/2014/592419
19. Shi, E., & Shofler, D. (2014). Clinical focus Maggot debridement therapy: a systematic review Maggot therapy and historical evidence. In *British Journal of Community Nursing* (Vol. 19).
20. Steenvoorde, P., & van Doorn, L. P. (2008). Maggot debridement therapy: serious bleeding can occur: report of a case. *Journal of Wound, Ostomy, and Continence Nursing : Official Publication of The Wound, Ostomy and Continence Nurses Society*, *35*(4), 412–414. https://doi.org/10.1097/01.WON.0000326662.32390.72
21. Steenvoorde, Pascal, Jacobi, C. E., Van Doorn, L., & Oskam, J. (2007). Maggot debridement therapy of infected ulcers: Patient and wound factors influencing outcome - A study on 101 patients with 117 wounds. *Annals of the Royal College of Surgeons of England*, *89*(6), 596–602. https://doi.org/10.1308/003588407X205404
22. Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson, J. E., Waycaster, C., Slade, H. B., & Collagenase Diabetic Foot Ulcer Study Group. (2013). Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. *Clinical Therapeutics*, *35*(11), 1805–1820. https://doi.org/10.1016/j.clinthera.2013.09.013
23. Yazdanpanah, L., Nasiri, M., & Adarvishi, S. (2015). Literature review on the management of diabetic foot ulcer. *World Journal of Diabetes*, *6*(1), 37–53. https://doi.org/10.4239/wjd.v6.i1.37