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Research Article

The Role of ECM and MMPS in Acute Wound Healing Process

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Abstract: ***Introduction:*** Skin, the largest organ in the human body, plays a crucial role in the sustenance of life through the regulation of water and electrolyte balance, thermoregulation, and by acting as a barrier to external noxious agents including micro-organisms A wound is defined as a break in the epithelial integrity of the skin. However, the disruption could be deeper, extending to the dermis, subcutaneous fat, fascia, muscle or even the bone. Wound is not just a defect in tissue, it is an insult initiated dynamic biological process. Wound healing involves the four overlapping but well-defined phases of haemostasis, inflammation, proliferation and remodeling.It involves a continuous and reciprocal interaction of variety of cells and Extracellular matrix (ECM) components. ECM not only acts as scaffold for healing but also involves in signaling, binding and acts as an activating substrate that interacts with highly organized wound healing process. There is a dynamic and reciprocal interaction among ECM and involving cells, cytokines, growth factors, Matrix Metallo Proteinases(MMP) and tissue inhibitors of metalloproteinases(TIMP). The controlled degradation of ECM by extracellular proteases particularly MMP/TIMP and serene proteases forms the basis of wound healing.understanding wound healing at molecular level after discovery of many molecules – Growth factors, cytokines, MMP/TIMP. Matrix metalloproteinases can be studied by various techniques- ELISA, Western Blot, Immunohistochemistry, Immunofluoresence, Zymography, Gel electrophoresis. There are many studies between MMP, TIMP and chronic wounds, levels of MMP,TIMP between acute and chronic wounds. Understanding where, when, how MMP activity is involved in acute wound healing has implications for acute wound management. Hence an attempt is made to study the initial tissue expression of MMP 9 and TIMP 1 by immunohistochemistry in acute surgical wounds and their relation to wound healing. A wound is defined as a break in the epithelial integrity of the skin. Wounds can be acute or chronic. Acute wounds achieve normal healing. When they fail to heal, becomes chronic. The process of wound healing involves a complex interaction between numerous cell types, extracellular matrix(ECM) molecules, and soluble mediators including growth factors and cytokines.

Keywords: ECM – Extra cellular Matrix, MMP- Matrix Metallo Proteinases, TIMP - tissue inhibitors of metalloproteinases, ELISA- Enzyme-Linked Immunosorbent Assay.

INTRODUCTION

Skin, the largest organ in the human body, plays a crucial role in the sustenance of life through the regulation of water and electrolyte balance, thermoregulation, and by acting as a barrier to external noxious agents including micro-organisms. A wound is defined as a break in the epithelial integrity of the skin. However, the disruption could be deeper, extending to the dermis, subcutaneous fat, fascia, muscle or even the bone. Wound is not just a defect in tissue, it is an insult initiated dynamic biological process.(1)

Wound healing involves the four overlapping but well-defined phases of haemostasis, inflammation, proliferation and remodeling.(2) It involves a continuous and reciprocal interaction of variety of cells and Extracellular matrix (ECM) components. ECM not only acts as scaffold for healing but also involves in signaling, binding and acts as an activating substrate that interacts with highly organized wound healing process.(3)

There is a dynamic and reciprocal interaction among ECM and involving cells, cytokines, growth factors, MatrixMetalloProteinases(MMP) and tissue inhibitors of metalloproteinases(TIMP). The controlled degradation of ECM by extracellular proteases particularly MMP/TIMP and serene proteases forms the basis of wound healing.

A completely healed wound, usually seen after simple injury, is defined as one that has returned to its normal anatomical structure, function and appearance within a reasonable period of time. Some wounds fail to heal in a timely and orderly manner, resulting in chronic, non-healing wounds. .Many factors affect wound healing , like Surgeon factors – experience, type of incision, suture material, Patient factors – age, nutrition status, sepsis , immunological component, Systemic disorders – Type II DM , Connective tissue disorders, Chronic use of steroids, Local factors- infection, foreign body, radiation.(4,5)

A number of other factors contribute to disrupted wound healing like growth factors and protease-antiprotease balance (MMP/TIMP). For a wound to heal there should be proper interaction of MMP and TIMP. Earlier, MMPs and TIMPs are thought to be involved in remodeling stages of wound healing, but recent evidence suggests that they involved in all phases of wound healinglike inflammation, reepithelialization and cell migration.(6,7) Hence it can be stated that MMPs and TIMPs have an effect on wound healing.

Various studies have been made in understanding wound healing at molecular level after discovery of many molecules – Growth factors, cytokines, MMP/TIMP. Matrix metalloproteinases can be studied by various techniques- ELISA, Western Blot, Immunohistochemistry, Immunofluoresence, Zymography, Gel electrophoresis.(8) There are many studies between MMP, TIMP and chronic wounds, levels of MMP,TIMP between acute and chronic wounds. Studies shown that elevated levels of MMP 9 associated with chronic wounds. The relationship between MMP activity and acute wounds is not very clear and requires further investigation. Understanding where, when, how MMP activity is involved in acute wound healing has implications for acute wound management. Hence an attempt is made to study the initial tissue expression of MMP 9 and TIMP 1 by immunohistochemistry in acute surgical wounds and their relation to wound healing.

MATERIALS AND METHODS

Study site:
Kamineni Hospitals, LB Nagar, Hyderabad

Study population:
Patients of all age, either sex, admitted under the Department of General Surgery, Kamineni Hospitals, Hyderabad and undergoing open abdominal surgeries.

Study Design
This is a prospective observational study.

Sample size: 50 subjects
This is a prospective observational study. The primary purpose of this study is to observe the initial expression of MMP 9 and TIMP 1 in acute wounds and their relation to wound healing. No sample size has been calculated.
Based on the admissions in the past 4 years it is noted that approximately 120 cases who fulfill the inclusion criteria got admitted. Sample size was expected to be between 50 - 60. During time period of my study total of 62 patients who fulfill inclusion criteria got admitted and operated. Excluding deaths and patients who were not in followup, it was 50 patients that was included in my study.

Inclusion criteria:
All patients undergoing open abdominal surgeries (elective and emergency)

Exclusion criteria:
1. Traumatic wounds
2. Patients referred from outside centres with abdominal wound dehiscence or non healing abdominal wounds.

Methodology
Sample collection:
Wound biopsy will be taken from the wound margin including skin and subcutaneous tissue measuring 5 x 5 mm at two intervals.

a. Immediately after giving skin incision
b. Before closure of incision (after surgical procedure)

Method of staining:
Staining of MMP 9 and TIMP 1 was done by Immunohistochemistry.
MMP 9 and TIMP 1 ANTIBODIES :

- Company : Leica Biosytems Newcastle Ltd., Newcastle, United Kingdom

- Supplier – Labindia Instruments Pvt. Ltd., Hyderabad, Andhra Pradesh
- 0.1ml Novo CastraTM Lyophilized Mouse Monoclonal Antibody Matrix Metalloproteinase 9 (NCL-MMP9-439) and NCL-TIMP1-485 for TIMP 1
- Novolink TM Mini Polymer Detection System (RE7290-K).
- Immunohistochemistry Scoring system for MMP-9 and TIMP was used.

Method of staining :
Biopsies were sent in a formalin fixative and were paraffin embedded.

Endogenous peroxidase activity is neutralized using the Peroxidase Block. This is followed by application of the NovocastraTM Protein Block to reduce non-specific binding of primary and polymer.

The section is subsequently incubated with optimally diluted primary antibody. This is washed with TBS (50mM tris-buffered saline)buffer for 5 minutes. Post Primary (Rabbit anti Mouse IgG) is then used to detect mouse antibodies. The NovolinkTM Polymer recognizes rabbit immunoglobulins, it detects the post primary and any tissue-bound rabbit primary antibodies. Sections are further incubated with the substrate/chromogen, 3,3' - diaminobenzidine (DAB), prepared from DAB Chromogen and NovolinkTM DAB Substrate Buffer (Polymer). This is washed with TBS buffer for 5minutes.

Incubated with peroxidase stained that produces a visible brown precipitate at the antigen site. Sections are washed under running tap water. Sections are counterstained with Hematoxylin and coverslipped. Results are interpreted using a light microscope and staining was given as weak or strong by comparing with controls.
It was analysed by pathologist and score will be given as follows

SCORE	STAINING
0	No
1+	Weak
2+	Mild
3+	Moderate
4+	Strong

MMP 9 AND TIMP 1 tissue expression is graded into weak (0, 1+, 2 +) and strong(3 +, 4+).
Wound status at 7th POD is graded clinically as healed or non healed by using Southampton wound grading score.[53]
Southampton wound grading score:

0 Normal healing
I Normal healing with mild bruising
Ia Some bruising
Ib Considerable bruising
Ic Mild erythema
II Erythema plus other signs of inflammation
IIa At one point
IIb Around sutures
IIc Along wound
IId Around wound
III Clear orhemoserous discharge
IIIa At one point (<2 cm)
IIIb Along wound (> 2 cm)
IIIc Large volume
IIId Prolonged(> 3 days)
Major complications
IV Pus
IVa At one point only (< 2 cm)
IVbAlong wound (> 2 cm)
V Deep or severe wound infection with or without tissue breakdown
Wound is graded as healed (Southampton grading 0,I) or non healed (Southampton grading II, III, IV, V)

Statistical Methodology:

Comparision between variables were made using Odds ratio for TIMP, MMPS vs wound status.
The odds ratio (OR), its standard error and 95% confidence interval are calculated according to Altman, 1991.
Test of significance: the P-value is calculated according to Sheskin, 2004.
BMI of ≥ 30 is considered as obese

DM into diabetic / non diabetic , MMP tissue expression into weak (0, 1+, 2 +) and strong(3 +, 4+) and wound status – healed/nonhealed.

PHOTOS

Figure 9 :Biopsy of wound tissue

Figure 10: Tissue specimen was sent to pathology lab for immunohistochemistry

Immunohistochemistry (IHC
WOUND STATUS AT 7TH POD

Figure 18: Healed wound

Showed weak expression of MMP 9 and strong expression of TIMP 1 before skin closure

Figure 19: Non healing wound

Showed strong expression of MMP 9 and weak expression of TIMP 1 before skin closure

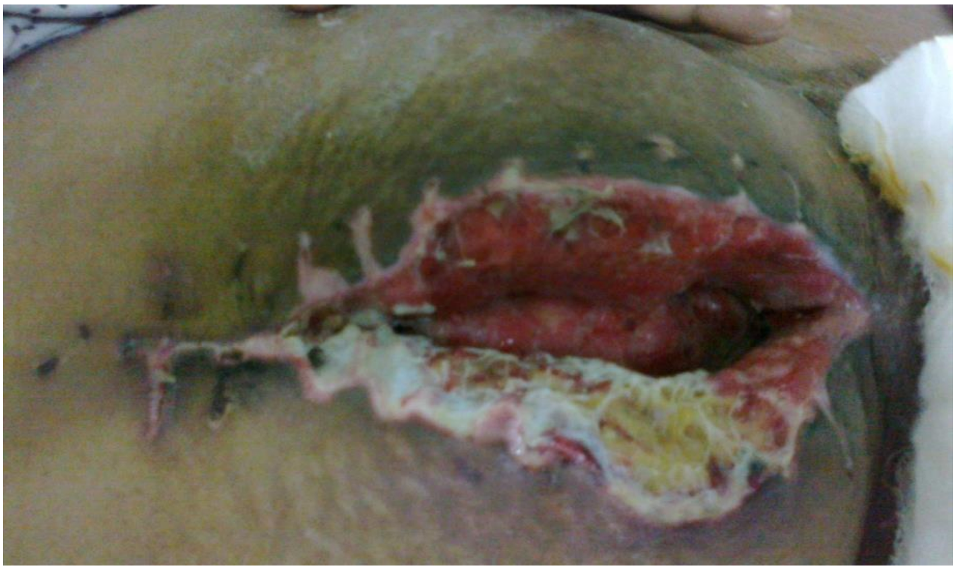
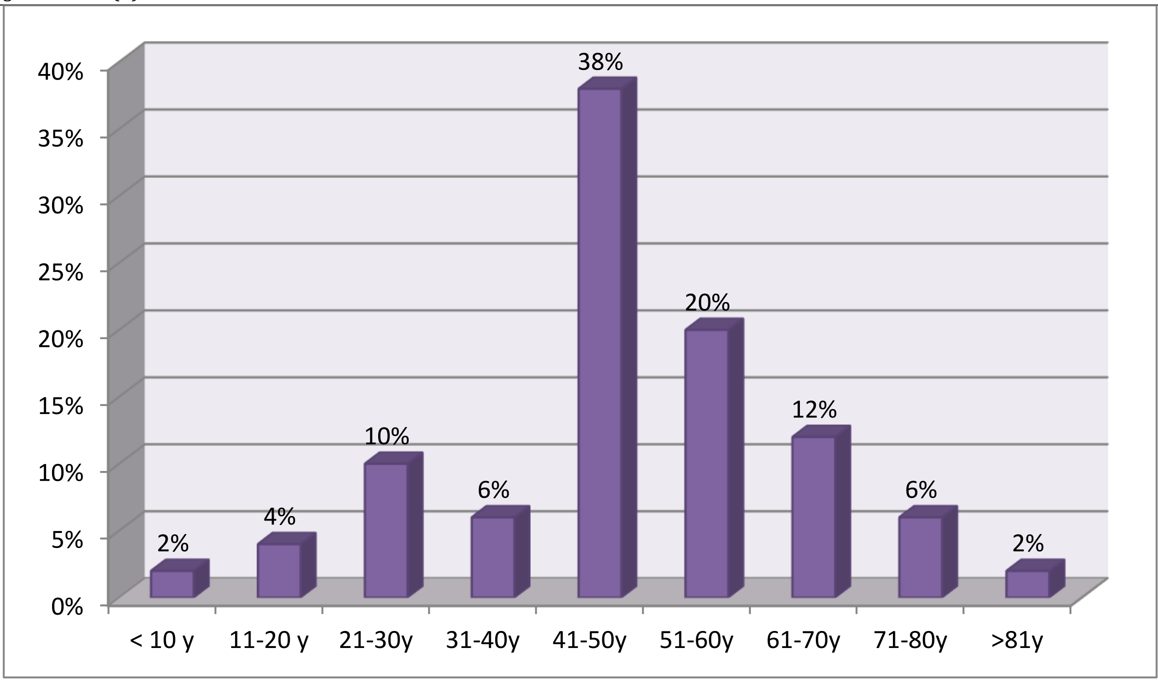


Figure 20: Non healing wound

Showed strong expression of MMP 9 and weak expression of TIMP 1 before skin closure

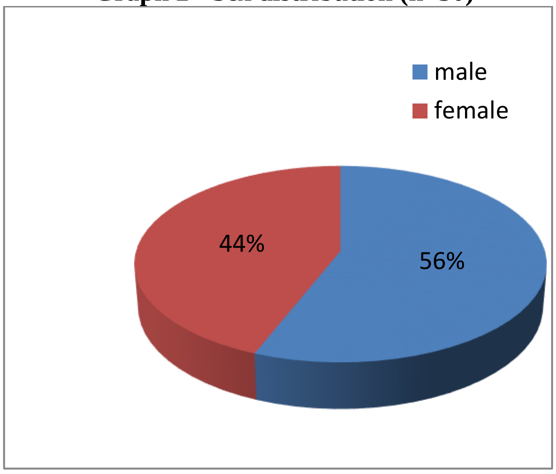
RESULTS

Graph 1 - Age distribution – age ranged from 1 year to 82 years (n=50)



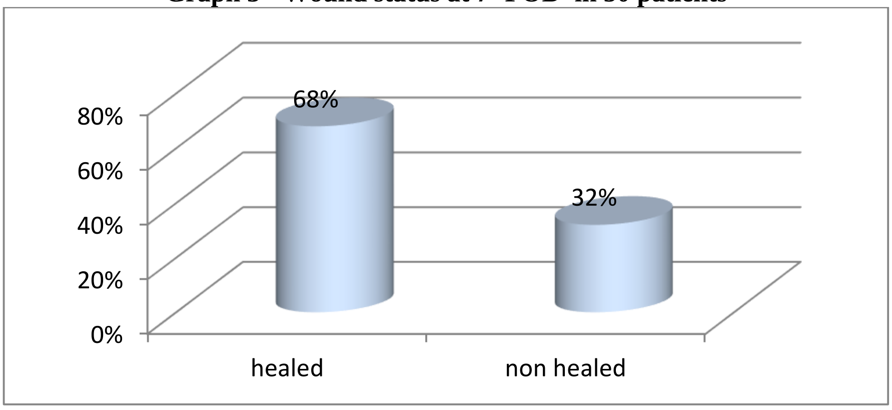
Bar diagram showing age distribution of 50 patients

Graph 2 - Sex distribution (n=50)



Pie diagram showing sex distribution of 50 patients

Graph 3 - Wound status at 7[th]POD in 50 patients



At 7[th] POD 68% of patients had normal healed wounds and 32% of patients showing non healing wounds

DISCUSSION

A wound is defined as a break in the epithelial integrity of the skin. Wounds can be acute or chronic. Acute wounds achieve normal healing. When they fail to heal, becomes chronic.

The process of wound healing involves a complex interaction between numerous cell types, extracellular matrix(ECM) molecules, and soluble mediators including growth factors and cytokines.

Many factors influence wound healing, these can be at molecular level too. Among them matrix metalloproteinases(MMP) and their inhibitors(TIMP) play a role in wound healing.
Among the many gene products that are essential for restoration of normal tissue architecture, several members of the matrix metalloproteinase (MMP) family function as positive and, at times, negative regulators of repair processes.
MMPs and TIMPs were initially thought to only function in the resolution phase of wound healing, particularly during scar resorption; however, recent evidence suggests that they also influence other wound-healing responses, such as inflammation and re-epithelialization.(7,8)

MMPs and their inhibitors are capable of processing many of signaling molecules, adhesion molecules, and ECM proteins and thus, are likely involved in the control of all aspects of wound healing.MMP and their interaction with TIMPs will effect wound healing. In many studies these have been used as a markers to predict wound healing status.

In most of studies it has been showed that high levels of MMP 9 is associated with wound failure resulting in chronic wounds. MMP 9 / TIMP 1 ratio is inversely related to wound healing state. If there is a chance to predict which wound becomes fails to achieve normal healing, necessary precautions can be taken to achieve normal healing state and thus prevent wound complications. It is beneficial to both patient and surgeon as well. Thus I had selected this study to predict the wound healing status with help of initial expression of MMP 9 and TIMP 1 in acute surgical wound tissue.

In our study initial expression of MMP 9 and TIMP 1 in wound tissue was done at two intervals – one after giving skin incision and other before closure of incision (after completion of surgical procedure).

In our study I observed that levels of MMP 9 (graph 4) and TIMP 1(graph 10) in wound tissue after skin incision has no significant relation to the final outcome of wound. The initial levels of MMP 9 and TIMP 1 after skin incision (before surgical insult) has no significant relation to wound healing ($p>0.05$) irrespective of diabetes or obesity.

Whereas the levels of MMP 9 and TIMP 1 before skin closure (after surgical procedure) has significant relation with wound healing status ($p<0.05$). 75% of non healingwouds are associated strong expression of MMP 9 and 25% with weak expression. Whereas 88% of healed wounds are associated with weak expression of MMP 9 and 12% with strong expression (graph 5, table 2).

82% of healed wounds are associated with strong expression of TIMP 1(graph 11, table 8) (before skin closure) and 18% weak expression. 81% of non healed wounds are associated with weak expression of TIMP 1 and 19% with strong expression ($p<0.05$).

The expression of MMP 9 and TIMP 1 before skin closure and relation to wound healing was significant in diabetes and obese people.

In diabetics (graph 7, table 4) 64.3% of healed wounds are associated with weak expression of MMP 9 and 35.7% with strong expression. 80% of non healed wounds associated with strong expression of MMP 9 and 20% with weak expression.
In diabetics (graph 13, table 10) 78.5% of healed wounds are associated with strong expression of TIMP1 and 21.5% with weak expression. 70% of non healed wounds are associated with weak expression of TIMP 1 and 30% with strong expression.

In obese patients (graph 9, table 6) 82% of healed wounds are associated with weak expression of MMP 9 and 18% with strong expression. 78% of non healed wounds are associated with strong expression of MMP 9 and 22% with weak expression.
In obese patients (graph 15, table 12) 64% of healed wounds are associated with strong expression of TIMP 1 and 36% with weak expression. 89% of non healed wounds are associated with weak expression of TIMP 1 and 11% with strong expression.

There are no similar studies done earlier relating initial expression of MMP 9 and TIMP 1 with wound status. But these are some studies showing the levels of MMP 9 and TIMP 1 in healing and non healed wounds.
Our results can be comparable with WysockiABetal(49), where they studied on levels of MMP 2 and MMP 9 in wound fluid of chronic ulcers. They found high levels of MMP 9 in non healing wounds. Non-healing ulcers develop an environment containing high levels of activated metalloproteinases, which may result in chronic tissue turnover and failed wound closure.

In our study even in patients with diabetes also showed(after surgical procedure) high levels of MMP 9 and low levels of TIMP 1 in non healing wounds(p<0.05).

This can be comparable with studies of Liu Y etal.Liu Y etal(50) studied the relationships of diabetic ulcer wound fluid matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) with wound healing rate. The ulcers were cleansed to remove exudates, and wound fluids were collected for analysis of MMP-2 and -9, TIMP-1. MMP-9 and the MMP-9-to-TIMP-1 ratio correlated inversely with the wound healing rate at 28 days (P < 0.001). MMP-9 and the MMP-9-to-TIMP-1 ratio were lower in the 23 patients who achieved complete healing at 12 weeks versus the 39 who did not. These findings suggest that a milieu with high MMP-9 may be indicative of inflammation and poor wound healing in diabetic ulcers.

Our results are contrary to study of Themis R. Kyriakidesetal(55), where there is delayed wound healing in MMP 9 null mice.

MMP 9 has definitely a role in wound healing. It's the high levels that result in poor helaing and optimum levels are required for normal healing. In study of Themis R. Kyriakidesetal the mice was lacking MMP 9 and so there is delayed wound healing.

It was observed in our study that levels of MMP 9 and TIMP 1 immediately after skin incision (before surgical procedure) has no impact in predicting the final status of wound. The levels of MMP 9 and TIMP 1 attained before skin closure (after surgical procedure) has significant effect on wound healing and can predict the final outcome. This indicate that response of body to surgical procedure resulted in changes of MMP 9 and TIMP 1 which had an impact on wound healing.

It will be useful if this study was done in a large number of people, and if results were same then patients at risk of poor healing can be identified prior, necessary precautions can be taken to attain normal healing. Dressings which lower MMP 9 levels can be useful in non healing wounds to achieve healing stage.

CONCLUSION

From present study it can be concluded that acute surgical wounds with strong expression of MMP 9 and weak expression of TIMP 1 at the end of surgical procedure has more chances of becoming non healing wounds. So they can be used as a predictors of wound healing.

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