Table 1. Summary of chronic wound fluid protein analyses

Protein Name	Ulcer Type	Analysis Method/s	Main findings	Author, Reference
α-1-antitrypsin	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
	V	Western	Specific cleavage and detection of enzyme – inhibitor complex in CWF and not plasma	Grinnell *et al.* (1996); [2]
	V	Western	Degraded to a 37 kDa band in all CWF samples with degraded fibronectin	Rao *et al.* (1995); [3]
	V	Western	Partially degraded; All forms detected in CWF	Schmidtchen *et al.* (2000); [4]
α-1-acid glycoprotein	V	2D-LC / MALDI-MS/MS, LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
α-1-globulin	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
α-2-macroglobulin	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
	V	Western	Whole and partially degraded protein detected; Higher degradation in CWF than plasma	Grinnell *et al.* (1996); [2]
	V	Western	Partially degraded	Schmidtchen *et al.* (2000); [4]
Alanine aminotransferase	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Albumin	V	Behring nephelometric analysis	No significant difference in albumin concentration between healing an non-healing patients	Harris *et al.* (1995); [6]
	V	Not stated	Below normal concentration compared to range in serum/plasma	Falanga (1992); [7]
	V	2D-LC / MALDI-MS/MS, LC-ESI-MS/MS, Western	Present in CWF	Fernandez *et al.* (2008); [1]
	V	BCG Assay	Higher in healing wounds	James *et al.* (2000); [8]
	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Alkaline phosphatase	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Angiostatin	V	Western, MALDI-MS	50, 65 and 10 kDa species detected	Smith *et al.* (2005); [9]
Antichymotrypsin	V	Western	Present in CWF and matched plasma equally	Schmidtchen *et al.* (2000); [4]
Apolipoprotein A-1	V	2D-LC / MALDI-MS/MS, LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Asparate aminotransferase	V	Automated clinical biochemical analysis	Significantly higher in wound fluid than matched serum	Trengove *et al.* (1996); [5]
β-1-globulin	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
β-globulin	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
β-2-glycoprotein-1	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Basic fibroblast growth factor	P	ELISA	Highly variable 47 – 697 pg/ml	Cooper *et al.* (1994); [10]
	V	ELISA	Generally higher in non-healing	Harris *et al.* (1995); [6]

			patients through not significant	
	V	ELISA	Concentration significantly correlated with ulcer size	Gohel *et al.* (2008); [11]
	V	ELISA	No statistical difference in concentration between healing ad non-healing wounds	Trengove *et al.* (2000); [12]
Calgranulin A	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Calgranulin B	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Cathepsin G	M	Photometric assay	Elevated in some CWF samples, while undetectable in others	Trengove *et al.* (1999); [13]
	V	Photometric assay	No significant difference between activity in serum, AWF and CWF	Weckroth *et al.* (1996); [14]
Ceruloplasmin	V	Western	Present in CWF; Intact	Schmidtchen *et al.* (2000); [4]
Collagen I (propeptide of type 1 collagen)	V	RIA	Present in CWF; Correlates well with healing rates	Rasmussen *et al.* (1992); [15]
	V	ELISA	No significant difference between healing and non-healing ulcers	Tarlton *et al.* (1999); [16]
Collagen III (amino terminal propeptide of type III collagen)	V	RIA	Present in CWF; Correlates well with healing rates	Rasmussen *et al.* (1992); [15]
Complement C3	V	2D-LC / MALDI-MS/MS, LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
	V	Western	Partial degradation of α-chain	Schmidtchen *et al.* (2000); [4]
	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Complement C4	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
C-reactive protein	V	Western	Present in CWF; Intact	Schmidtchen *et al.* (2000); [4]
	V	Automated clinical biochemical analysis	Not significantly different between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Creatine kinase	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Cytokeratin-1	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Elafin	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Elastase	P	Activity assay	Present and active in CWF	Edwards *et al.* (1999); [17]
	V	Western	Close correlation between elastase activity and fibronectin degradation	Grinnell *et al.* (1996); [2]
	V	Fluorogenic assay	Activity varied between different patient wounds; Significant correlation to MMP activity	Latijnhouwers *et al.* (1998); [18]
	V	Chromogenic assay	CWF with fibronectin degradation had 10 to 40 times the elastase activity of CWF samples without fibronectin degradation; AWF and serum had less activity than CWF	Rao *et al.* (1995); [3]
	M	Photometric assay	Higher levels in CWF compared to AWF; Lower level in healing	Trengove *et al.* (1999); [13]

			wounds, compared to non-healing wounds, but not significant	
	V	Photometric assay	No significant difference between activity in serum, AWF and CWF	Weckroth *et al.* (1996); [14]
Elastase (Neutrophil)	V	Chromogenic assay	Higher activity in most CWF when compared to AWF	Hoffman *et al.* (1998); [19]
	M	ELISA	Significantly higher than in matched plasma	James *et al.* (2003); [20]
	V	Zymography	Activity detected in all CWF samples; No activity detected AWF samples; Lower activity in improving wounds than static or deteriorating wounds; Significantly higher activity in deteriorating regions than improving regions of same wound	Tarlton *et al*. (1999); [16]
Endostatin	V	Western, ELISA	20 kDa protein detected as well as higher MW bands across CWF samples	Smith *et al.* (2005); [9]
Epithelial growth factor	P	ELISA	Highly variable: below detection to 247.5 pg/ml	Cooper *et al.* (1994); [10]
	V	ELISA	No statistical difference in concentration between healing and non-healing wounds;*	Trengove *et al.* (2000); [12]
Epithelial neutrophil activating peptide -78	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Factor B	V	Western	No proform (98kDa) in CWF	Schmidtchen *et al.* (2000); [4]
Fibrinogen-α chain	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Fibrinogen-β chain	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Fibrinogen-γA chain	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Fibronectin	V	Western	Degradation to 54, 93, 125 kDa in some patients	Grinnell *et al.* (1992); [22]
	V	Western	Variable degradation between patients and time points; Elastase suspected to be responsible for protease activity	Grinnell *et al.* (1996); [2]
	V	Western	Some intact fibronectin observed, though partial degradation to 38, 55, 95, 127 kDa and smaller fragments observed across CWF samples; Degradation unrelated to ulcer state	Harris *et al.* (1995); [6]
	V	Western	Multiple fragments detected	Latijnhouwers *et al.* (1998); [18]
	V	Western	19/22 samples showed differing degrees of degradation	Palolahti *et al.* (1993); [23]
	V	Western	Multiple fragments between 20 and 140 kDa detected in 9/10 samples in contrast to serum and AWF; Likely a result of elastase or	Rao *et al.* (1995); [3]

			chymotrypsin-like enzyme	
	V	Western	Many degradation products in CWF compared to matched plasma	Schmidtchen *et al.* (2000); [4]
	D	Western	Fragmentation evident in CWF	Stanley *et al.* (2008); [24]
	V	Western	No intact protein; Dominant degradation products at 93 and 125 kDa	Wysocki *et al.* (1990); [25]
	D	Western	Partially degraded; Dominant degradation products at 93 and 125 kDa	Wysocki *et al.* (1990); [25]
Ferritin	V	Immunoturbidimetric Assay	Significantly greater levels than AWF; Significant reduction in level in healing compared to non-healing ulcers	Yeoh-Ellerton *et al.* (2003); [26]
γ-globulin	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
γ-glutamyltranspeptidase	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Glypican-1	V	Immunoprecipitation	Detected in CWF bound to endostatin	Smith *et al.* (2005); [9]
Granulocyte macrophage colony-stimulating factor	V	ELISA	Generally higher in non-healing patients though not significant	Harris *et al.* (1995); [6]
Growth regulated oncogene-α	V	ELISA	No significant trend, but significant differences identified at later time points over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Haemopexin	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Hepatocyte growth factor	V	Elisa; Western	No correlation between albumin concentration and HGF; Significantly higher in CWF compared to AWF; Three bands detected at 85, 65 and 40 kDa	Nayeri *et al.* (2005); [27]
Haptoglobin	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Heparin binding protein	V	Western	Significantly higher in CWF compared to AWF	Lundqvist *et al.* (2004); [28]
H,L-kininogen	V	Western	Present in CWF; Intact	Schmidtchen *et al.* (2000); [4]
IgA	V	Western	70 kDa signal in CWF; Intact	Schmidtchen *et al.* (2000); [4]
	V	LC-ESI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
IgG	V	Western	60 kDa signal in CWF; Intact	Schmidtchen *et al.* (2000); [4]
	V	LC-ESI-MS/MS, western	Present in CWF	Fernandez *et al.* (2008); [1]
Insulin-like growth factor-1	NS	RIA	Concentration did not change over 14 day healing period; Consistently lower in CWF than in serum	Wagner *et al.* (2003); [29]
Insulin-like growth factor binding protein-2	NS	RIA	Concentration did not change over 14 day healing period; Similar concentration in CWF and serum	Wagner *et al.* (2003); [29]
Insulin-like growth	NS	RIA	Concentration did not change over	Wagner *et al.* (2003); [29]

factor binding protein-3			14 day healing period; Consistently lower in CWF than in serum	
Inter-α-inhibitor	V	Western	High MW bands were less intense and low MW bands more intense in CWF compared to matched plasma	Schmidtchen *et al.* (2000); [4]
Interferon-inducible protein-10	V	ELISA	No significant trend or interspersed changes over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Interleukin-1	V	Cell-based bioassay	Activity significantly greater in non-healing ulcers	Trengove *et al.* (2000); [12]
Interleukin-1α	P	ELISA	Concentration significantly higher in chronic wound fluids than AWFs; Concentration significantly dropped with clinical improvement	Barone *et al.* (1998); [30]
	V	ELISA, bioassay	Mostly inactive; Generally higher in non-healing patients though not significant	Harris *et al.* (1995); [6]
	V	ELISA	Higher Concentration in non-healing wounds with significant decrease over healing	Trengove *et al.* (2000); [12]
Interleukin-1β	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
	V	ELISA	No relationship between healing and concentration	Gohel *et al.* (2008); [11]
	V	ELISA, bioassay	Generally higher in non-healing patients though not significant; Significant decrease with healing	Harris *et al.* (1995); [6]
	V	ELISA	Higher concentration in non-healing wounds with significant decrease over healing (p>/= 0.05)	Trengove *et al.* (2000); [12]
	NS	ELISA	Higher in inflamed wounds	Wagner *et al.* (2003); [29]
Interleukin-1 receptor antagonist protein	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Interleukin-6	V	ELISA, bioassay	High concentration in CWF	Harris *et al.* (1995); [6]
	NS	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
	NS	Cell-based bioassay, ELISA	Activity greater in non-healing ulcers (p>/= 0.05); Total concentration no different between healing and non-healing wounds	Trengove *et al.* (2000); [12]
Interleukin-8	V	ELISA	Significant upwards trend detected over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Interleukin-10	V	ELISA	No significant trend, but gradual increase after week 3 over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Keratin 6	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
H, L-Kininogens	V	Western	Present in wound fluid; Slight degradation in CWF	Schmidtchen *et al.* (2000); [4]
Lactate	V	LDH Assay	Higher in wound fluid compared to	James *et al.* (2000); [8]

Dehydrogenase			plasma; No correlation to healing	
	V	Automated clinical biochemical analysis	Significantly higher in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Macrophage inflammatory protein 1 alpha	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Macrophage inflammatory protein 1 beta	V	ELISA	No significant trend over 8 wk healing period when compared to baseline; Decline until week 4 then a subsequent rise until end of 8 wk healing period	Fivenson *et al.* (1997); [21]
Matrix metalloproteinase-1	V	Western	Present in CWF as monomer and in complexes; α-2-macroglobulin is required for MMP-1 to form complexes	Grinnell *et al.* (1998); [31]
	D	ELISA	Significantly higher in good healers compared to poor healers at wk 0; Downward trend over healing in good healers compared to no change in poor healers; #	Muller *et al.* (2008); [32]
	V; P	ELISA	Significantly higher concentration in chronic wounds than acute wounds	Nwomeh *et al.* (1999); [33]
	V	Zymography, Western	Present in CWF; Higher activity than in CWF than AWF or serum; Major CWF collagenase	Weckroth *et al.* (1996); [14]
Matrix metalloproteinase-2	V	Zymography	Much greater activity in some CWF samples compared to AWFs; Multiple active MW species	Bullen *et al.* (1995); [34]
	V	ELISA	No relationship between healing and concentration	Gohel *et al.* (2008); [11]
	V	Zymography	Activity detected in CWF; Elevated activity compared to plasma	Grinnell *et al.* (1996); [2]
	D	ELISA	Concentration at presentation not significantly different between ulcers that heal and ulcers that don't within 12 weeks	Liu *et al.* (2009); [35]
	D	Zymography	Levels not statistically different between good healers and poor healers at wk 0	Muller *et al.* (2008); [32]
	V	ELISA	Elevated in non-healing patients, but not significantly associated with wound healing	Mwaura *et al.* (2006); [36]
	V	Zymography	Higher activity in CWF than AWFs	Tarlton *et al.* (1999); [16]
	M	Bioassay (AZOCOLL)	Combined with MMP-9, activity in CWF was significantly higher than AWF	Trengove *et al.* (1999); [13]
	NS	Western	Blots showed no significant difference between acute and inflamed wounds	Wagner *et al.* (2003); [29]
	NS	Zymography	Active bands detected at 64 and 57 kDa; Significantly more active material at 57 kDa in inflamed wounds compared to acute wounds	Wagner *et al.* (2003); [29]
	V	Zymography	Pro and active forms detected; No	Wysocki *et al.* (1999); [37]

			trend determinable over healing	
	P	Zymography	Significantly higher levels in CWF compared to AWFs	Yager *et al.* (1996); [38]
Matrix metalloproteinase-8	D	ELISA	Concentration not statistically different between good healers and poor healers at wk 0; Concentration decreased over healing in good healers, but remained the same for poor healers	Muller *et al.* (2008); [32]
	V; P	ELISA	Significantly higher concentration in chronic wounds than acute wounds; 100-fold higher than concentration of MMP-1	Nwomeh *et al.* (1999); [33]
	V	Zymography; Western	Present in CWF; Not major collagenase in CWF	Weckroth *et al.* (1996); [14]
Matrix metalloproteinase-9	V	Zymography	Much greater activity in some CWF samples compared to AWFs; Multiple active MW species	Bullen *et al.* (1995); [34]
	V	ELISA	No relationship between healing and concentration	Gohel *et al.* (2008); [11]
	V	Zymography	High activity in CWF compared to plasma	Grinnell *et al.* (1996); [2]
	P	Zymography	Significantly higher levels at day 0 for patients with poor healing response	Ladwig *et al.* (2002); [39]
	D	ELISA	Concentration at presentation inversely correlated to wound size at 28 wks (MMP-9 to TIMP-1 ratio also inversely correlated); Pro-form predictive of healing within 12 wks	Liu *et al.* (2009); [35]
	D	Zymography	Levels not statistically different between good healers and poor healers at wk 0; Downward trend over healing in good healers, but no change for poor healers	Muller *et al.* (2008); [32]
	V	Zymography, ELISA	Identified as predominant MMP in CWF; Significantly elevated activity in CWF when compared to AWF; Higher concentration correlate to clinical severity of ulcer	Rayment *et al.* (2008); [40]
	V	Zymography	Higher activity in CWF than AWFs; Significantly lower activity in healing wounds than non-healing wounds; Significantly higher activity in deteriorating regions than improving regions of same wound	Tarlton *et al.* (1999); [16]
	M	Bioassay (AZOCOLL)	Combined with MMP-2, activity in CWF was significantly higher than AWF	Trengove *et al.* (1999); [13]
	V	Zymography	High activity in CWF when compared to AWF; Substantial decrease in activity with healing	Wysocki e*t al.* (1999); [37]
	P	Zymography	Significantly higher levels in CWF	Yager *et al.* (1996); [38]

			compared to AWFs	
Monocyte chemoattractant protein-1	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Nucleosome assembly protein 2	V	ELISA	No significant trend, but interspersed significant differences over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Neutrophil cathepsin-D	M	Bioassay	Activity elevated in some chronic wound patients	Trengove *et al.* (1999); [13]
Orosomucoid 1	V	Western	Present in CWF; Intact	Schmidtchen *et al.* (2000); [4]
	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008);[1]
p55	V	ELISA	Similar concentration in healing and non-healing ulcers	Wallace *et al.* (1998); [41]
p75	V	ELISA	Significantly higher concentration in non-healing compared to healing ulcers	Wallace *et al.* (1998); [41]
Plasmin	V	Chromogenic assay	Higher activity per mg protein than AWFs	Hoffman *et al.* (1998); [19]
	V	Chromogenic assay; Proteolytic assay	Present and active; Strong suggestion that plasmin is involved in the degradation of VEGF in CWF	Lauer *et al.* (2000); [42]
Plasminogen	V	Chromogenic assay	Present and active	Lauer *et al.* (2000); [42]
	V	Western; MALDI-MS	Both intact protein and multiple fragments detected across CWF samples	Smith *et al.* (2005); [9]
Plasminogen activator	V	Radial caseinolysis	19/25 samples had PA activity	Palolahti *et al.* (1993); [23]
Plasminogen activator inhibitor	V	Zymography; Western; Chromogenic assay	Significantly higher levels in CWF compared to AWF	Wysocki *et al.* (1999); [37]
Platelet derived growth factor - AA	V	ELISA	Significantly higher in healing patients	Mwaura *et al.* (2006); [36]
	V	ELISA	Generally higher in non-healing patients though not significant	Harris *et al.* (1995); [6]
	V	ELISA	No statistical difference in concentration between healing ad non-healing wounds;*	Trengove *et al.* (2000); [12]
Platelet derived growth factor - AB	P	ELISA	Highly variable: 49 – 867 pg/mL	Cooper *et al.* (1994); [10]
Platelet factor-4	V	ELISA	No significant trend or interspersed changes over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Regulated on activation, normal T expressed and secreted	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
Tenascin-C	V	Western	Extensively degraded in CWF	Latijnhouwers *et al.* (1998); [18]
Tetranectin	V	Western	Present in CWF; Slightly degraded	Schmidtchen *et al.* (2000); [4]
Tissue inhibitor of metal proteinases-1	V	RIA	Mean concentration of 952.5 ± 291.6 ng/mL; Less than half the level of the peak value in healing	Bullen *et al.* (1995); [34]

			acute wounds	
	P	ELISA	Significantly lower concentration at day 0 for patients with poor healing response	Ladwig *et al.* (2002); [39]
	D	ELISA	Concentration at presentation significantly lower in unhealed ulcers at 12 wks; Used to help predictive power of MMP-9 scoring	Liu *et al.* (2009); [35]
	D	ELISA	No significant difference between good healers and poor healers; [#]Ratio with MMP-1 may be useful predictor of healing	Muller *et al.* (2008); [32]
	V; P	ELISA	Concentration consistently low or not detectable in CWF; Concentration lower than AWFs	Nwomeh et al. (1999); [33]
	M	ELISA	Lower in CWF compared to AWF; Inverse correlation to MMP concentration	Trengove *et al.* (1999); [13]
	V	Western	Present in CWF; Additional bound and truncated forms detected	Weckroth *et al.* (1996); [14]
	P	ELISA	Significantly more TIMP-1 bound to collagenases than in AWFs	Yager *et al.* (1996); [38]
Tissue inhibitor of metal proteinases-2	V	ELISA	Elevated in healing patients, but not significantly associated with wound healing	Mwaura *et al.* (2006); [36]
	V	Western	Present in CWF; Additional bound and truncated forms detected	Weckroth *et al.* (1996); [14]
Tumor necrosis factor-α	V	ELISA; Bioassay	Significantly higher concentration in CWF compared to AWF	Cowin *et al.* (2006); [43]
	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
	V	ELISA	No relationship between healing and concentration	Gohel *et al.* (2008); [11]
	V	ELISA	Concentration at 0.254±19 ng/mL (indicative of inflammation)	Mendez *et al.* (1999); [44]
	V	ELISA	Higher concentration in non-healing wounds with significant decrease over healing; *Inverse relationship with PDGF and EGF	Trengove *et al.* (2000); [12]
	V	ELISA	Concentration is significantly higher in CWF from non-healing ulcers compared to healing ulcers; Bioactive levels do not differ between healing and non-healing; Bioactivity relative to total TNF-α shows down regulation in non-healing wounds compared to healing wounds	Wallace *et al.* (1998); [41]
Transferrin	V	LC-ESI-MS/MS, western	Present in CWF	Fernandez *et al.* (2008); [1]
	V	Immunoturbidimetric Assay	Significantly lower levels in CWF compared with AWFs	Yeoh-Ellerton *et al.* (2003); [26]
Transforming growth	P	ELISA	Highly variable: below detection to	Cooper *et al.* (1994); [10]

factor-β			160 pg/ml; Detected in only 3/20 patients	
	V	ELISA	No significant trend over 8 wk healing period when compared to baseline	Fivenson *et al.* (1997); [21]
	V	ELISA	No statistical difference in concentration between healing ad non-healing wounds	Trengove *et al.* (2000); [12]
Transforming growth factor-β_1	V	ELISA	Significant inverse correlation to ulcer size	Gohel *et al.* (2008); [11]
	D	ELISA	Concentration at presentation significantly lower in unhealed ulcers at 12 wks; Used to help predictive power of MMP-9 scoring	Liu *et al.* (2009); [35]
Urokinase plasminogen activator	V	Chromogenic assay; Zymography; Western	Significantly higher levels in CWF compared to AWF; Active forms detected only in CWF; Active form decreases with healing; Direct relationship to change in ulcer size	Wysocki *et al.* (1999); [37]
Vascular endothelial growth factor	V	ELISA	No relationship between healing and concentration	Gohel *et al.* (2008); [11]
	V	ELISA	Higher in CWF than in AWF	Lauer *et al.* (2000); [42]
	NS	ELISA	Higher in inflamed wounds than acute wounds	Wagner *et al.* (2003); [29]
Vitamin D binding protein	V	2D-LC / MALDI-MS/MS	Present in CWF	Fernandez *et al.* (2008); [1]
Vitronectin	V	Western	Complete degradation in some CWF samples	Grinnell *et al.* (1992); [22]

V, Venous ulcer; **D,** Diabetic ulcer; **P,** Pressure ulcer; **NS,** Ulcer type not stated; **M,** Mixed ulcer aetiology; **ELISA,** Enzyme-linked immuno-sorbent assay; **CWF,** Chronic wound fluid; **AWF,** Acute wound fluid; **RIA,** Radio immuno-assay; **2D-LC / MALDI-MS/MS,** Two-dimensional liquid chromatography / Matrix-assisted laser desorption/ionisation tandem mass spectrometry; **Wk,** Weeks

Table 2. Summary of chronic wound fluid small molecule and elemental analyses

Metabolite / Small Molecule	Ulcer Type	Analysis Methods	Main Findings	Author, Reference
8-Isoprostane	V	GC-ECNI-MS; EIA	Elevated in CWF compared to AWF	Yeoh-Ellerton *et al.* (2003); [26]
Allantoin	V; MAV; VD	HPLC	Higher in CWF than in matched plasma	James *et al.* (2003); [20]
Bicarbonate	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Bilirubin	V	Automated clinical biochemical analysis	Significantly higher in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Calcium	V	Not stated	Similar to normal range in serum/plasma	Falanga (1992); [7]
Calcium (Albumin adjusted calcium)	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Carbon dioxide	V	Not stated	Similar to normal range in serum/plasma	Falanga (1992); [7]
Cholesterol	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Chloride	V	Not stated	Similar to normal range in serum/plasma	Falanga (1992); [7]
	V	Automated clinical biochemical analysis	Significantly higher in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Creatinine	V	Jaffe Assay	Present and unrelated to total protein concentration or albumin concentration	James *et al.* (2000); [8]
	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Glucose	V	Not stated	Much lower than normal serum/plasma range	Falanga (1992); [7]
	V	Hexokinase assay	Lower than matched plasma	James *et al.* (2000); [8]
	D	YSI 2300 Glucose-Lactate Analyzer	No significant difference between ulcer tissue and intact skin	Simonsen *et al.* (1998); [45]
	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Iron	V	ICP-AES	No significant differences in level between healing, non-healing and AWFs	Yeoh-Ellerton *et al.* (2003); [26]
Lactate	V	Enzyme assay	Higher in wounds with *S. aureus* infection; Higher compared to matched plasma	James *et al.* (2000); [8]
	D	YSI 2300 Glucose-Lactate Analyzer	Significantly higher lactate in the ulcer tissue than intact skin	Simonsen *et al.* (1998); [45]
	V	Automated clinical biochemical analysis	Significantly higher in wound fluid than matched serum	Trengove *et al.* (1996); [5]
	NS	Lactate analyzer	Similar levels between inflamed and acute wounds	Wagner *et al.* (2003); [29]
Magnesium	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Malondialdehyde	V	Chromogenic assay	So significant difference detected between CWF and AWFs	Moseley *et al.* (2004); [46]
Phosphate	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Phosphorus	V	Not stated	Above normal range in serum/plasma	Falanga (1992); [7]
Potassium	V	Not stated	Similar to normal range in serum/plasma	Falanga (1992); [7]

	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]
Sodium	V	Not stated	Similar to normal range in serum/plasma	Falanga (1992); [7]
	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Urea	V	Urease assay	No difference between healing and non-healing patient samples	James *et al.* (2000); [8]
	V	Automated clinical biochemical analysis	Not significantly difference between wound fluid and matched serum	Trengove *et al.* (1996); [5]
Uric Acid	V; MAV; VD	HPLC	Lower in CWF than in matched plasma	James *et al.* (2003); [20]
	V	Automated clinical biochemical analysis	Significantly lower in wound fluid than matched serum	Trengove *et al.* (1996); [5]

V, Venous ulcer; **D,** Diabetic ulcer; **P,** Pressure ulcer; **NS,** Ulcer type not stated; **A,** Arterial ulcer; **M,** Mixed ulcer aetiology; **CWF,** Chronic wound fluid; **AWF,** Acute wound fluid; **GC-ECNI-MS,** Gas chromatography/electron capture negative ionisation mass spectrometry; **EIA,** Enzyme immuno-assay; **HPLC,** High performance liquid chromatography: **ICP-AES,** Inductively coupled plasma atomic emission spectroscopy

Table 3. Summary of chronic wound tissue analyses

Protein Name	Ulcer Type	Analysis Method/s	Main findings	Author; Reference
A disintegrin and metalloproteases 12	V	IHC	Increased staining in chronic wound tissue compared to normal epidermis and acute wound tissue; Membranous staining more widespread in chronic wound tissue	Harsha *et al.* (2008); [47]
Arginase	V	IHC; Western	Localized mainly to blood vessels; More prominent staining in ulcer tissue than healthy tissue; Little staining in ulcer base; 70 kDa band detected; More prominent band in chronic ulcer homogenate than normal skin homogenate	Abd-El-Aleem *et al.* (2000); [48]
	D	IHC; Western	Increased staining in ulcer tissue over diabetic skin and normal skin; Fibroblasts at the ulcer margin; Staining decreased towards the centre of the ulcer; Elevated band intensity compared to normal skin; Low levels in diabetic skin	Jude *et al.* (1999); [49]
CD1a	V; D	IHC	Decreased staining at edge of venous calf ulcers compared to control tissue; Increased staining of the margins of diabetic ulcers compared to control skin	Galkowska *et al.* (2005); [50]
CD44	V	IHC	Staining in keratinocytes, fibroblasts and inflammatory cells; Very similar to normal skin staining	Lundqvist *et al.* (2001); [51]
CD45	V	IHC	No difference in staining between ischemic and non-ischemic wound tissues	Dalton *et al.* (2007); [52]
CD105	V	IHC	Staining in blood vessels and keratinocytes in ischemic and non-ischemic wound tissue samples; Staining over greater area in ischemic wound tissues; Co-localization with type IV collagen more prominent in ischemic than non-ischemic wound tissue samples	Dalton *et al.* (2007); [52]
Chondroitin Sulphate	V; D	IHC	High staining in all chronic wounds in basement membrane and dermis	Loots *et al.* (1998); [53]
Collagen I (propeptide of type 1 collagen)	V	ELISA	Significantly elevated in ischemic compared to matched non-ischemic wound tissue samples as well as varicose vein and total knee replacement control tissues	Dalton *et al.* (2007); [52]
Connexin 26	M; D	Indirect IF	Staining at and proximal to wound margins	Brandner *et al.* (2004); [54]
Connexin 30	M; D	Indirect IF	Staining at and proximal to wound margins	Brandner *et al.* (2004); [54]
Connexin 43	M; D	Indirect IF	Staining at wound margins in 10/11 cases; Staining proximal and distal to wound margins in all cases; in 3/9 mixed ulcers less staining was observed at wound margins compared	Brandner *et al.* (2004); [54]

			to distal tissue	
Endothelial nitric oxide synthase	V	IHC; Western	Staining of blood vessels; Localized to vascular endothelial cells; Staining of epidermal cells with highest density staining at ulcer edge; 140 kDa band detected; More prominent band in chronic ulcer homogenate than normal skin homogenate	Abd-El-Aleem *et al.* (2000); [48]
	D	IHC; Western	Localized to endothelial cells; Staining in ulcer tissue increased over normal skin with a gradient of high to low staining moving from intact tissue to ulcer bed; Western blot indicated most intense band occurred from ulcer tissue	Jude *et al.* (1999); [49]
Epithelial growth factor	D	IHC	Significantly increased staining in epidermis compared to control tissues	Galkowska *et al.* (2006); [55]
Epithelial neutrophil-activating peptide 78	V	ELISA	No difference between ulcer edge and centre at wk 0	Fivenson *et al.* (1997); [21]
E-selectin	V	IHC	Staining not significantly different between healthy and peripheral ulcer tissue	Weyl *et al.* (1996); [56]
Extracellular matrix metalloproteinase inducer	V	IHC	No significant difference between healing a non-healing patient ulcers	Mwaura *et al.* (2006); [36]
	V	IHC	More intense staining in dermis compared to normal skin; Localized intense staining in perivascular region of ulcer tissue; Intense staining in papillary and reticular dermis excluding vasculature compared to normal skin	Norgauer *et al.* (2002); [57]
Ferric iron	V	Perl's Prussian blue reaction	Staining in dermal region of leg ulcer tissue; Higher in ulcer tissue than normal skin	Yeoh-Ellerton *et al.* (2003); [26]
Ferritin	V	IHC	Little to no staining in the intact epidermis and slightly more in the ulcer edge epidermis; Higher in ulcer tissue than normal skin	Yeoh-Ellerton *et al.* (2003); [26]
Fibronectin	V; D	IHC	Whole dermis staining at 12-18 mth wound duration in all diabetic wounds and 2/12 venous ulcer patients	Loots *et al.* (1998); [53]
Fms-related tyrosine kinase 1	V	IHC	Increased in papillary dermal micro-vessels near the ulcer edge; Virtually no staining distant to the ulcer edge	Lauer *et al.* (2000); [42]
Glypican	V	IHC	Staining adjacent to wound edge and basal regions of epidermis	Lundqvist *et al.* (2001); [51]
Granulocyte colony-stimulating factor	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue; Ulcer tissue concentration significantly reduced following 4 wks compression therapy	Beidler *et al.* (2009); [58]
Granulocyte	V	Multiplex ELISA	Significantly higher in ulcer tissue	Beidler *et al.* (2009); [58]

macrophage colony-stimulating factor			compared to healthy tissue; Ulcer tissue concentration significantly reduced following 4 wks compression therapy; Significantly higher concentration in rapidly healing ulcers	
	V; D	IHC	Increased staining of keratinocytes the margins of diabetic ulcers compared to control skin	Galkowska *et al.* (2005); [50]
	D	IHC	Significantly increased staining in epidermal keratinocytes and dermal endothelial cells compared to control tissues	Galkowska *et al.* (2006); [55]
Growth regulated oncogene-α	V	ELISA	No significant changes reported over 8 wk healing period	Fivenson *et al.* (1997); [21]
Heparin binding protein	V	IHC	Identified in inflammatory filtrate, including macrophages and leukocytes; Variable staining in extracellular environments	Lundqvist *et al.* (2004); [28]
Hepatocyte growth factor	V	IHC	Staining on basement membrane and capillary endothelial cells; Higher in chronic wounds than acute wounds but not significant	Nayeri *et al.* (2005); [27]
Hepatocyte growth factor receptor	V	IHC	Staining on capillary endothelial cells, basal membrane epidermis, lymphocytes and fibroblasts in wound tissue; Significantly increased staining in chronic ulcer tissue compared to healthy skin	Nayeri *et al.* (2005); [27]
HLA-DR	V; D	IHC	Increased staining of the margins of diabetic ulcers compared to control skin	Galkowska *et al.* (2005); [50]
Human-β-defensin 2	V; D	IHC	No differential staining in ulcerated tissue compared to control skin	Galkowska *et al.* (2005); [50]
	V	IHC	All chronic wound tissues showed elevated staining over normal skin specimens; Strongest staining in the Malpighian layer of skin and minimal staining of the basal cells; Dermal staining of chronic wound tissue showed mild to moderate staining in inflammatory cells	Butmarc *et al.* (2004); [59]
Hyaluronan	P	ELISA	Large variation between ulcer tissues; Significantly lower concentration in comparison to acute wound tissue at days 7 and 14 only (of 28 days monitoring)	Dechert *et al.* (2006); [60]
Inducible nitric oxide synthase	V	IHC; Western	Large number of immunoreactive vessels present in ulcer tissue; Localized to vascular endothelial cells and smooth muscle cells; Most staining at ulcer edge and base; Little staining in healthy skin; 130 kDa band detected; Much more intense band in ulcer tissue homogenate	Abd-El-Aleem *et al.* (2000); [48]

			compared to healthy skin homogenate	
	D	IHC; Western	Intense staining at margins of ulcer tissue predominantly localized to vascular smooth muscle; large number of inflammatory cells also stained positive in ulcer region; Western blot indicated most intense band occurred from ulcer tissue	Jude *et al.* (1999); [49]
	V; D; A	Western Blot	Concentration showed weak correlation to linear healing rate	Luk *et al.* (2005); [61]
Insulin-like growth factor-1	D	IHC; IF	Staining absent in diabetic skin and diabetic foot ulcers compared to normal skin	Blakytny *et al*. (2000); [62]
Insulin-like growth factor-2	D	IHC; IF	Intense staining in diabetic skin and diabetic foot ulcers compared to normal skin	Blakytny *et al.* (2000); [62]
Intercellular adhesion molecule-1	V	IHC	No epidermal staining in healthy skin; 7 of 21 specimens showed staining on basal keratinocytes in peripheral ulcer tissue; 15 of 27 showed staining of keratinocytes in peripheral ulcer tissue; Higher staining in dermal endothelial cells of peripheral ulcer tissue; Strong staining of capillary loops in peripheral ulcer tissue compared to healthy tissue	Weyl *et al.* (1996); [56]
Interferon-γ	V	Multiplex ELISA	Significantly elevated in ulcer tissue compared to healthy tissue; Ulcer tissue concentration showed significant reduction after 4 wks of compression therapy; Significantly higher concentration in rapidly healing ulcers	Beidler *et al.* (2009); [58]
Interferon-inducible protein-10	V	ELISA	Significant changes at ulcer edge over first 4 wks from baseline	Fivenson *et al.* (1997); [21]
Interleukin-1α	V	Multiplex ELISA	Significantly lower concentration in ulcer tissue compared to healthy tissue; Ulcer tissue concentration showed significant decrease in concentration following 4 wks of compression therapy; Significantly higher concentration in rapidly healing ulcers	Beidler *et al.* (2009); [58]
Interleukin-1 receptor agonist	V	Multiplex ELISA	Significantly higher concentration in rapidly healing ulcers	Beidler *et al.* (2009); [58]
Interleukin-1β	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue; Ulcer tissue concentration significantly reduced following 4 wks compression therapy; Significantly higher concentration in rapidly healing ulcers	Beidler *et al.* (2009); [58]
	V	ELISA	Inverse relationship to Inlerleukin-1β throughout 8 wk healing period	Fivenson *et al.* (1997); [21]

	D	ELISA	Significantly elevated at day 8 of 8 day observation period	Lobmann *et al.* (2006); [63]
Interleukin-1 receptor antagonist protein	V	ELISA	Inverse relationship to Inlerleukin-1 receptor agonist protein throughout 8 wk healing period	Fivenson *et al.* (1997); [21]
Interleukin-2	V	Multiplex ELISA	Not detectable or not statistically different between ulcerated and healthy tissue	Beidler *et al.* (2009); [58]
Interleukin-4	V	Multiplex ELISA	Significantly higher in ulcer tissue than in comparison to healthy tissue	Beidler *et al.* (2009); [58]
Interleukin-5	V	Multiplex ELISA	Not detectable or not statistically different between ulcerated and healthy tissue	Beidler *et al.* (2009); [58]
Interleukin-6	V	Multiplex ELISA	Significantly elevated in ulcer tissue when compared to healthy tissue; Concentration significantly decreased in ulcer tissue after 4 wks of compression therapy	Beidler *et al.* (2009); [58]
	V	ELISA	Significant trend identified in ulcer edge between baseline and week 4 of healing period	Fivenson *et al.* (1997); [21]
Interleukin-7		Multiplex ELISA	Not detectable or not statistically different between ulcerated and healthy tissue	Beidler *et al.* (2009); [58]
Interleukin-8	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue when compared to healthy tissue; Concentration significantly decreased in ulcer tissue after 4 wks of therapy	Beidler *et al.* (2009); [58]
	V	ELISA	No significant changes reported over 8 wk healing period	Fivenson *et al.* (1997); [21]
Interleukin-8 receptor-α	D	IHC	Significantly higher staining in endothelial cells of wound dermis compared to control tissue	Galkowska *et al.* (2006); [55]
Interleukin-10	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue when compared to healthy tissue	Beidler *et al.* (2009); [58]
	V	ELISA	No significant changes reported over 8 wk healing period	Fivenson *et al.* (1997); [21]
	D	IHC	Significantly lower staining in endothelial cells of wound dermis compared to control tissue	Galkowska *et al.* (2006); [55]
Interleukin-10 receptor	D	IHC	Significantly higher staining in endothelial cells of wound dermis compared to control tissue	Galkowska *et al.* (2006); [55]
Interleukin-12p40	V	Multiplex ELISA	Concentration significantly higher in ulcer tissue compared to healthy tissue; Concentration significantly decreased in ulcer tissue following 4 wks of compression therapy; Significantly higher concentration in rapidly healing ulcers	Beidler *et al.* (2009); [58]
Interleukin-12p70	V	Multiplex ELISA	Not detectable or not statistically different between ulcerated and healthy tissue	Beidler *et al.* (2009); [58]

Interleukin-13	V	Multiplex ELISA	Concentration significantly higher in ulcer tissue compared to healthy tissue	Beidler *et al.* (2009); [58]
Interleukin-15	V	Multiplex ELISA	Not detectable or not statistically different between ulcerated and healthy tissue	Beidler *et al.* (2009); [58]
Interleukin-17	V	Multiplex ELISA	Not detectable or not statistically different between ulcerated and healthy tissue	Beidler *et al.* (2009); [58]
Kinase insert domain receptor	V	IHC	Increased in papillary dermal micro-vessels near the ulcer edge; Virtually no staining distant to the ulcer edge	Lauer *et al.* (2000); [42]
Lactate	V	Colorimetric assay	Significantly elevated in ischemic compared to matched non-ischemic wound tissue samples; No difference between non-ischemic and control tissues	Dalton *et al.* (2007); [52]
Leukocyte function-associated antigen-1	V	IHC	Strong staining of leukocytes in peripheral ulcer tissue compared to healthy skin; ~40% increase in capillary loop staining in peripheral ulcer tissue compared to healthy skin	Weyl *et al.* (1996); [56]
Macrophage inflammatory protein 1 alpha	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue	Beidler *et al.* (2009); [58]
	V	ELISA	Significant rise at ulcer centre between wks 0 and 4 of 8 wk healing period	Fivenson *et al.* (1997); [21]
Macrophage inflammatory protein 1 beta	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue	Beidler *et al.* (2009); [58]
	V	ELISA	No significant changes detected in association with healing; Gradual decrease in concentration over 8 wk healing period	Fivenson *et al.* (1997); [21]
Matrix metalloproteinase-1	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Similar concentration following 4 wks of compression therapy – some decrease; Significantly lower concentration in rapid healing ulcers after 4 wks compression therapy	Beidler *et al.* (2008); [64]
	D	ELISA	Significantly higher concentration in diabetic foot ulcer tissue compared to non-diabetic traumatic wounds	Lobmann *et al.* (2002); [65]
	D	ELISA	Not statistically different over 8 day observation period	Lobmann *et al.* (2006); [63]
Matrix metalloproteinase-2	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Similar concentration following 4 wks of compression therapy – some decrease; Significantly lower concentration in rapid healing ulcers after 4 wks compression therapy	Beidler *et al.* (2008); [64]
	V	Zymography	Less active zymogen in cells from	Cook *et al.* (2000); [66]

			unaffected skin than ulcerated skin	
	D	ELISA	Significantly higher concentration in diabetic foot ulcer tissue compared to non-diabetic traumatic wounds; Pro-form increased 3-fold; Active-form increased 6-fold	Lobmann *et al.* (2002); [65]
	D	ELISA	Not statistically different over 8 day observation period	Lobmann *et al.* (2006); [63]
	V	IHC	Perivascular and stromal staining; No significant difference between healing and non-healing patient ulcers	Mwaura *et al.* (2006); [36]
	V	IHC	More intense staining in dermis compared to normal skin; Localized intense staining in perivascular region of ulcer tissue; Intense staining in papillary and reticular dermis excluding vasculature compared to normal skin	Norgauer *et al.* (2002); [57]
Matrix metalloproteinase-3	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Significant decrease in concentration following 4 wks of compression therapy; Significantly lower concentration in rapid healing ulcers after 4 wks compression therapy	Beidler *et al.* (2008); [64]
Matrix metalloproteinase-7	V	Multiplex ELISA	Similar concentration in ulcer tissue compared to healthy tissue; Similar concentration following 4 wks of compression therapy – some decrease; Similar concentration in rapid and slow healing ulcers after 4 wks compression therapy – lower concentration in slow healing ulcers	Beidler *et al.* (2008); [64]
Matrix metalloproteinase-8	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Significantly lower concentration following 4 wks of compression therapy; Similar concentration in rapid and slow healing ulcers after 4 wks compression therapy – lower concentration in rapid healing ulcers	Beidler *et al.* (2008); [64]
	D	ELISA	Significantly higher concentration in diabetic foot ulcer tissue compared to non-diabetic traumatic wounds	Lobmann *et al.* (2002); [65]
	D	ELISA	Not statistically different over 8 day observation period	Lobmann *et al.* (2006); [63]
Matrix metalloproteinase-9	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Significantly lower concentration following 4 wks of compression therapy; Similar concentration in rapid and slow healing ulcers after 4 wks	Beidler *et al.* (2008); [64]

			compression therapy – lower concentration in rapid healing ulcers	
	D	ELISA	Significantly higher concentration in diabetic foot ulcer tissue compared to non-diabetic traumatic wounds	Lobmann *et al.* (2002); [65]
	D	ELISA	Not statistically different over 8 day observation period	Lobmann *et al.* (2006); [63]
Matrix metalloproteinase-12	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Similar concentration following 4 wks of compression therapy – lower concentration following therapy; Similar concentration in rapid and slow healing ulcers after 4 wks compression therapy – lower concentration in rapid healing ulcers	Beidler *et al.* (2008); [64]
Matrix metalloproteinase-13	V	Multiplex ELISA	Significantly higher concentration in ulcer tissue compared to healthy tissue; Similar concentration following 4 wks of compression therapy – higher concentration following therapy; Similar concentration in rapid and slow healing ulcers after 4 wks compression therapy – lower concentration in rapid healing ulcers	Beidler *et al.* (2008); [64]
Matrix metalloproteinase-14	V	IHC	Intense staining in papillary and reticular dermis excluding vasculature compared to normal skin	Norgauer *et al.* (2002); [57]
Matrix metalloproteinase-15	V	IHC	Intense staining in papillary and reticular dermis excluding vasculature compared to normal skin	Norgauer *et al.* (2002); [57]
Monocyte chemoattractant protein-1	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue	Beidler *et al.* (2009); [58]
	V	ELISA	Slight increase over 8 wk healing period	Fivenson *et al.* (1997); [21]
	D	IHC	Significantly higher staining in endothelial cells of wound dermis compared to control tissue	Galkowska *et al.* (2006); [55]
Myeloperoxidase	P	Photometric assay	Activity significantly higher in chronic wound tissue than acute dermal wound tissue at any point during healing	Dechert *et al.* (2006); [60]
Neutrophil-activating peptide-2	V	ELISA	Significant changes at ulcer edge and approaching significant trend at ulcer centre over first 4 wks from baseline;	Fivenson *et al.* (1997); [21]
Perlecan	V	IHC	Staining in basement membrane and capillaries; Less intense staining than normal skin	Lundqvist *et al.* (2001); [51]
Phospho-smad 2/3	V	IHC	Greater spread of staining in ischemic tissues	Dalton *et al.* (2007); [52]
Platelet derived growth factor - AA	V	IHC	Significantly increased staining in the perivascular area in healing ulcers	Mwaura *et al.* (2006); [36]
Platelet derived	D	IHC	Significantly increased staining in	Galkowska *et al.* (2006);

growth factor receptor-β			endothelial cells compared to control tissues	[55]
Platelet factor-4	V	ELISA	Concentration at wound centre found to have inverse correlation to wound closure	Fivenson *et al.* (1997); [21]
Regulated on activation, normal T expressed and secreted	V	ELISA	No significant changes identified in association with healing	Fivenson *et al.* (1997); [21]
Smad 7	V	IHC	Lower staining in ischemic tissues	Dalton *et al.* (2007); [52]
Syndecan-1	V	IHC	Staining in pericellular regions; Less staining at wound edge than control skin	Lundqvist *et al.* (2001); [51]
Syndecan-2	V	IHC	Protruding basal cells appeared to lack staining in wound tissue	Lundqvist *et al.* (2001); [51]
Syndecan-4	V	IHC	Staining in basal layer keratinocytes (cytoplasmic) and endothelial cells; Less staining near the wound edge	Lundqvist *et al.* (2001); [51]
Tenascin	V; D	IHC	Highly variable staining amongst patient cohort	Loots *et al.* (1998); [53]
Tissue inhibitor of metal proteinases-1	V	ELISA	Significantly higher concentration compared to healthy tissue; Similar concentrations before and after 4 wks compression therapy – some decrease following therapy	Beidler *et al.* (2008); [64]
Tissue inhibitor of metal proteinases-2	V	ELISA	concentration compared to healthy tissue; Similar concentrations before and after 4 wks compression therapy	Beidler *et al.* (2008); [64]
	D	ELISA	Significantly higher concentration in diabetic foot ulcer tissue compared to non-diabetic traumatic wounds	Lobmann *et al.* (2002); [65]
	D	ELISA	Not statistically different over 8 day observation period	Lobmann *et al.* (2006); [63]
	V	IHC	Not detected in healing or non-healing patient ulcer tissue	Mwaura *et al.* (2006); [36]
Tissue plasminogen activator	V; P	ELISA; Bioimmunoassay	Only detected in small number of wound tissue samples	Stacey *et al.* (1993); [67]
Transferrin	V	IHC	More intense staining in epidermis than dermis	Yeoh-Ellerton *et al.* (2003); [26]
Transforming growth factor-β	V	ELISA	No significant changes at ulcer edges or centre over 8 wk healing period	Fivenson *et al.* (1997); [21]
	V	IHC	Slight staining on capillary endothelial cells, basal membrane epidermis, lymphocytes and fibroblasts; Cells at chronic ulcer edge had increased staining	Nayeri *et al.* (2005); [27]
Transforming growth factor-β_1	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue; Significant increase in ulcer tissue following 4 wks compression therapy	Beidler *et al.* (2009); [58]
	V	Indirect IF	Staining in ulcer tissue markedly reduced; Staining at margins obvious; Staining observed associated with blood vessels and fibroblasts in	Cowin *et al.* (2001); [68]

			healing ulcers	
	V	ELISA	Significantly elevated in ischemic compared to matched non-ischemic samples; No correlation to lactate	Dalton *et al.* (2007); [52]
	D	IHC	Significantly increased staining in suprabasal keratinocytes compared to control tissues; Significantly decreased in endothelial cells compared to control tissues	Galkowska *et al.* (2006); [55]
	D	IHC; Western	Staining considerably less than diabetic skin or normal skin; Some staining in the epidermis adjacent to the ulcer edge; Staining absent in the dermis, blood vessels and dermis of adjacent tissue; Low intensity band in ulcer sample compared to normal or diabetic skin	Jude *et al.* (1999); [49]
	D; V	IHC; IF; Western	Comparable levels across ulcer tissues, diabetic skin and normal skin	Jude *et al.* (2002); [69]
Transforming growth factor-β_2	V	Indirect IF	No staining observed in epidermal margin of ulcer; Positive staining of fibroblasts and inflammatory cells within wound margins; Staining intensity reduced in ulcer tissue compared to control tissues; Marked cellular staining of healing ulcer tissue compared to non-healing in fibroblasts and granulation tissue	Cowin *et al.* (2001); [68]
	D; V	IHC; IF; Western	Significantly higher IF staining over normal skin; Significantly higher IF staining over diabetic skin	Jude *et al.* (2002); [69]
Transforming growth factor-β_3	V	Indirect IF	Reduced epidermal staining at wound margins; Inflammatory cell staining at wound margins; No staining within any non-healing ulcers; Positive staining for all healing ulcers	Cowin *et al.* (2001); [68]
	D; V	IHC; IF; Western	Staining in all three epidermal layers of at margin of ulcers; Staining greatest at the edge of the ulcer; No staining within the ulcer; Staining only in basal epidermal layers of healthy skin; Western blot showed comparable levels at ulcer edge, diabetic skin and normal skin	Jude *et al.* (2002); [69]
Transforming growth factor-β receptor 1 (TRI)	V	Indirect IF	Intense staining at wound epidermal margins in contrast to control tissue; Staining in fibroblasts in dermal ulcer margin; Staining of inflammatory cells and fibroblasts of ulcer bed	Cowin *et al.* (2001); [68]
	V	IHC	Staining of vessel endothelium, keratinocytes and fibroblasts; Staining in dermis higher in ischemic than control tissues; More staining than TRII	Dalton *et al.* (2007); [52]
	D	IHC	Significantly increased staining in	Galkowska *et al.* (2006);

			suprabasal keratinocytes compared to control tissues; Significantly increased in endothelial cells compared to control tissues	[55]
	D; V	IHC; IF	Distribution the same as diabetic skin and normal skin, though significantly less intense	Jude *et al.* (2002); [69]
Transforming growth factor-β receptor 2 (TRII)	V	Indirect IF	Lower staining a epidermal margins compared to control tissue; Staining of inflammatory cells and fibroblasts in ulcer margins; No staining within ulcer bed; Staining in healing ulcers localised to fibroblasts	Cowin *et al.* (2001); [68]
	V	IHC	Staining of vessel endothelium, keratinocytes and fibroblasts; Staining in dermis higher in ischemic than control tissues	Dalton *et al.* (2007); [52]
	D; V	IHC; IF	Distribution the same as diabetic skin and normal skin, though less intense	Jude *et al.* (2002); [69]
Tumour necrosis factor-α	V	Multiplex ELISA	Significantly higher in ulcer tissue compared to healthy tissue; Ulcer tissue concentration significantly reduced following 4 wks compression therapy	Beidler *et al.* (2009); [58]
	V	IHC	Staining was significantly higher in ulcer tissue compared to normal skin; Ulcers with shorter duration had significantly lower staining	Charles *et al.* (2009); [70]
	V	ELISA	No significant changes reported over 8 wk healing period	Fivenson *et al.* (1997); [21]
Urokinase plasminogen activator	V; P	ELISA; Bioimmmunoassay	Detected in 27/28 wound edge biopsies at significantly lower concentrations that surrounding skin; Concentration were greater in venous than ischemic ulcer tissues	Stacey *et al.* (1993); [67]
Vascular cell adhesion molecule-1	V	IHC	Staining increased ~30% in peripheral ulcer tissue over healthy tissue	Weyl *et al.* (1996); [56]
Vascular endothelial growth factor	V	ELISA	Significantly elevated in ischemic compared to matched non-ischemic samples; Close correlation to lactate concentration	Dalton *et al.* (2007); [52]
	V; D	IHC	Variable staining across ulcer and control tissues	Galkowska *et al.* (2005); [50]
	V	IHC	Increased staining compared to normal skin in basal and suprabasal layers of the hyperplastic epidermis	Lauer *et al.* (2000); [42]
Vascular endothelial growth factor receptor 1	V	IHC	Low levels of staining in endothelial cells, keratinocytes and non-endothelial cells in non-ischemic wound tissue; Similar in ischemic tissues with some elevated staining associated with papillary vessels	Dalton *et al.* (2007); [52]
Vascular endothelial growth	V	IHC	Staining in vessel endothelium in the dermis of both ischemic and non-	Dalton *et al.* (2007); [52]

factor receptor 1			ischemic wound tissue; Staining always associated with type IV collagen; Both area and intensity elevated in ischemic tissues	
Very late activated antigen-4	V	IHC	Strong surface staining of leucocytes in peripheral ulcer tissue compared to healthy skin; ~50% increase in capillary loop staining in peripheral ulcer tissue compared to healthy skin	Weyl *et al.* (1996); [56]

V, Venous ulcer; **D,** Diabetic ulcer; **P,** Pressure ulcer; **NS,** Ulcer type not stated; **ELISA,** Enzyme-linked immuno-sorbent assay; **IHC,** Immunohistochemistry; **Wks,** Weeks; **IF,** immunoflourescence; **Mth,** Months

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