

Role of small fibre neuropathy and microvascular hyperaemia in wound healing in diabetes

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Foot ulceration and wound healing

- In the absence of macrovascular disease the pathogenic mechanisms involved in foot ulceration are not fully understood
- Hyperglycaemia, neuropathy and in particular microvascular dysfunction have been believed to play a role in the development of foot ulceration and delayed wound healing in diabetes

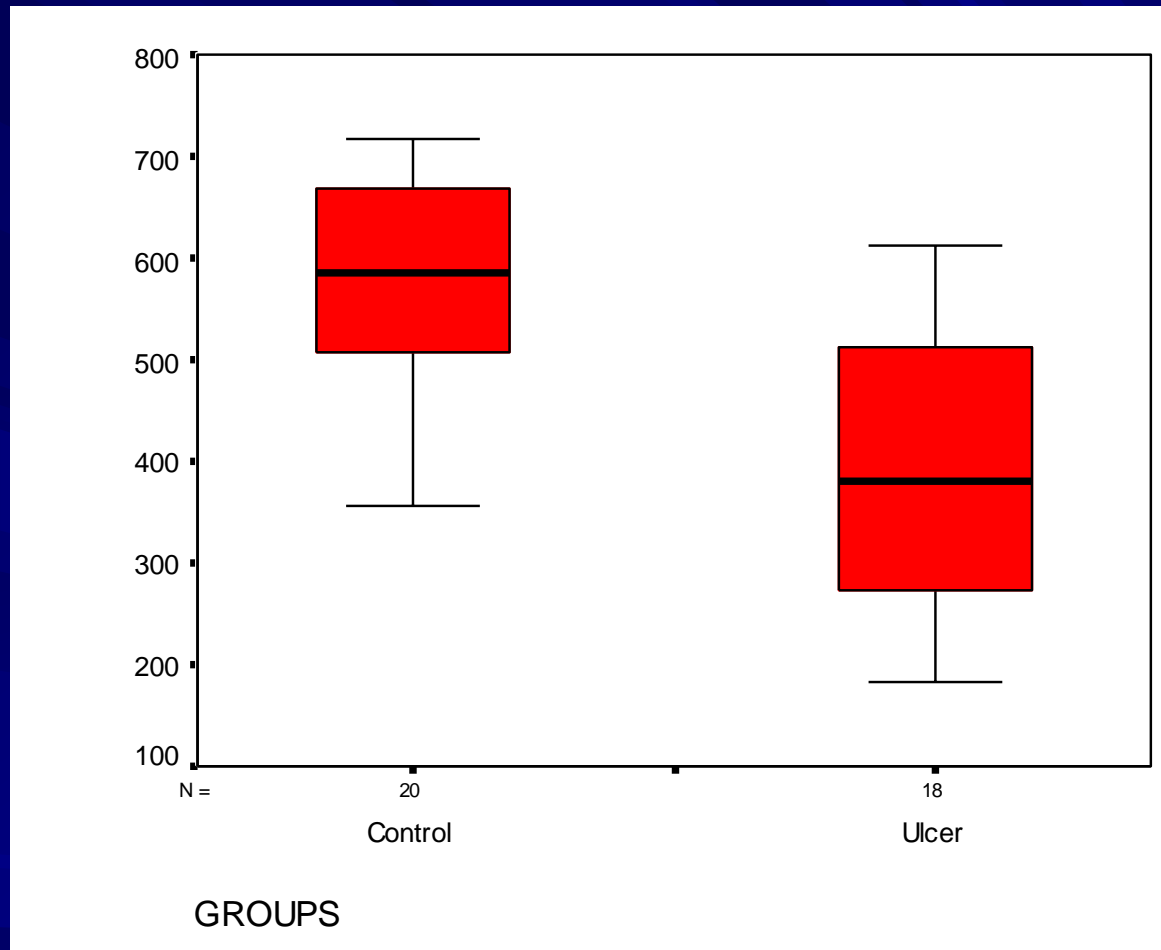
Microcirculation in diabetes

- A variety of cutaneous microvascular abnormalities have been described in people with diabetes, of which impaired vasodilatation appears to be a consistent finding
 - iontophoresis of vasoactive substances
 - post occlusive hyperaemia
 - tissue injury including skin heating (44⁰ C) and mechanical trauma (needle injury)

Microvascular function and Foot Ulceration

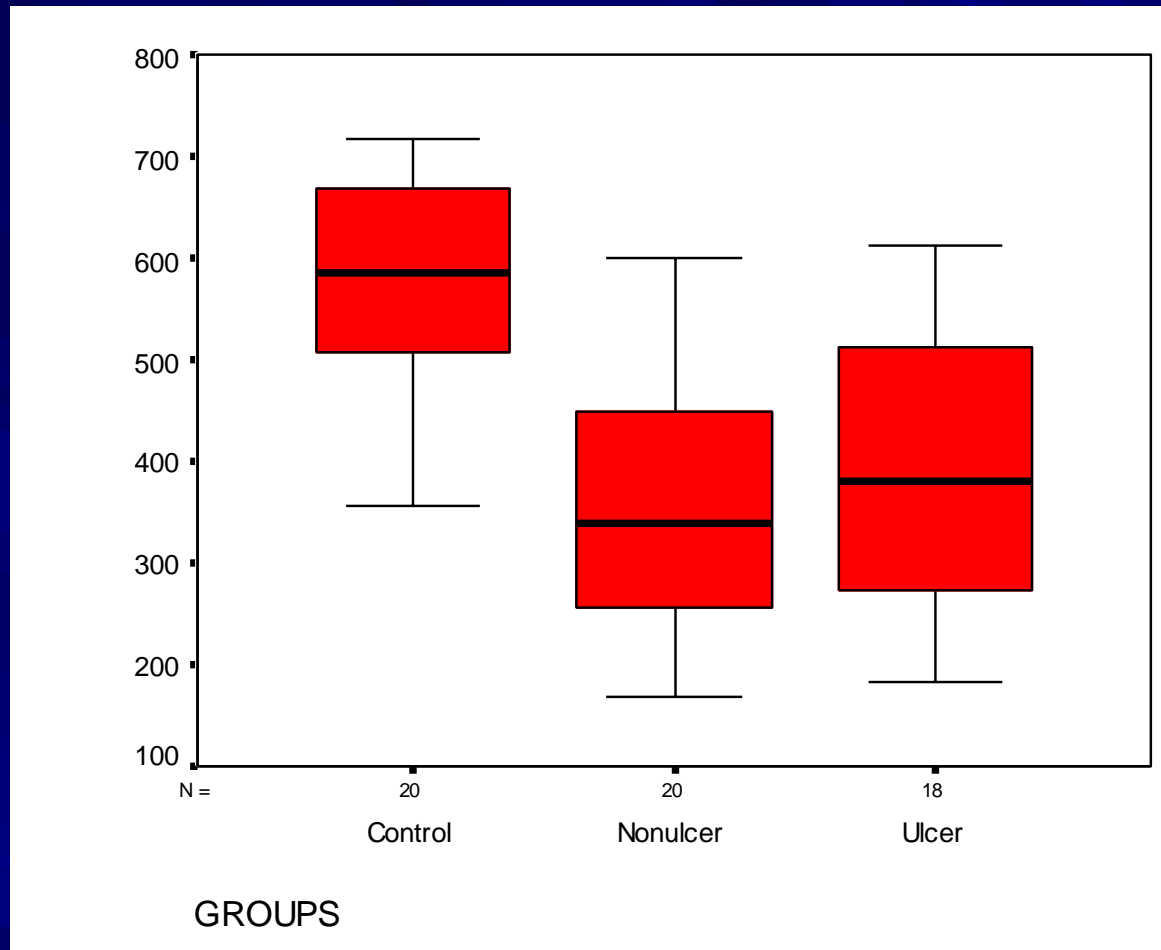
- If microvascular dysfunction is involved in the development of foot ulceration, these abnormalities would be expected to be more severe in those who have ulcerated
- Until recently, there have been no studies which have specifically compared microvascular function in patients with and without foot ulceration

Microvascular Dysfunction and Foot Ulceration



Median [Inter-quartile range]

Microvascular Dysfunction and Foot Ulceration



Median [Inter-quartile range]

Microvascular function and Foot Ulceration

- Thus, microvascular function alone may not play an aetiological role in the development of foot ulceration
- However, this does not exclude a role for microvascular dysfunction in delayed wound healing

Wound healing in Diabetes

- There have been few human studies examining wound healing in patients with diabetes

Wound healing in Type 2 diabetes

Aim

- To examine wound healing in human subjects with diabetes and to determine whether this is influenced by microvascular function

Subjects

- Two groups were studied
 - Group DN- 12 Type 2 diabetics with neuropathy
 - Group HC - 12 Age and sex matched healthy volunteers
- Subjects with macrovascular disease were excluded (ABPI of < 0.8)

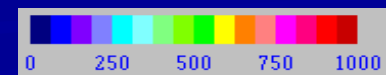
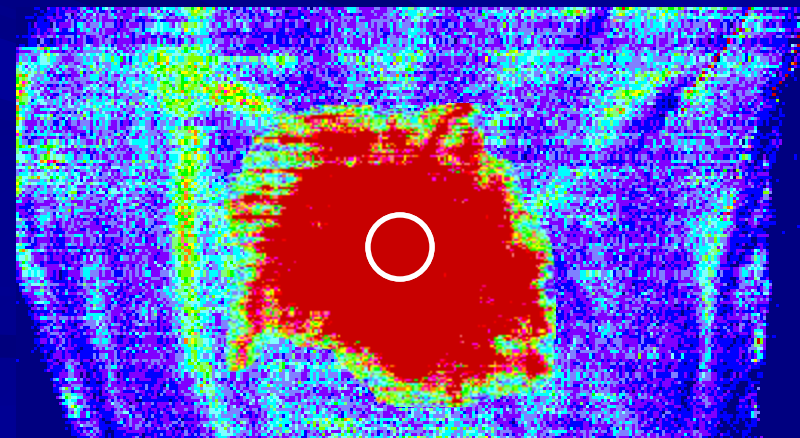
Subject characteristics

	NC [n = 12]	DN [n = 12]
Age [years]	50.2 [56.0, 62.2]	54.0 [55.0, 61.5]
Duration [years]	--	10.0 [5.8, 14.8]
BMI [Kg/m ²]	25.40 [22.9, 27.4]	32.3 [30.6, 34.8]
HbA1 _c [%]	--	8.80 [8.40, 9.1]
ABPI	1.1 [1.0, 1.2]	1.2 [1.0, 1.3]
VPT (Volts)	7.0 [4.3, 8.0]	40.7 [23.7, 51.0]
10g MF / PP	Normal	Abnormal

Median [Inter-quartile range]

Methods - Laser Doppler

- Acclimatisation - 30 minutes in a temperature controlled room
- The skin heated with the skin heater to 44°C for 20 minutes
- The area was scanned with laser doppler imager
- The scan images were stored and processed offline



Neurovascular Assessment

- The mean flux within the hyperaemic area (LDI_{max}) was calculated by using MoorLDI version 3.11 software™
- A region of interest was drawn around the flare in the flux image and the area was calculated (LDI_{flare})

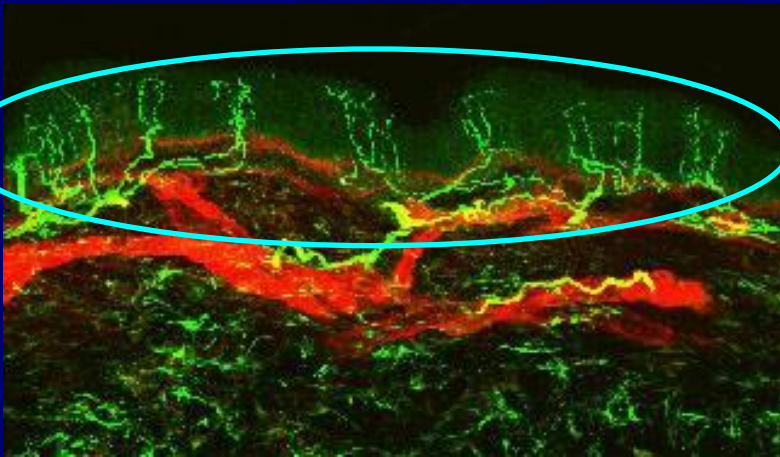
Methods - Skin biopsy

- 3mm punch biopsies from the same area of the foot
- Serial 5 μ m sections of paraffin embedded specimens were immunostained with protein gene product 9.5
- Counting was performed with light microscopy at 400X magnification
- The density of dermal nerve fibres were calculated per mm²

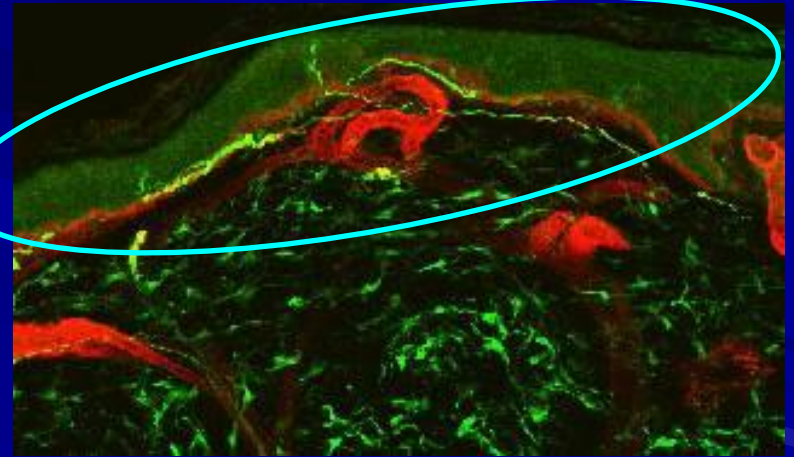
Methods - Skin biopsy

- *Dermal nerve fibres with PGP 9.5 immunostaining*

HC



DN



Methods - Wound Closure

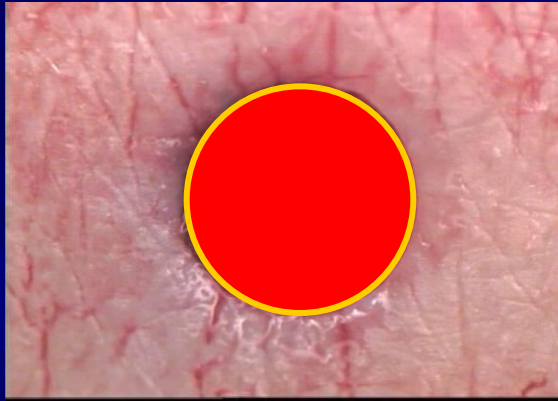


Methods - Wound Closure

- Wound closure was assessed by digital microscopy (magnification x50)
- Images were taken immediately after biopsy, day 3 and 10
- All the images were stored in a computer in windows bitmap™ format
- From computerised images wound area was calculated using “Mouseeyes” software
- The wounds were dressed with sterile lyofoam™ dressings

Methods - Wound Closure

Day 0



Day 3



Day 10



Results

	HC	DN	p - value
LDI flare cm ²	5.18 +/- 1.8	1.8 +/- 0.68	p < 0.0001
LDI max (PU)	577.4 +/- 125.3	310.33 +/- 97.3	p < 0.0001
NFD mm ²	456.7 +/- 160	216.4 +/- 143.7	p = 0.006

(mean +/- SD)

Results

	HC	DN	p - value
Day 0	6.28+/-0.3	6.17 +/- 0.5	p = 0.78
Day 3	4.89 +/- 0.8	4.63 +/- 0.4	p = 0.56
Day 3	3.01 +/- 0.7	2.93 +/- 0.5	p = 0.95

(area in mm², mean +/- SD)

Results

- Thus, despite neuropathy and microvascular dysfunction, wound healing is not delayed in type 2 diabetes

Discussion

- What causes chronic ulcers and delayed wound healing in subjects with diabetes?

Discussion

- Clearly in those with neuropathic ulcers, pressure is a key factor and thus off loading is essential for wound healing



Infection



Discussion

- Subjects with diabetes have an increased risk of infection
- Several immune function factors are related to this increased risk
- Defective neutrophil function affects adherence to endothelium, chemotaxis, and phagocytosis
- Impaired antioxidant systems involved in bactericidal activity and cell-mediated immunity
- Hyperglycaemia exacerbates these defects

Discussion

- Good glycaemic control, appropriate use of antibiotics and wound debridement is essential in treating infection and to facilitate wound healing



Conclusion

- In the absence of infection, wound healing is not delayed in type 2 diabetes despite neuropathy and microvascular dysfunction

Thank you for your
attention