



Can't see the wood for the trees ... PAD?

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Hello from a slightly warm Kuwait and welcome again to another *Diabetes Digest*. The main paper that I have chosen focuses upon a topic that, as I have mentioned before, is not given enough applied attention. It is without doubt the major contributing factor to lower-limb amputation ... peripheral arterial disease (PAD). The paper by Manu et al (2020) is from Kings College, London, and looks at PAD within the foot. Sadly, over the past few decades there has been very little progress or change in the way we clinically determine the presence of PAD at the bedside in the diabetic lower limb. This paper is well worth reading. It does have some flaws but equally, it does point the way forward for further research/ investigation, which hopefully it will stimulate. Manu et al (2020) raise the point that the emphasis upon determining PAD is within the leg and not the foot, using ankle brachial indices (ABI) and pulse palpation as the standard clinical tests. This, as they point out, does not determine the arterial supply within the foot and ask is where our focus should in fact lie? They have attempted to answer this by conducting a cross-sectional observational study.

They used four tests to determine PAD, two proximally by palpation of pedal pulses and ABI, and two distally by Toe Brachial Index (TBI), forefoot transcutaneous oxygen tension (TcPO₂). A total of 154 patients were consecutively recruited from the diabetic foot clinic with a mean age of 63 years. Seventy-nine-per-cent were males, 77% had type 2 diabetes and there was a mean diabetes duration of 21 years. At the time of assessment, 59% had active foot ulceration. From the 154 subjects recruited, 308 limbs were examined, of which 37 were unable to undergo ABI due to previous amputation, recent bypass surgery and leg ulceration. Only 59% of subjects had active ulceration. In total, 301 limbs were assessed for pulses, TBI and TcPO₂.

The study criteria for determining PAD were the

absence of one or both pulses, an ABI of <0.9, TBI of <0.75 and TcPO₂ of <60 mmHg. They used Arterial Duplex as the gold standard for corroborating PAD against the study tests. However, this was only performed against a subset of subjects who had Duplex waveform studies performed as part of the patient's routine clinical care within a month of their recruitment to the study. A triphasic waveform was deemed normal, while anything else was considered to be PAD.

Using these criteria, foot PAD was detected in 70% and 74% by TBI and forefoot TcPO₂, respectively, and ankle PAD in 51% and 34% by pulse palpation and ABI, respectively. In those with "normal" ABI, foot PAD was present in 70% indicated by low TBI and in 73% by low TcPO₂. When compared with arterial Duplex waveforms, TBI gave an excellent AUC (area under the curve of the receiver operating characteristic curve) of 0.81 (95% confidence interval: 0.73–0.89), but ABI gave a poor AUC of 0.65 (95% confidence interval: 0.55–0.76).

In conclusion, the authors state that PAD in the foot may be missed if relying upon ABI as a measure of PAD and that TBI should be performed to determine foot PAD routinely. This study is interesting and again highlights the need to review how we clinically determine PAD. However, we need to be mindful of correctly identifying significant PAD, as opposed to some reduction in arterial inflow. Longitudinal data would be required to truly identify the prognostic value of foot PAD. The message is clear for those with foot ulceration; either or both TcPO₂ or TBI should routinely be performed for all ulcerated patients. Hopefully, this commentary and the paper will stimulate debate and clinical practice reflection. ■

Manu C, Freedman B, Rashid H et al (2020) Peripheral Arterial Disease Located in the Feet of Patients with Diabetes and Foot Ulceration Demands a New Approach to the Assessment of Ischemia. *Int J Low Extrem Wounds* 1534734620947979 [Online ahead of print]

Pain

Increased peptidergic fibers as a potential cutaneous marker of pain in diabetic small fiber neuropathy

Readability ✓✓✓✓
Applicability to practice ✓✓
WOW! Factor ✓✓✓

1 As a common complication of diabetes, diabetic polyneuropathy (DPN) is often associated with neuropathic pain. The authors undertook a detailed skin biopsy analysis in a well-characterised group of DPN patients.

2 Due to the fact that the underlying mechanisms of painful DPN are predominantly unknown, the authors posited that the identification of possible pain pathophysiological biomarkers in patients with painful DPN could improve knowledge of the mechanisms supporting neuropathic pain. In addition, the apparatuses underlying the quantification of intraepidermal nerve fiber density (IENFD) from skin biopsy do not differentiate between those with and without pain.

3 The DPN patients in the study had primarily small fiber involvement, with and without pain, while the controls involved healthy people. Peptidergic nerve fiber density correlated with pain ratings in those with painful DPN ($R=0.33$; $P=0.019$) but not with quantitative sensory testing results.

4 It was found there was an increased density of dermal peptidergic fibers in painful DPN. Compared with painless DPN and healthy controls. This opens the door to further research towards new therapeutic targets.

Karlsson P, Provitera V, Caporaso G et al (2020) Increased peptidergic fibers as a potential cutaneous marker of pain in diabetic small fiber neuropathy. *Pain* j.pain.000000000002054. [Online ahead of print]. *D* 14(4): 341–6

Nutrients

High-dose vitamin D supplementation improves microcirculation and reduces inflammation in diabetic neuropathy patients

Readability ////
 Applicability to practice ////
 WOW! Factor //

- 1 Different doses of vitamin D supplementation were analysed on microcirculation, signs and symptoms of peripheral neuropathy and inflammatory markers in type 2 diabetes (T2DM) patients and those with peripheral neuropathy (PN).
- 2 A total of 67 patients with T2DM and 34 with PN were earmarked for this study. They were randomised into two treatment groups whereby one was treated with cholecalciferol 5,000 IU and 40,000 IU once per week orally for 24 weeks.
- 3 After a number of signs (severity of neuropathy, cutaneous microcirculation parameters and inflammatory markers) were measured before and after treatment, vitamin D deficiency/insufficiency was found in 78% of the 62 completed subjects.
- 4 Treatment with the higher dose of cholecalciferol resulted in a significant decrease in neuropathy severity, as well as an improvement of cutaneous MC and an increase in IL-10 level. No changes were detected in the lower dose cholecalciferol group.
- 5 It was deduced that high-dose cholecalciferol supplementation was linked to improvement in clinical manifestation, cutaneous microcirculation and inflammatory markers in T2DM patients and PN.

Karonova T, Stepanova A, Bystrova A, Jude EB (2020) High-dose vitamin D supplementation improves microcirculation and reduces inflammation in diabetic neuropathy patients. *Nutrients* 12(9): E2518.

Int Wound J

Wound assessment, imaging and monitoring systems in diabetic foot ulcers: a systematic review

Readability ////
 Applicability to practice ////
 WOW! Factor ////

- 1 Existing literature on the available wound assessment and monitoring systems for diabetic foot ulceration (DFU) was reviewed. These were articles published between 1974 and March 2020 on PubMed and Embase with all studies related to wound assessment or monitoring systems in DFUs included.
- 2 A total of 531 suitable articles were found with papers on other types of wounds, review articles and non-English texts excluded. It was decided that 17 studies were eligible for the final analysis and five modalities were identified: 1) hand-held devices or computer applications ($n=5$); 2) mobile applications ($n=2$); 3) optical imaging ($n=2$); 4) spectroscopy or hyperspectral imaging ($n=4$); and 5) artificial intelligence ($n=4$).
- 3 While 16 studies focused on wound assessment or monitoring, just one reported on data capturing. The two reporting on the use of computer applications found low inter-observer variability in wound measurement. High accuracy was found in hand-held commercial devices and the use of spectroscopy or hyperspectral imaging in prediction of wound healing had a sensitivity and specificity of 80% to 90% and 74% to 86%, respectively.
- 4 The authors concluded that the majority of wound imaging systems are superior to traditional wound assessment and, therefore, should be used as adjuncts in DFU monitoring.

Chan KS, Joseph Lo Z (2020) Wound assessment, imaging and monitoring systems in diabetic foot ulcers: A systematic review. *Int Wound J* doi: 10.1111/iwj.13481. [Online ahead of print]. *BMJ Open* 10(3): e026345

Mater Sci Eng C Mater Biol Appl

Impact of sleep apnoea-hypopnoea syndrome on diabetic neuropathy. A systematic review

Readability ///
 Applicability to practice ///
 WOW! Factor ////

- 1 As it has been postulated that diabetes mellitus and sleep apnoea-hypopnoea syndrome are linked, the authors conducted a systematic review to this effect.
- 2 Three electronic databases were searched with only studies published from 2000 onwards in the English, French, Portuguese or Spanish language included. Twelve articles met the inclusion criteria with six of these focusing on people with type 2 diabetes.
- 3 In the selected studies, overall prevalence of sleep apnoea-hypopnoea syndrome was found to be 43.7% (1,559 of 3,564 patients). In nine studies, diabetic neuropathy was more frequent in those with sleep apnoea-hypopnoea syndrome. Four of these nine studies found a significant prevalence (60% vs 27%, $P<.001$; 64.5% vs 36%, $P=0.03$; 37% vs 23.4%, $P<0.02$; 66.6% vs 0%, $P=0.007$). Diabetic neuropathy was found to be more frequent in patients without sleep apnoea-hypopnoea syndrome (although not statistically significant) in one study.
- 4 The study's results implied a not insignificant relationship between diabetes mellitus and sleep apnoea-hypopnoea syndrome in terms of the occurrence of diabetic neuropathy.

Abelleira R, Zamarron C, Ruano A et al (2020) Impact of sleep apnoea-hypopnoea syndrome on diabetic neuropathy. A systematic review. *Med Clin (Barc)* S0025-7753(20)30567-4 [Online ahead of print]. *Mater Sci Eng C Mater Biol Appl* 111: 110837

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