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Assessment of Tissue Glycation on Plantar Soft Tissue Stiffness

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SUMMARY
Clinically, it has been recognized that tissue glycation due to hyperglycemia increases plantar soft tissue stiffness and leads to development of foot ulcer (plantar soft tissue injury that penetrates the foot skin). Despite the severity and prevalence of ulcer formation, little is known about the risk factors associated with foot ulcers and their objective diagnoses. There are several existing tools used by clinicians to assess ulcer risk in diabetic patients like monofilament, tuning forks, biothesiometers, neurothesiometers etc.

However, these measure subjective sensing ability which only indirectly indicates foot ulceration risk. The objective of this study is to hence investigate the relationship between plantar tissue stiffness and tissue glycation due to diabetes mellitus.

INTRODUCTION
Diabetes mellitus is a '21st century epidemic' affecting 8.3% of the world's adult population. This figure is expected to rise to 9.9% by 2030 [1]. Singapore has a diabetic prevalence of 11.3%, which is one of the highest in the developed world [2]. The profound impact of diabetes on life expectancy and quality of life warrants continuous improvement in screening modalities to allow early detection and complication reduction.

Core pathological changes among diabetics occur at cellular level. Reactions between reducing sugars and cellular proteins leads to the formation of multiple compounds collectively referred to as advanced glycation end products [3]. These are laid down in tissues throughout the body, including skin, connective tissue and blood vessels, significantly altering the tissue's innate micro-architecture. Electron microscopy studies have supported this theory, showing evidence of glycation induced irregular collagen alignment and increased collagen fibril density in patients with diabetes, as well as in in-vitro models [4,5]. In fact, there has been data from a large diabetic cohort, suggesting glycated collagen measured via skin biopsies to be a highly consistent parameter associated with diabetes complications, even comparable to HbA1c levels [6]. Accumulation of glycation end products accelerates age-related changes in the skin and connective tissue, decreasing elasticity [7] and in turn making the tissues stiffer. It is therefore postulated that plantar tissue stiffness serves as an indirect measure of tissue glycation, and in turn a reflection of the body's overall glycemic control.

Furthermore, a stiffer plantar tissue, regardless of glycemic control, makes the foot less compliant to pressures and stresses, and contributes to skin breakdown, which can rapidly lead to ulcers among diabetics. Tissue stiffness therefore, along with neuropathy and vasculopathy, may be an additional contributing factor to ulcer formation.

METHODS
Identification of the localized mechanical response of the plantar soft tissue to external loading is the key to understanding diabetic foot abnormality and predicting whether ulceration is imminent. The tissue mechanical response depends on various parameters, such as the external load (direction and rate) and tissue properties (anisotropy and viscoelasticity).

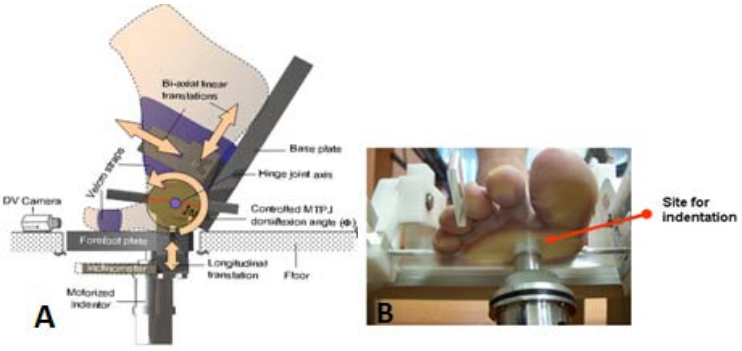

Figure 1: (A) Schematic diagram of indentor system (B) Experimental setting.

35 normal and 5 diabetic subjects of similar physical attributes participated. Indentor system [8] used was shown in Figure 1. During testing, indentor tip probed the plantar soft tissue to obtain localized mechanical response underneath the 2nd metatarsal head pad, hallux and heel. Maximum tissue deformation was set at 5.6mm (close to literature data) [9].

RESULTS AND DISCUSSION

Preliminary data on a small sample of non-diabetic subjects and diabetic patients has been obtained (Figure 2). The diabetic group was noted to have significantly stiffer plantar tissues than their age-matched control counterparts (Table 1). Preliminary results demonstrate the capability to discriminate diabetics from non-diabetics at a stiffness level of 7N/mm, with 90% accuracy (Table 2). For the pilot study, serum HbA_{1c} levels were not measured, nor was the linkage between stiffness with diabetic foot complications examined.

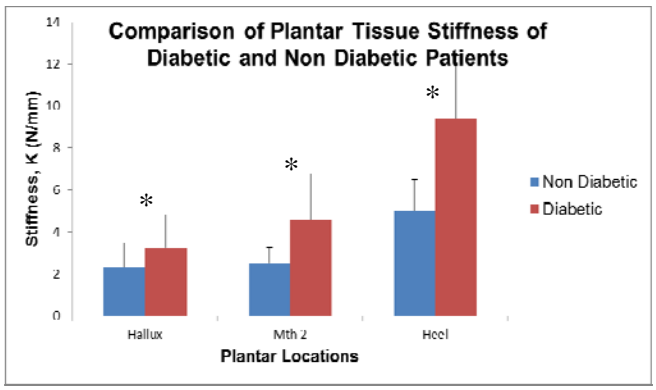

Figure 2. Comparison of plantar soft tissue stiffness between diabetic and non diabetic healthy subjects

Table 1: Comparison of tissue stiffness between diabetic and control groups

Group	Number	Mean Stiffness (N/mm)	Standard Deviation	95% *CI*
Control	35	4.9995	1.48869	4.4881 – 5.510
Diabetic	5	9.3822	3.02387	5.6276 - 13.1368
Total	40	5.5473	2.24157	4.8305 - 6.2642

P-value *<0.001*

Table 2: Discrimating DM vs non-DM at a stiffness level of 7N/mm^2

Stiffness	Diabetes	Non-Diabetes	
Stiffness > 7N/mm	4	3	7
Stiffness < 7N/mm	1	32	33
Total	5	35	40
Sensitivity	4/5 (80%)		
Specificity	32/35 (91%)		
PPV	4/7 (57%)		
NPV	32/33 (97%)		
Accuracy	36/40 (90%)		

CONCLUSIONS

Notably based on the study conducted on the limited samples, tissue glycation resulted in stiffer tissue property. This critical scenario was of utter importance as stiffer tissue indicated higher ulceration risk. This study successfully demonstrated the positive relationship between tissue glycation and plantar soft tissue stiffness in a realistic manner.

To further quantify the subtle relationship between hyperglycemia (diabetes) and plantar tissue stiffness, a cross-sectional study comparing plantar tissue stiffness and related parameters among diabetics and non-diabetics as well as an additional analysis within the diabetic group based on the presence of foot ulcers will be conducted.

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REFERENCES

1. No Authors. The Global burden, Diabetes Atlas. *International Diabetes Federation* (2011).
2. No Authors. National Health Survey 2004 and 2010. *National Registry of Diseases* (2011)
3. Ahmed N, Thornalley PJ: Advanced glycation end products: what is their relevance to diabetic complications? *Diabetes Obes Metab* 9:233–245, 2007
4. Bai P, Phua K, Hardt T, Cernadas M, Brodsky B. Glycation alters collagen fibril organization. *Connect Tissue Res* 1992;28:1-12.
5. Grant WP, Sullivan R, Sonenshine DE, et al. Electron microscopic investigation of the effects of diabetes mellitus on the Achilles tendon. *J Foot Ankle Surg* 1997;36:272-8.33.
6. Monnier VM, Bautista O, Kenny D, Sell DR, Fogarty J, Dahms W, Cleary PA, Lachin J, Genuth S: Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. DCCT Skin Collagen Ancillary Study Group. *Diabetes* 48: 870 – 880, 1999
7. Sell DR, Biemel KM, Reihl O, Lederer MO, Strauch CM, Monnier VM: Glucosepane is a major protein cross-link of the senescent human extracellular matrix. Relationship with diabetes. *J Biol Chem* 280: 12310 –12315, 2005
8. Chen WM, Shim VPW, Park SB et al. An instrumented tissue tester for measuring soft tissue property under the metatarsal heads in relation to metatarsophalangeal joint angle. J Biomech 44(9): 1801-1804, 2011.
9. Cavanagh PR. Plantar soft tissue thickness during ground contact in walking. J Biomech 32(6): 623-628, 1999.