Genetic Polymorphisms May Influence the Development and Healing of Sitting-Acquired Pressure Ulcers Following Spinal Cord Injury

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Sitting-acquired pressure ulcers (SAPUs) are serious secondary complications in individuals with spinal cord injury (SCI). The incidence of pressure ulcers in adults with SCI living in the community is more than 30% per year and up to 80% over a lifetime.¹⁻³ They occur over the bony prominences of the pelvis, and multiple risk factors have been associated with their development and recurrence. One factor that has been associated with a higher rate of recurrence of SAPU is African American race,⁴ which suggests the possibility of a genetic predisposition to the development of ulceration.

Studies on different types of chronic wounds, in particular venous leg ulcers, have found that there is an association between the development of the chronic wound and a number of genetic polymorphisms⁵⁻⁸ (Table 1). One of the polymorphisms has also been associated with impaired healing of chronic venous leg ulcers.⁹ Most of these polymorphisms are in genes that regulate the expression of different proteins.

Genetic polymorphisms are differences in the DNA sequences that occur between individuals, groups, or populations. The variation may occur in the coding region for a protein or may occur in a region that regulates protein expression. Single nucleotide polymorphism (SNP) is a source variance in a genome that is a single base mutation in DNA.¹⁰ SNPs are the most simple form and most common source of genetic polymorphism in the human genome (90% of all human DNA polymorphisms).

Table 1. Associations between genetic polymorphisms and venous leg ulcers

Polymorphisms associated with venous ulcer development	
Tumour necrosis factor α promoter ⁵	TNF α -308A
Fibroblast growth factor receptor 2 ⁶	FGF-R2
Haemochromatosis gene ⁷	HFE
Estrogen receptor β ⁸	Er β
Polymorphisms associated with venous ulcer healing	
Coagulation factor XIII ⁹	F XIII-V34L

The association of genetic polymorphisms with other types of chronic wounds raises the possibility that the same factors may be associated with the development of SAPUs following SCI. This concept is supported by the clinical observation that some individuals with the similar risk profile develop SAPUs while others are pressure ulcer free, suggesting an inherent predisposition. The association between race and ulcer recurrence after controlling for socioeconomic status strongly suggests a role for genetic factors.

The objectives of this work within our research group have been to further examine associations between genetic polymorphisms and venous leg ulcers and more recently to assess associations with SAPUs following SCI.

Table 2. Polymorphisms associated with venous leg ulcers.

Series	Cases	N	Controls	N	Polymorphisms associated with venous ulceration
1	Venous leg ulceration	181	Able-bodied - leg	181	Tumour necrosis factor α promoter (TNF α -308A) ⁵
2	Severe venous changes following DVT	125	Minor changes following DVT	116	Hemochromatosis gene (HFE) Prothrombin gene mutation (G20210A)
3	Varicose veins with ulcer	107	Varicose veins with no ulcer	119	Tumour necrosis factor α promoter (TNF α -308A) Fibroblast growth factor receptor 2 (FGF-R2)

Note: DVT = deep vein thrombosis.

Methods

Venous ulcer studies

Three studies have been conducted using different series of subjects with venous ulcers, each with their own group of control subjects.

- Series 1 – To assess factors associated with venous ulceration compared to a control group: Subjects with proven venous ulceration and a control group of subjects with no evidence of venous disease
- Series 2 – To assess factors that are associated with the development of the severe venous changes of lipodermatosclerosis and ulceration, following a previous deep vein thrombosis (DVT): Subjects with evidence of previous DVT who on evaluation at least 2 years after the DVT were categorized as having either severe venous changes with lipodermatosclerosis or venous ulceration, or minor or no venous changes
- Series 3 – To assess factors that are associated with the development of venous ulceration in subjects with varicose veins, but no evidence of DVT: Subjects with venous ulceration and varicose veins but no DVT and a control group of subjects with varicose veins with no DVT and no evidence of ulceration.

SCI and sitting-acquired pressure ulcer

This study is about to commence patient recruitment. The study aims to develop the

AusCAN risk assessment for the development of SAPUs following SCI. The study will assess multiple risk factors for SAPUs including psychosocial, biomechanical, nutritional, blood markers, genetics, comorbidities, and evaluation of function. This is a prospective study of 480 individuals with SCI who will be followed for 3 years. The analysis will be based on whether subjects do or do not develop a SAPU at 3 years.

Evaluation of genetic polymorphisms

In the venous studies, SNPs have been evaluated based on theoretical determination of polymorphisms that may be associated with development of a wound. In the study of SAPUs, genome-wide comparison of polymorphisms will be performed.

Results

Results from the 3 venous ulcer studies are shown in **Table 2**. These studies have confirmed that a number of genetic polymorphisms are associated with the development of venous ulceration. Different polymorphisms are associated with venous ulceration in each of the 3 studies that were undertaken. All but one of these factors has been found to be associated with venous ulceration in previous studies.

The AusCAN study will determine whether genetic polymorphisms are associated with the development of a SAPU following SCI and will take up to 5 years to complete.

Conclusions

The association of venous ulcers with genetic polymorphisms strongly suggests that similar associations may be found with SAPUs following SCI. With any genetic study, large sample sizes make for more valid observations. Ideally, collaboration between different sites would increase sample size and the time taken to make these observations.

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