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"Tread softly because you tread on my dreams."

William Butler Yeats (1865 – 1939)
Irish poet

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ANNALS
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Free Papers

Editorial

Can We End the Human Immunodeficiency Virus (HIV) in Singapore?

Roy KW Chan, [1] *MBBS, FRCP (London), FAMS (Dermatology)*

Reports of clusters of patients with *Pneumocyctis carinii* pneumonia and Kaposi's sarcoma were first reported among homosexual men in 1981 in the United States (US). That year, the New York Times published the first news article on this mysterious new disease and the Gay Men's Health Crisis (GMHC), the first acquired immune deficiency syndrome (AIDS) service organisation was founded. In 1982, additional cases among haemophiliacs, women, infants and blood recipients were reported. In 1983, a major outbreak of AIDS among both men and women in central Africa was reported. In 1984, the causative agent of AIDS was codiscovered by teams in the US and France, and the names 'human immunodeficiency virus (HIV)' and 'acquired immune deficiency syndrome (AIDS)' were adopted. The first cases of HIV infection were reported in Singapore in 1985.

In 1988, the first World AIDS Day was commemorated on 1 December, as an opportunity for people worldwide to unite in the fight against HIV, to show support for people living with HIV, and to commemorate those who have died from an AIDS-related illness. World AIDS Day was the first ever global health day. Also, in 1988 a small group of concerned citizens, banded together to set up Action for AIDS (AfA), a registered society dedicated to tackling AIDS and the accompanying ramifications, complications and consequences of HIV infection in Singapore. In a short space of time, a raft of programmes was rolled out; they covered public education on how HIV was and was not transmitted, outreach programmes to groups at greatest risk of contracting HIV infection that included safer sex campaigns and counselling of infected persons. The scope of programmes expanded to include anonymous HIV testing, improving access to anti-HIV medications, financial assistance for patients and their families, funding behavioural research projects, and advocacy for persons infected with and affected by HIV.

For those who were there at the start of the HIV epidemic, the memories of confusion, fear, anger, pain and death are still haunting, although they have become blurry and somewhat faded. Those were desperate times, but they were at the same time also inspiring and uplifting. In the 1990s, community mobilisation and volunteerism around AIDS was at its height in Singapore as well as around the world. The nascent networks of activist gay men, sex workers, persons living with HIV, and their supporters, organised to seek answers and to come up with solutions to lessen the suffering in their communities. Community mobilisation, activism, close collaboration between scientists, physicians and affected communities, leadership and funding have been the hallmarks of the global response. The history and stories of the AIDS pandemic have been chronicled for posterity in numerous movies, plays, books and other media.

Today, HIV infection has become a chronic manageable disease, the result of their unprecedented collaborative efforts. Yet, while antiretroviral medications may have removed the prospect of almost certain death from AIDS for many who are infected, we have not yet been able to stop the transmission of HIV.

The World Health Organisation estimates that since the beginning of the epidemic, more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV. Globally, 36.7 million (30.8-42.9 million) people were living with HIV at the end of 2016. An estimated 0.8% (0.7%-0.9%) of adults aged 15 to 49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions.[1]

Over the past 10 years, more people infected with HIV have started to receive antiretroviral treatment. The rates of new HIV infections have slowed and the number of people dying of AIDS-related causes each year has decreased. These are major achievements, but are not good enough. New HIV infections are still occurring every day. In Singapore in 2017, 434 persons were diagnosed with HIV. Ninety-six percent of infections were contracted through sexual intercourse, 93% were males, 50% were homosexuals, 10% bisexuals and 36% heterosexuals; 41% of those diagnosed were already in the late stage of HIV infection. Disparities are seen between risk groups—more heterosexuals were diagnosed in late stages compared to homosexual/bisexuals, and more homosexuals/bisexuals (33%) had their HIV infection detected via voluntary screening compared to

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heterosexuals (8%).[2] We still have some way to go to making HIV a thing of the past.

HIV infection today is still an incurable disease that needs to be managed with daily medications, and regular medical consultations. Persons with HIV infection have also to contend with the effects of chronic inflammation that HIV infection inflicts on the body, the potential for drug toxicity and viral resistance, the omnipresent fear of stigmatisation by friends and discrimination by society, and practical issues like completing education, getting and retaining employment, getting health and life insurance, and developing personal and family relationships.

'90-90-90' is the Joint United Nations Programme on HIV and AIDS' (UNAIDS') strategy to curb the HIV epidemic based on expanded access to anti-HIV treatment. This treatment-as-prevention concept has been adopted as a matrix for countries to plan, monitor and evaluate their programmes.[3] When this 3-part target is achieved globally, it is estimated that at least 73% of all people living with HIV worldwide will be virally suppressed. Modelling exercises predict that achieving these targets by 2020 will enable the world to end AIDS as a major global health issue by 2030.

Singapore, while not a country with a high burden of HIV infection, has yet to achieve the 90-90-90 targets. In the most recent analysis (2015) of the HIV testing and treatment cascade (Dr Vernon Lee, oral presentation, 11th Singapore AIDS Conference on 8 December 2018), the estimated number of HIV infections was 7150 (95% CI 6900, 7350), of which 5164 had been diagnosed and notified, leaving a gap of 28% of infections undiagnosed. The number of new infections in 2015 was estimated to have been 350 (95% CI 280, 410). Compared to the analysis for 2013, improvements were recorded in all 3 measures—the proportion of infected persons diagnosed rose from 69% to 72%, the proportion of HIV-infected persons on treatment rose from 77% to 89%, and the proportion of treated persons virally-suppressed rose from 82% to 94%. Overall, it is estimated that 60% of persons living with HIV infection were virally-suppressed in 2015. To achieve better results, earlier and easier HIV testing, more complete linkage of persons testing positive to HIV to care, easier access to affordable treatment and follow-up, and a concerted effort to address HIV-related stigma are needed.

While acting to maximise the prevention effects of anti-HIV treatment, greater efforts are needed to scale up prevention programmes. Anti-HIV treatment alone will not lead to the end of the HIV epidemic. We need to increase resources to implement effective prevention methods that are evidence-based and proven.[4,5,6] The arsenal of HIV prevention strategies has expanded, from conventional methods of HIV testing and counselling, promotion of condoms, blood screening, education and behaviour modification, harm reduction for injecting drug users, treatment of sexually-transmitted infections, to newer methods, for example medical male circumcision and the use of antiretroviral drugs for pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP).[7]

Ending AIDS as a public health threat by 2030 is feasible if high HIV burden cities fast-track their AIDS responses that include these new approaches. Since the World AIDS Day 2014 launch, mayors and other municipal leaders have joined forces with civil society representatives to action the Paris Declaration on Fast-Track Cities.[8] Many cities around the world have committed to the Fast-Track Cities approach.

Singapore is unique because it has a small population, high literacy and educational standards, an active community response, active clinician advocates, and a relatively well funded HIV programme. It is, therefore, in a good position to join the ranks of cities that can end the HIV epidemic by 2030.

It is to this end that a group of interested parties have got together to draft a 'Community Blueprint to End HIV Transmission in Singapore'. Inspired by a similar blueprint produced by the Australian Federation of AIDS Organisations,[9] this project will involve the collective efforts and contributions of relevant stakeholders in the HIV/AIDS programme. It will review the current state of the epidemic in detail, paying attention to key populations affected by HIV, which in Singapore are men-who-have-sex-with-men (MSM), sex workers, heterosexual men with multiple partners, and injecting drug users. For each of these groups, we will review existing programmes, estimate gaps and additional resources needed to close those gaps. We will examine the group of late presenters to understand why they presented late and recommend ways to increase reach and effectiveness of educational and testing programmes. The blueprint will also look for ways to scale-up the use of PrEP for those at highest risk of HIV infection. Cities like Seattle, San Francisco, London and Sydney that have introduced PrEP programmes have registered significant declines in HIV notifications, and Singapore can do the same. To achieve all the above, we will need to estimate the workforce needed, both clinical as well as in the community. Existing programmes are understaffed, for example the AfA MSM programme has 2 fulltime staff, for a target audience size estimated to be somewhere between 140,000 to 300,000. Additional resources to fund manpower training and retention will be needed.

There are 2 other big pieces of the equation. One is to estimate by mathematical modelling the number of HIV infections that could be averted if we can improve prevention programmes by increasing condom use and scaling up PrEP. The other big piece is to calculate the savings for each of these infections averted, based on present-day costs

of treatment and care, on a per annum and lifetime basis. The blueprint will be a living document, to be updated and refreshed as more information becomes available. It is hoped that this community blueprint will form part of the national HIV strategy to end HIV in Singapore.

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Original Article

Incipient Albuminuria in Persons with Newly Diagnosed Type 2 Diabetes Mellitus: A 5-Year Retrospective Cohort Study

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Abstract

Introduction: This study aimed to determine the 5-year incidence of albuminuria among Asian persons with newly diagnosed type 2 diabetes mellitus (DM), and to identify the risk factors at diagnosis for progression to albuminuria. Materials and Methods: A retrospective 5-year closed cohort study was conducted among 1016 persons aged ≥18 years old who were diagnosed with type 2 DM between 1 January 2007 and 31 December 2009 at primary care facilities in Singapore. The cumulative incidence of progression from normoalbuminuria to albuminuria—termed "progression"—was determined. The risk factors associated with progression were evaluated using multiple logistic regression analysis. Results: A total of 541 (53.2%) participants were men. The mean (SD) onset age of type 2 DM was 54 (11) years. From diagnosis of type 2 DM, the 5-year cumulative incidence of progression was 17.3% and mean (SD) duration to progression was 2.88 (1.23) years. Higher onset age (OR 1.02; 95% CI, 1.00-1.04), history of hypertension (OR, 1.88; 95% CI, 1.32-2.70) and higher glycated haemoglobin (HbA1c) (OR, 1.17; 95% CI, 1.09-1.26) at diagnosis were associated with progression. In addition, being on angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) treatment at baseline modified the effect of hypertension on progression. Conclusion: This study highlighted the importance of early screening and treatment of diabetes as well as prevention of hypertension, which could potentially delay the onset of microalbuminuria in persons with type 2 DM. Persons on ACEI or ARB treatment should continue to be monitored regularly for progression to albuminuria.

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Key words: Incidence, New onset, Proteinuria, Risk factors

Introduction

The global prevalence of diabetes among adults over 18 years of age has increased from 4.7% in 1980 to 8.5% in 2014.[1] In Singapore, about 440,000 residents aged 18 years and above had diabetes in 2014, and the number is projected to increase to 1 million in 2050.[2] The incidence of end-stage kidney disease among adults with diabetes is up to 10 times as high as those without diabetes.[1] Singapore ranks first in the world for prevalence of diabetes-induced kidney failure, with diabetes accounting for about 60% of incident cases of end-stage kidney disease which require renal replacement therapy.[3]

Diabetic kidney disease is detected in its early stage by the presence of microalbuminuria, which is defined as urine albumin creatinine ratio of 3.4 mg/mmol or more,[4] or if using gender-specific cutoffs, 2.5 mg/mmol or more for men and 3.5 mg/mmol or more for women.[5] About 20% to 40% of persons with diabetes develop microalbuminuria within 10 to 15 years of diagnosis of diabetes, and approximately 80% to 90% of those with microalbuminuria progress to more advanced stages of kidney disease.[6] Microalbuminuria has also been shown to be an independent determinant of coronary heart disease and death.[7]

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Early kidney disease can be treated with drugs such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), which have been shown to reduce the risk or retard the progression of diabetic nephropathy.[8] Hence, it is recommended that urine albumin excretion should be assessed annually for all persons with type 2 diabetes mellitus (DM), starting at diagnosis of diabetes.[9] The most widely recommended method of testing is the urine creatinine/albumin ratio (UACR), which is determined from a freshly collected random spot urine sample.[10] Due to variability in urinary albumin excretion, 2 or 3 specimens collected within a 3- to 6-month period should be abnormal before a patient is considered to have developed albuminuria.[11]

Given the high health and socioeconomic burden associated with diabetic kidney disease, and the potential for intervention in early disease, it is important to understand the rate of progression to microalbuminuria, and the clinical characteristics of persons with type 2 DM who develop microalbuminuria within the first few years after being diagnosed with type 2 DM. Previous studies in Denmark, Israel, and the United Kingdom[12-14] have shown that the incidence of microalbuminuria in persons with newly diagnosed type 2 DM was about 2% per year, and the prevalence of microalbuminuria was 20% to 24% after 10 years from diagnosis of type 2 DM. A variety of risk factors for microalbuminuria, such as increased age, higher baseline glycated haemoglobin (HbA1c) and serum cholesterol were identified. While there have been a few cross-sectional studies in Asian populations—including a study of 6482 patients in 10 Asian countries where the prevalence of microalbuminuria was found to be 39.8%[15-16]—to our knowledge, no similar cohort study on the incidence of and risk factors for microalbuminuria was done in a Singaporean or Southeast Asian population.[17]

The objectives of this study were to determine: 1) the 5-year cumulative incidence of albuminuria among patients with newly diagnosed type 2 DM in the primary care setting in Singapore; and 2) the risk factors at diagnosis for progression to albuminuria.

Materials and Methods

A retrospective closed cohort study among patients with newly diagnosed type 2 DM was conducted, using electronic medical data from the National Healthcare Group (NHG) Diabetes Registry. This enterprise-wide electronic database links key administrative and clinical information from hospitals, specialty centres and primary care clinics in 1 of the 3 public healthcare clusters in Singapore, and is used to harmonise clinical health records and facilitate seamless care for about 1.2 million patients with diabetes.[18] The following algorithm was used to capture patients into the Registry: 1) rule 1: patients from existing stand-alone diabetes registries; 2) rule 2: patients with diagnosis code of 250.x0, 240.x2 or 363.xx under the International Classification of Diseases, 9th Revision, Clinical Modification (ICD9CM), coded as either the primary or secondary diagnosis; 3) rule 3: patients on antidiabetes medication; and 4) rule 4: patients with 2-hour blood sugar level of ≥11.1 mmol/L on oral glucose tolerance test (OGTT), or a random blood sugar level of ≥11.1 mmol/L on 2 occasions within 2 years, or fasting plasma glucose ≥7.0 on 2 occasions within 2 years, or random blood sugar level of ≥11.1 mmol/L and fasting plasma glucose ≥7.0 within 2 years. Data elements such as the dates and values of key laboratory tests are captured in the system, and a summary of care records, including reminders to order the necessary tests for patients are provided to clinicians.[19]

The study included all patients with: 1) type 2 DM aged ≥18 years old, newly diagnosed between 1 January 2007 to 31 December 2009; 2) normal UACR within 2 months of diabetes onset date; and 3) at least 3 UACR readings during the 5-year follow-up period, where the last UACR was within 15 months of the end of the follow-up period.

Participants seen at 9 public primary care institutions under the NHG who were diagnosed between 1 January 2007 and 31 December 2009 with type 2 DM and had a normal UACR result (UACR <2.5mg/mmol for men and <3.5mg/mmol for women)[5] within 2 months after diagnosis, were followed-up for a period of 5 years. The outcome was progression to albuminuria—termed "progression"—defined as 2 abnormal consecutive UACR tests (UACR ≥2.5 mg/mmol for men and ≥3.5 mg/mmol for women) done maximally 15 months apart.

Ideally, a baseline UACR test should be done at the time of diagnosis,[9] and repeated yearly, if normal. However, in order to allow for any operational or patient-related constraints on the completion of the baseline UACR test at the point of type 2 DM diagnosis, a 2-month postdiagnosis cutoff was used. Sensitivity analysis using a 3-month cutoff did not show any significant differences in participant characteristics, hence a 2-month cutoff period was used. While the diagnostic criteria for diabetic nephropathy is generally accepted as positive results on 2 or 3 UACR tests in a 6-month period,[9] a 15-month cutoff period was used, in line with local recommendations to repeat UACR yearly and to similarly allow for some time buffer for the test to be performed.

There were 31,973 records of patients diagnosed with type 2 DM between 1 January 2007 and 31 December 2009. A total of 27,089 patients did not have a baseline UACR result and hence were excluded. Out of the remaining 4884 records of patients with newly diagnosed type 2 DM, an additional 3426 patients who had abnormal UACR tests at

diagnosis, and 442 patients with missing data during the follow-up period, were excluded. A total of 1016 patient records were used for this analysis (Fig. 1). Participants were termed "Progressors" if they developed albuminuria during the 5-year follow-up period and "Non-progressors" if they did not.

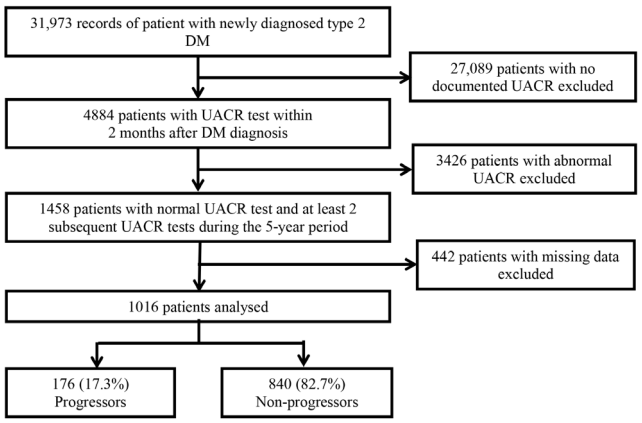

Fig. 1. Study selection flow chart. DM: Diabetes mellitus; UACR: Urine creatinine/albumin ratio.

The 5-year cumulative incidence, and the time from diagnosis to onset of albuminuria (defined as the duration between onset date of diabetes and the test date of the second abnormal UACR) was determined. Participant demographics (age, gender, ethnicity), medical history and other baseline measures which were collected as part of routine standard of care at diagnosis of diabetes—HbA1c, blood pressure, lipid panel, estimated glomerular filtration rate (eGFR), serum creatinine, and body mass index (BMI)—were analysed.

Records of medication prescriptions were also used as a proxy indicator for whether participants were taking ACEIs or ARBs at the time of diagnosis. Participants were considered to be on ACEIs or ARBs if they were prescribed either class of medications within 4 months before diagnosis or within 2 months after diagnosis of type 2 DM (as locally, patients are usually not prescribed more than 6 months' supply of medications at 1 time).

Baseline measures and use of ACEIs or ARBs were compared between progressors and non-progressors to determine factors associated with increased risk of progression to kidney disease. Patient with hypertension were thus stratified by the presence of ACEI or ARB, to determine if the use of ACEI or ARB was a confounder or effect modifier.

Forward stepwise multiple logistic regression analysis was performed to identify significant risk factors. As the first HbA1c reading was positively skewed, the median was used. Statistical significance was defined as $P < 0.05$. Pearson's chi squared test was used for categorical variables, Fisher's exact test was used for discrete variables, and T test and Mann-Whitney U tests were used for continuous variables. Stepwise forward logistic regression analysis was used to identify factors associated with progression to microalbuminuria. Data was analysed using SPSS Statistics 20.0. The study was approved by the NHG Domain Specific Review Board.

Results

Of the 1016 participants, there were 176 progressors and 840 non-progressors. The baseline characteristics of progressors and non-progressors are shown in Table 1.

The mean onset age of diabetes among progressors was higher than that of non-progressors, and there was a slightly larger proportion of males in the study population. Indians accounted for a disproportionately higher number of participants, since they made up 9.2% of the population. This is consistent with the local National Health Survey in 2010 which found that a higher proportion of males were diabetic, and diabetes was most prevalent among Indians (17.2%), compared to Malays (16.6%) and Chinese (9.7%).[20] There were no statistically significant differences in the incidence of microalbuminuria between the different ethnic groups. This is in contrast to a previous cross-sectional study in Singapore, which found that fewer Indians have microalbuminuria (21.0%) compared with Chinese and Malay patients (30.0% and 35.3%, respectively).[21]

More than 40% and 50% of participants had hypertension and hyperlipidaemia, respectively. The mean BMI was 26.9 ± 5.1 kg/m^2, which is higher than the Asian cutoff for moderate risk of cardiovascular disease (i.e. >23 kg/m^2). The mean HbA1c at diagnosis was 8.0%.

Univariate analysis showed that higher onset age of diabetes, higher baseline HbA1c, systolic blood pressure and serum creatinine was associated with increased risk of progression. A history of hypertension (RR 1.54, 95% CI, 1.18-2.01) and use of ACEIs or ARBs (RR 1.49, 95% CI, 1.10-2.02) at diagnosis were significantly associated with progression.

Among participants with hypertension, stratified analysis showed that being on ACEI or ARB at baseline modified the effect of hypertension on development of microalbuminuria Participants on ACEI or ARB had a RR of 3.31, 95% CI, 0.81 to 12.20, while those not on ACEI or ARB had a RR of 1.33, 95% CI, 0.97 to 1.83.

The cumulative incidence of microalbuminuria within 5 years from diagnosis of type 2 DM was 17.3%, or a rate of 3.5% per year. The mean duration between diagnosis of type 2 DM and microalbuminuria incidence was $2.88 \pm$

Table 1. Baseline Variables of 1016 Patients with Newly Diagnosed Type 2 Diabetes Mellitus According to Progression to Albuminuria

Variable	All n = 1016	Progressors n = 176	Non-Progressors n = 840	*P* Value
Onset age (years)	54 ±11	56 ± 11	54 ± 11	0.004
Gender, n (%)				
Male	541 (53.2)	98 (55.7)	443 (52.7)	0.507
Female	475 (46.8)	78 (44.3)	397 (47.3)	0.507
Ethnicity n (%)				
Chinese	663 (65.3)	113 (64.2)	550 (65.5)	0.124
Malay	143 (14.1)	30 (17.0)	113 (13.5)	0.124
Indian	141 (13.9)	17 (9.7)	124 (14.8)	0.124
Others	69 (6.8)	16 (9.1)	53 (6.3)	0.124
Medical history,* n (%)				
Hypertension	434 (42.7)	94(53.4)	340 (40.5)	0.002
Hyperlipidaemia	576 (56.7)	107 (60.8)	469 (55.8)	0.242
Stroke	26 (2.6)	8 (4.5)	18 (2.1)	0.109
On ACEI or ARB	181 (17.8)	43 (24.4)	138 (16.4)	0.017
BMI (kg/m^2)	26.9 ± 5.1	27.2 ± 5.2	26.8 ± 5.1	0.418
SBP (mmHg)	130 ± 17	133 ± 16	129 ± 17	0.004
DBP (mmHg)	77 ± 9	77 ± 9	77 ± 9	0.723
HbA1c† (%)	8.0 (5.1 – 17.6)	8.6 (5.1 – 16.9)	7.9 (5.1 – 17.6)	0.010
LDL-C (mmol/L)	3.31 ± 0.92	3.26 ± 0.86	3.32 ± 0.93	0.465
HDL-C (mmol/L)	1.21 ± 0. 31	1.20 ± 0.32	1.22 ± 0.31	0.537
Triglycerides (mmol/L)	1.61 ± 0.89	1.70 ± 0.87	1.59 ± .089	0.168
Total cholesterol (mmol/L)	5.24 ± 1.02	5.22 ± 0.97	5.25 ± 1.03	0.721
eGFR (ml/min/1.73m^3)	92.51 ± 24.31	90.13 ± 27.82	93.00 ± 23.49	0.154
Serum creatinine (umol/L)	72 ± 20	75 ± 23	72 ± 19	0.022

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BMI: Body mass index; CI: Confidence interval; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SBP: Systolic blood pressure

Values are mean (standard deviation) unless stated otherwise.

*Medical history of hypertension, hyperlipidaemia and stroke were determined by diagnosis codes.

†Median (interquartile range).

1.22 years. With exception of the first year, the cumulative incidence of microalbuminuria over the subsequent 4-year follow-up period increased in a linear fashion (Fig. 2).

In the multiple logistic regression analysis (Table 2), onset age, a history of hypertension and higher baseline HbA1c were found to be significant and independent risk factors associated with progression. For every 1-year increase in type 2 DM onset age, participants had a 1.02 times increased probability of becoming progressors. Likewise, for every 1% increase in baseline HbA1c, participants had a 1.17 times increased risk of becoming progressors. Participants with hypertension were found to be 1.88 times more likely to become progressors.

Discussion

The 5-year cumulative incidence of albumunuria was 17.3%, or 3.5% per year. This is higher than the incidence rate of 2.0% per year in the United Kingdom Prospective Diabetes Study (UKPDS).[12] This may be due to the stricter exclusion criteria for the UKPDS, such as age of more

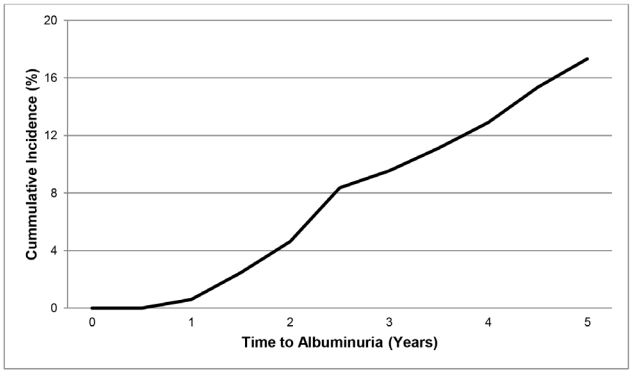

Fig. 2. Cumulative incidence of albuminuria among 1016 patients with newly diagnosed type 2 diabetes mellitus.

Table 2. Multiple Logistic Regression of Variables Associated with Progression to Albuminuria among 1016 patients with Newly Diagnosed Type 2 Diabetes Mellitus

Characteristics*	Univariate Model		Multivariate Model (Stepwise Forward)	
	Odds ratio (95% CI)†	*P* Value	Odds ratio (95% CI)‡	*P* Value
Onset age (year)	1.03 (1.01 – 1.05)	0.010	1.02 (1.00 – 1.04)	0.012
Gender (male vs female)	1.10 (0.69 – 1.76)	0.694	Eliminated	0.290
Hypertension (yes vs no)	1.40 (0.90 – 2.14)	0.134	1.88 (1.31 – 2.70)	0.001
Hyperlipidaemia (yes vs no)	1.10 (0.76 – 1.58)	0.629	-	0.584
On ACEI or ARB (yes vs no)	1.33 (0.86 – 2.07)	0.204	-	0.145
Body mass index (kg/m^2)	1.02 (0.98 – 1.05)	0.343	-	0.206
SBP (mmHg)	1.01 (1.00 – 1.03)	0.028	-	0.081
DBP (mmHg)	0.99 (0.97 – 1.01)	0.99	-	0.876
Baseline HbA1c (%)	1.16 (1.06 – 1.27)	0.001	1.17 (1.09 – 1.26)	0.000
LDL-C (mmol/L)	1.09 (0.47 – 2.50)	0.845	-	0.342
HDL-C (mmol/L)	1.05 (0.38 – 2.92)	0.923	-	0.273
Triglycerides (mmol/L)	1.16 (0.80 – 1.68)	0.442	-	0.311
Total cholesterol (mmol/L)	0.82 (0.36 – 1.88)	0.638	-	0.383
eGFR (ml/min/1.73m^3)	1.01 (1.00 – 1.02)	0.178	-	0.535
Serum creatitine (umol/L)	1.02 (1.00 – 1.04)	0.079	-	0.069
Average HbA1c (%)	1.10 (0.91 – 1.33)	0.326	-	0.282

ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CI: Confidence interval; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated haemoglobin; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; SBP: Systolic blood pressure

*All variables are baseline characteristics except for 5-year average HbA1c.

†Forward stepwise analyses showed the 3 variables which were independently associated with progression.

‡Odds ratio (95% CI) indicates change in risk per unit increase in each variable.

than 65 years, elevated serum creatinine levels, myocardial infarction in the preceding year, existing cardiac failure or malignant hypertension. Gender-specific cutoff values for the UACR were also not used in the UKPDS. On the other hand, the incidence was lower than the 23% found in the study by Gall et al,[13] possibly due to the difference in diagnostic criteria for persistent microalbuminuria. Despite this, both studies showed similar linear increases in incidence after the first year of follow-up.

It is not surprising that higher onset age and baseline HbA1c were associated with faster progression to albuminuria, as these participants could have developed early kidney disease during the lag time between disease development and diagnosis of diabetes. Hypertension is also a known risk factor for kidney disease.[22] On the other hand, baseline eGFR was not found to be risk factor, likely due to the underestimation of GFR at near-normal ranges.[23]

The association between the use of ACEI or ARB and progression to albuminuria was not observed in the logistic regression analysis, likely due to the confounding effect of hypertension, or pre-existing microalbuminuria which was masked by ACEI or ARB treatment prior to the start of the study.[24-25] It is also disconcerting that the use of ACEI or ARB among patients with hypertension was not protective against subsequent kidney disease. This is in contrast with other studies which showed that use of ACEI reduced the absolute risk of developing microalbuminuria by 2% to 4% over 4 to 5 years among normoalbuminuria patients with type 2 DM and hypertension.[26-28]

The risk factors identified in this study were similar to those found in other studies.[13,14] However, some factors such as baseline lipid control, gender, and BMI were not found to be associated with risk of progression, possibly due to genetic and lifestyle differences between the study populations.

There were 27,089 patients who did not have a documented UACR at diagnosis and hence were excluded from the study. Hence, a key recommendation from this study would be that routine UACR be performed for all patients with newly diagnosed type 2 DM. Other findings of particular concern was that 70% of patients were found to have an abnormal UACR at baseline, compared to 38% of patients in the study by Gall et al.[13] Coupled with the finding that the baseline mean HbA1c of participants was 8.0%, these suggest that current screening efforts for diabetes were not identifying persons with diabetes sufficiently early. In addition, more than 40% and 50% of participants had hypertension and hyperlipidaemia, respectively, which is significantly higher than the prevalence of these conditions in the general local population.[20]

The limitations of the study were mainly related to the use of secondary data from a registry. These included the lack of complete data, such as socioeconomic status, cigarette

smoking status,[29] and reasons why patients were on ACEIs or ARBs. In addition, 442 participants were excluded due to missing data. There is scope for further prospective cohort studies on patients across different care settings, and inclusion of these variables which were unavailable for this study. Future studies could also examine patients who had albuminuria at the onset of type 2 DM, to determine their risk factors for albuminuria or progression to chronic kidney disease.

While the NHG Diabetes Registry captures 69% of all detected cases of diabetes in Singapore,[30] it is not a national registry, hence the findings may not be fully generalisable to the Singapore population. Moreover, patients could have been diagnosed with type 2 DM prior to entry into the registry, in which case, the incidence rate of albuminuria could have been overestimated.

Some of the strengths of this study include the large sample size, and the analysis of multiple risk factors at diagnosis, which could potentially impact disease management. It is also one of the few studies which looked at the development of incipient nephropathy in newly diagnosed type 2 DM patients, and to our knowledge, is the first such study in the Asian context.

Conclusion

Among the 1016 patients with newly diagnosed type 2 DM, the 5-year incidence of microalbuminuria was 17.3%. Higher onset age, hypertension and higher baseline HbA1c were found to be significant, independent risk factors for progression to microalbuminuria.

This study highlighted the importance of close monitoring of patients who are older, have hypertension or have poorer diabetic control at diagnosis of type 2 DM. Clinicians should remain vigilant in monitoring patients using ACEIs or ARBs, as these patients were also found to have a higher relative risk, likely due to underlying hypertension, for which the ACEI or ARB was prescribed.

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Original Article

Radiofrequency Microtenotomy with Concurrent Gastrocnemius Recession Improves Postoperative Vitality Scores in the Treatment of Recalcitrant Plantar Fasciitis

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Abstract

Introduction: Gastrocnemius recession and radiofrequency microtenotomy treat plantar fascia via different mechanisms. While studies have shown additive effects in performing plantar fasciotomy in conjunction with gastrocnemius recession, no such study exists examining the effects of performing radiofrequency microtenotomy with gastrocnemius recession. We hypothesised that performing both gastrocnemius recession and radiofrequency microtenotomy concurrently for recalcitrant plantar fasciitis is more effective than performing either procedure individually. Materials and Methods: We analysed all patients who underwent either a radiofrequency microtenotomy, a gastrocnemius recession, or both procedures concurrently between 2007 and 2014. The American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale, the SF-36 Health Survey, and 2 questions regarding patient satisfaction and met expectations were assessed preoperatively and postoperatively up to 1-year. Results: Patients who underwent both procedures concurrently had significantly higher vitality scores on the SF-36 Health Survey at 1-year postoperatively compared to patients who underwent either procedure individually. Type of intervention offered and preoperative factors were not predictive for patient outcomes. Conclusion: Combining radiofrequency microtenotomy and gastrocnemius recession in patients with recalcitrant plantar fasciitis and an underlying gastrocnemius contracture shows favourable medium-term outcomes compared to performing either procedure in isolation.

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Key words: Patient outcomes, SF-36

Introduction

Plantar fasciitis has been reported to be the most common cause of heel pain.[1-3] Conservative treatment options include rest, non-steroidal anti-inflammatory drugs (NSAIDs) medication, physiotherapy, night splinting, orthotics, corticosteroid injections, extracorporeal shock wave therapy (ESWT) and laser therapy.[1,4-8] While up to 90% of plantar fasciitis resolve with conservative treatment, 1 in 10 patients will go on to develop recalcitrant plantar fasciitis that usually requires some form of surgical intervention.[9-12] Surgical treatment for plantar fasciitis is reserved for patients who have failed conservative therapy and is generally viewed as a last resort. Potential complications include poor wound healing, chronic pain and arch collapse. Surgical options include plantar fasciotomy, cryosurgery, nerve ablation, tendoachilles lengthening and gastrocnemius recession.

Despite a name suggestive of inflammatory pathology, histopathological studies of the plantar fascia in plantar fasciitis reveal an absence of inflammation and instead show myxoid degeneration, disorganised collagen hypertrophy and angiofibroblastic hyperplasia with features consistent with a non-inflammatory degenerative fasciosis similar to tendinosis.[13-17] Consequently, the radiofrequency microtenotomy is a surgical procedure that has gained popularity as a safe, effective, and minimally invasive means of treating recalcitrant plantar fasciitis.[9,18-21] The procedure relieves pain via an anti-nociceptive effect of acute degeneration and/or ablation of sensory nerve fibres in the early period,[22] followed by regeneration of nerve fibres within 90 days.[23] The transient anti-nociceptive response is later replaced by a longer term angiogenic healing response.[24]

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Gastrocnemius tightness has been shown to cause altered foot biomechanics, giving rise to various foot pathologies including plantar fasciitis.[6,25-27] Up to 80% of patients with plantar fasciitis have been found to have isolated gastrocnemius contractures[28-30] and trials have shown that gastrocnemius release[31] is successful in treating recalcitrant cases of plantar fasciitis.[32] While studies have shown additive effects in performing a plantar fasciotomy in conjunction with a gastrocnemius recession, no such study exists examining the effects of performing radiofrequency microtenotomy with a gastrocnemius recession.[33,34]

As the procedures act to relieve the symptoms of plantar fasciitis via separate mechanisms, we hypothesised that performing a gastrocnemius recession in conjunction with a radiofrequency tenotomy of the plantar fascia in patients with plantar fasciitis and gastrocnemius contracture results in improved outcomes compared to performing either procedure individually.

Materials and Methods

Patient Recruitment

We reviewed the prospectively collected data of all patients who underwent radiofrequency microtenotomy with or without a gastrocnemius recession from May 2007 to July 2014 at our institution. The inclusion criteria of this study was designed to include only patients with clinically documented plantar fasciitis with a tight gastrocnemius (presence of a positive Silfverskiold test) who had failed at least 6 months of conservative therapy inclusive of stretching exercises, orthotics, and analgesia, had undergone radiofrequency microtenotomy and/or a gastrocnemius recession, and had a full set of clinical data for at least 1 year postoperatively. Patients who were lost to follow-up, had an incomplete set of data, had other concurrent lower limb conditions, or who underwent surgery of the lower limbs concurrently or during the follow-up period were not included for analysis. The full selection criteria is shown in Table 1. Data collected included the patient's age, gender, height, weight, body mass index (BMI), procedures performed, if bilateral surgery was performed, length of operation (LOP), length of surgery (LOS), and outcome metrics.

Table 1. Study Selection Criteria

Inclusion	Exclusion
• Clinical diagnosis of plantar fasciitis	• Incorrect diagnosis
• Gastrocnemius contracture	• Incomplete data
• Failed at least 6 months of conservative therapy	• Concurrent foot and ankle condition
• Underwent radiofrequency microtenotomy, isolated gastrocnemius recession or both procedures concurrently	• Underwent other lower limb surgery concurrently or during the follow-up period
• Full set of clinical data available for at least 1 year postoperatively	

The inclusion and exclusion criteria of this study were designed to select only patients with recalcitrant plantar fasciitis who had undergone radiofrequency microtenotomy with or without gastrocnemius recession only.

Surgical Procedures

Radiofrequency microtenotomy was performed using a TOPAZ microdebrider device (Arthrocare, Sunnyvale, CA), connected to a System 2000 generator set at setting 4 (175V-RMS). Access to the plantar fascia was obtained either via an open incision or percutaneously, the TOPAZ tip was connected to a sterile isotonic saline drip with a flow of 1 drop every 1 to 2 seconds. The microtenotomy was performed in a grid-like pattern over the most painful aspect of the plantar surface. Following microtenotomy, the wound was washed with saline and closed in layers.

The gastrocnemius recession was performed either proximally or at the level of the proximal tibia or distally at the musculotendinous junction of the gastrocnemius muscle. The open proximal medial gastrocnemius release was where the fascia of the medial head of the gastrocnemius is released via an open medial popliteal skin crease incision.

The distal gastrocnemius recession was performed via an endoscopic technique which involves a small medial and lateral skin incision at the level of the gastrocnemius aponeurosis. This was at the level where the Achilles tendon is palpated to fan out (musculotendinous junction). An obturator was inserted from medial to lateral, between the subcutaneous fat and gastrocnemius layers to develop the correct plane. A 4.0 mm scope was inserted into the medial cannula portal and the hook blade is inserted through the lateral cannula portal. The hook blade was advanced medially, to engage the medial edge of the aponeurosis, before it was withdrawn laterally to transect the aponeurosis.

Outcome Metrics

The primary aim of this study was to measure and compare the clinical and patient-reported outcomes of patients who had undergone either radiofrequency microtenotomy, gastrocnemius recession, or both procedures concurrently. Specifically, we focused on reduction in pain scores, improvement in functional scores, meeting expectations regarding surgery, and patient satisfaction scores. Patients were evaluated preoperatively during their initial hospital stay and postoperatively at the 3-month, 6-month, and 12-month follow-up appointments by trained physiotherapists and staff using a standardised foot and ankle assessment form. Consisting of both objective and patient-reported outcome metrics, the form included the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale, the Short Form (36) Health Survey (SF-36), and 2 questions adapted from the North American

Spine Society (NASS) questionnaire specifically written to assess patient satisfaction and met expectations with regard to their operation.

The AOFAS Ankle-Hindfoot Scale is a clinical outcome scale designed to include both objective and subjective measures with the aim of comprehensively assessing function and pain following foot and ankle surgeries. In particular, we focused on pain as measured on a Visual Analogue Scale (HINDVAS) and daily function as measured using the overall Ankle-Hindfoot Score (HINDTOT). HINDVAS is measured on a scale of 0 to 10 (the minimum score representing no pain; the maximal score representing the worst pain imaginable). HINDTOT is measured from 0 (the minimum and worst score) to 100 (the maximum and best score).

The SF-36 Health Survey is a patient-reported health survey used to assess for general health and quality of life that is frequently used in health economics and cost-effectiveness analyses. The survey broadly assesses 8 domains—physical functioning (SFPF), role functioning-physical (SFRP), bodily pain (SFBP), general health (SFGH), vitality (SFVI), social functioning (SFSF), role functioning-emotional (SFRE), and mental health (SFMH)—which can further be averaged into a physical component score (PCS), a mean of the SFPF, SFRP, SFBP, and SFGH scores, and a mental component score (MCS), a mean of the SFVI, SFSF, SFRE, and SFMH scores.

At the postoperative visits only, the patients were asked 2 questions adapted from the NASS regarding whether or not the surgery met their expectations (EXP) and if they were satisfied with the results of their surgery (SAT). Met expectations was measured on a Likert scale from 1 to 7, where a score of 1 represented fully met expectations and a score of 7 represented expectations not met all. Similarly, satisfaction was measured on a Likert scale of 1 to 6, where a score of 1 represented maximal satisfaction, while a score of 6 represented no satisfaction. For the purposes of regression analyses, met expectations and patient satisfaction scores were further coded as binary variables. Expectations were considered met if the score was 1 to 4 and not met if the score was 5 to 7, while patients were considered satisfied if their score was 1 to 3 and unsatisfied if their score was 4 to 6.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 22 was used for all statistical analyses in this study. Results are presented as means with standard deviations and percentages of the total number of feet in the patient group. Analysis of variance (ANOVA) with Bonferroni correction was used to compare outcome metrics between patients who underwent radiofrequency microtenotomy only, patients who underwent gastrocnemius recession only, and patients who underwent both procedures concurrently. Linear logistic regression was used to identify whether or not preoperative measurements and the type of intervention could predict HINDTOT, HINDVAS, SF-36 component scores, SFPCS, and SFMCS scores, while binary logistic regression was used to identify whether or not the same factors could predict for met expectations and patient satisfaction. Statistical significance was defined as $P<0.05$.

Results

Patient Demographics

A total of 51 feet belonging to 43 patients met the selection criteria for this study and were included for analysis. Of these patients, 10 feet belonging to 8 patients underwent gastrocnemius recession only, 34 feet belonging to 28 patients underwent radiofrequency microtenotomy only, and 7 feet belonging to 7 patients underwent both procedures concurrently. All procedures were performed by a fellowship-trained foot and ankle surgeon. No patients who underwent both procedures concurrently underwent a bilateral operation. There was no statistically significant difference in age, gender, preoperative height, preoperative weight, preoperative BMI, length of operation, and length of stay ($P>0.05$). Patient demographics are shown in full in Table 2.

Comparison of Intervention Efficacy

ANOVA with a Bonferroni correction for multiple comparisons showed that mean SFVI scores measured 1 year postoperatively were significantly higher for patients who underwent both procedures concurrently compared to patients who underwent either procedure individually ($P<0.05$). Additionally, mean SFMCS scores measured at 1 year postoperatively were significantly higher in patients who underwent both procedures concurrently compared to patients who underwent gastrocnemius recession only ($P<0.05$), but not compared to patients who only underwent radiofrequency microtenotomy ($P = 0.08$). There was otherwise no statistically significant difference in HINDTOT, HINDVAS, individual or component SF scores, EXP scores, and SAT scores measured 1 year postoperatively ($P>0.05$). There were no statistically significant differences in HINDTOT, HINDVAS, individual or component SF scores, EXP scores, or SAT scores at the 3-month or 6-month differences ($P>0.05$). The mean values for each patient group at each time frame are shown in full in Table 3.

Regression Analyses

Measurements included for regression analyses included age, gender, height, weight, BMI, whether or not both

Table 2. Patient Demographics

	Gastrocnemius Recession	Radiofrequency Microtenotomy	Both
Number of feet (patients)	10 (8)	34 (28)	7 (7)
Gender			
Male	4 (50%)	19 (68%)	5 (71%)
Female	4 (50%)	9 (32%)	2 (29%)
Age (years)	45.59 ± 10.13	45.42 ± 9.15	48.67 ±12.83
Preoperative height (cm)	166.56 ± 11.47	160.43 ± 8.81	160.14 ± 7.40
Preoperative weight (kg)	73.31 ± 12.16	69.88 ± 11.93	71.81 ± 12.48
Preoperative BMI (kg/m^2)	26.46 ± 3.99	27.07 ± 3.35	27.87 ± 3.68
Bilateral operation	2 (25%)	6 (21%)	0 (0%)
Length of operation (min)	23.33 ± 7.64	20.32 ± 11.78	32 ± 7.58
Length of stay (day)	0.56 ± 0.60	0.53 ± 0.84	0.49 ± 0.49

BMI: Body mass index
Values are shown as means with standard deviations and percentage of the patients within the patient group. There were no statistically significant differences in age, gender, preoperative height, preoperative weight, preoperative BMI, length of operation, and length of stay.

feet were operated on, type of intervention offered, and the baseline HINDVAS, HINDTOT, and SF-36 scores. Linear regression showed that none of the preoperative measurements or the type of intervention performed were found to be predictive for HINDTOT, HINDVAS, SF-component scores, SFPCS, or SFMCS scores (P >0.05). Similarly, binary logistic regression showed that none of the preoperative measurements or the type of intervention performed were found to be predictive for met expectations or patient satisfaction (P >0.05).

Table 3. Mean Outcome Metrics

	Gastrocnemius Recession	Radiofrequency Microtenotomy	Both
Preoperative			
HINDVAS	6.86 ± 1.57	7.21 ± 1.69	6.86 ± 1.77
HINDTOT	39.14 ± 15.91	42.00 ± 13.47	50.57 ± 18.75
SFPF	54.38 ± 18.60	54.46 ± 26.75	72.86 ± 26.75
SFRP	18.75 ± 37.20	17.86 ± 31.07	46.43 ± 50.89
SFBP	33.00 ± 11.17	25.68 ± 14.67	38.43 ± 26.01
SFGH	53.75 ± 27.87	65.64 ± 24.58	73.57 ± 24.38
SFVI	62.50 ± 22.52	61.79 ± 21.27	68.57 ± 25.45
SFSF	71.88 ± 33.91	48.66 ± 34.75	57.14 ± 47.25
SFRE	86.50 ± 35.36	95.24 ± 15.48	66.67 ± 43.03
SFMH	83.50 ± 11.20	79.29 ± 13.60	79.43 ± 19.65
SFPCS	39.97 ± 14.80	40.91 ± 18.54	57.82 ± 27.96
SFMCS	76.34 ± 10.45	71.24 ± 15.06	67.95 ± 29.57
3-months			
HINDVAS	2.43 ± 2.57	3.65 ± 2.85	3.14 ± 3.81
HINDTOT	78.86 ± 13.31	71.64 ± 19.44	73.17 ± 22.45
SFPF	73.13 ± 13.08	68.7- ± 22.27	79.29 ± 22.44
SFRP	34.38 ± 44.19	41.30 ± 43.04	50.00 ± 43.30

EXP: Met expectations; HINDVAS: American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Visual Analogue Scale; HINDTOT: American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score; SAT: Satisfied with results of surgery; SFBP: Bodily pain (SF-36 Health Survey); SFGH: General health (SF-36 Health Survey); SFMCS: SF-36 Health Survey Mean Component Score; SFMH: Mental health (SF-36 Health Survey); SFPCS: SF-36 Health Survey Physical Component Score; SFPF: Physical functioning (SF-36 Health Survey); SFRE: Role functioning-emotional (SF-36 Health Survey); SFRP: Role functioning-physical (SF-36 Health Survey); SFSF: Social functioning (SF-36 Health Survey); SFVI: Vitality (SF-36 Health Survey)
Values are shown as means with standard deviations.
*Statistically significant difference compared to patients undergoing both procedures concurrently.
†Statistically significant difference compared to patients undergoing radiofrequency microtenotomy only.
‡Statistically significant difference compared to patients undergoing gastrocnemius recession only.

Table 3. Mean Outcome Metrics (Cont'd)

	Gastrocnemius Recession	Radiofrequency Microtenotomy	Both
3-months			
SFBP	52.63 ± 24.80	48.96 ± 22.09	54.43 ± 28.76
SFGH	62.38 ± 18.12	64.00 ± 24.90	67.29 ± 26.51
SFVI	70.00 ± 13.09	61.96 ± 20.44	66.43 ± 23.93
SFSF	90.63 ± 12.94	82.71 ± 25.21	87.50 ± 27.95
SFRE	100.00 ± 0.00	85.51 ± 34.56	71.43 ± 48.80
SFMH	84.00 ± 11.90	77.57 ± 12.86	78.29 ± 15.12
SFPCS	55.63 ± 16.16	55.74 ± 22.08	62.75 ± 25.17
SFMCS	86.16 ± 6.26	75.91 ± 17.98	75.91 ± 25.60
SAT	0.75 ± 0.46	0.74 ± 0.45	0.71 ± 0.49
EXP	0.75 ± 0.46	0.70 ± 0.47	0.71 ± 0.49
6-months			
HINDVAS	2 ± 2.65	2.39 ± 2.90	4.00 ± 2.10
HINDTOT	85.29 ± 14.12	81.07 ± 21.27	75.40 ± 15.18
SFPF	82.50 ± 18.13	75.00 ± 20.77	81.67 ± 19.41
SFRP	56.25 ± 49.55	58.93 ± 44.73	58.33 ± 49.16
SFBP	64.88 ± 24.39	57.39 ± 21.23	72.67 ± 22.57
SFGH	68.88 ± 9.23	65.36 ± 23.33	76.67 ± 19.51
SFVI	65.00 ± 20.00	63.04 ± 19.12	74.17 ± 15.63
SFSF	84.38 ± 25.66	88.39 ± 25.89	93.75 ± 10.46
SFRE	100.00 ± 0.00	97.62 ± 12.60	83.33 ± 40.82
SFMH	88.00 ± 5.24	84.14 ± 10.18	84.67 ± 17.66
SFPCS	68.13 ± 19.73	64.17 ± 21.41	72.33 ± 25.42
SFMCS	84.34 ± 8.51	83.30 ± 10.66	83.98 ± 14.65
SAT	0.63 ± 0.52	0.75 ± 0.44	0.50 ± 0.55
EXP	0.63 ± 0.52	0.79 ± 0.42	0.83 ± 0.41
1-year			
HINDVAS	1.57 ± 2.30	1.50 ± 2.43	1.29 ± 2.22
HINDTOT	87.00 ± 12.95	88.54 ± 16.79	90.71 ± 13.51
SFPF	86.88 ± 6.51	82.50 ± 16.69	90.71 ± 9.76
SFRP	59.38 ± 49.89	72.32 ± 34.25	89.29 ± 19.67
SFBP	58.88 ± 21.54	60.86 ± 29.58	73.71 ± 25.60
SFGH	59.88 ± 10.91	65.79 ± 28.11	88.14 ± 8.51
SFVI	63.75 ± 15.76*	51.96 ± 19.78*	89.29 ± 14.27†‡
SFSF	76.56 ± 30.21	91.96 ± 17.75	96.43 ± 9.45
SFRE	91.67 ± 23.57	96.43 ± 13.88	100.00 ± 0.00
SFMH	84.00 ± 8.82	843.43 ± 13.10	90.29 ± 15.64
SFPCS	66.25 ± 17.13	70.37 ± 17.56	85.46 ± 13.57
SFMCS	78.99 ± 12.34*	83.45 ± 11.49	94.00 ± 5.21‡
SAT	0.63 ± 0.52	0.82 ± 0.39	0.86 ± 0.38
EXP	0.50 ± 0.54	0.86 ± 0.36	0.86 ± 0.38

EXP: Met expectations; HINDVAS: American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Visual Analogue Scale; HINDTOT: American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score; SAT: Satisfied with results of surgery; SFBP: Bodily pain (SF-36 Health Survey); SFGH: General health (SF-36 Health Survey); SFMCS: SF-36 Health Survey Mean Component Score; SFMH: Mental health (SF-36 Health Survey); SFPCS: SF-36 Health Survey Physical Component Score; SFPF: Physical functioning (SF-36 Health Survey); SFRE: Role functioning-emotional (SF-36 Health Survey); SFRP: Role functioning-physical (SF-36 Health Survey); SFSF: Social functioning (SF-36 Health Survey); SFVI: Vitality (SF-36 Health Survey) Values are shown as means with standard deviations.

*Statistically significant difference compared to patients undergoing both procedures concurrently.

†Statistically significant difference compared to patients undergoing radiofrequency microtenotomy only.

‡Statistically significant difference compared to patients undergoing gastrocnemius recession only.

Discussion

The aetiology of plantar fasciitis is multifactorial. Inflammation was once thought to be the source of pain in plantar fasciitis but histological studies have since shown that it is a non-inflammatory degenerative fasciosis similar to tendinosis. As such, the use of radiofrequency microtenotomy addresses this pathology and has been demonstrated to have high success rates with quick recovery times in various forms of chronic tendinosis including that of the plantar fascia.[9,18-24]

It has also been shown that tightness of the posterior muscle group has a statistically significant relationship with the presence of plantar fasciitis.[35] This suggests that evaluating patients for gastrocnemius contracture and addressing the equinus deformity in patients with plantar fasciitis may alleviate the symptoms. In recent years, isolated gastrocnemius recession has been shown to be a viable treatment option for refractory foot pain with limited patient morbidity.[31,32,36,37]

A recent study with an average follow-up of 3.7 months for the 23 patients involved, showed the additive effects in performing a plantar fasciotomy in conjunction with a gastrocnemius recession in patients with plantar fasciitis and gastrocnemius equinus recalcitrant to conservative treatment,[33] but there is a paucity of literature evaluating the clinical outcomes following concurrent radiofrequency microtenotomy and gastrocnemius recession in such patients.

In light of the above, combining radiofrequency microtenotomy with gastrocnemius recession in patients with plantar fasciitis and an underlying gastrocnemius contracture appears to make sense. Our study shows that vitality scores were higher in patients undergoing combined procedures compared to either one individually. In addition, the mental component scores in those undergoing combined procedures was higher than gastrocnemius recession alone. This suggests a possible synergistic effect of both procedures as they work via different mechanisms to address the symptoms of plantar fasciitis.

There are limitations to our present study. The sample size for patients undergoing both procedures was modest as radiofrequency microtenotomy is a relatively newer procedure that has not been fully characterised. As we wanted to character the full course of postoperative recovery, patients who were lost to follow-up or had incomplete data sets were excluded from analysis, which further reduced the sample size. Furthermore, our medium-term follow-up period is 1-year postoperatively, which limits our study's conclusions regarding long-term efficacy of the interventions studied. That being said, many similar studies[9,19,31] had at a maximum of 12 months follow-up, with others[4,18,20] only having a maximum of 6 months follow-up. Unlike our previous studies analysing outcomes for radiofrequency microtenotomy in conjunction with plantar fasciotomy, we did not distinguish between open, percutaneous, and endoscopic approaches in view of low patient numbers. Nonetheless, studies[19] have shown no significant difference in SF-36 scores between open and percutaneous radiofrequency microtenotomy at 1-year follow-up, hence this is unlikely to affect the significant improvement in SFVI and SFMCS scores that we have found in our combined procedures (both radiofrequency microtenotomy and gastrocnemius recession) group at 1-year follow-up.

Conclusion

In summary, we found that performing radiofrequency microtenotomy in conjunction with gastrocnemius recession significantly improves vitality scores measured 1-year postoperatively compared to performing either procedure individually. Additionally, we found that the type of intervention and preoperative factors were not predictive for clinical outcome, met expectations, or patient satisfaction scores. Presently, this is the only study to have compared outcomes in patients suffering from chronic plantar fasciitis and gastrocnemius contracture who underwent gastrocnemius recession, radiofrequency microtenotomy, and both procedures. Randomised controlled trials with sufficient patient numbers and longer follow-up periods are needed to fully characterise the long-term efficacy and safety of performing radiofrequency microtenotomy with gastrocnemius recession in the treatment of recalcitrant plantar fasciitis.

Combining radiofrequency microtenotomy and gastrocnemius recession in patients with plantar fasciitis and an underlying gastrocnemius contracture shows favourable medium-term outcomes compared to performing either procedure in isolation.

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Review Article

Psychological Profile of Patients with Psoriasis

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Abstract

Introduction: Psoriasis is a chronic inflammatory disease with a global prevalence of approximately 2% and significant psychiatric comorbidity. There is a great deal of existing literature assessing different aspects of psychology in psoriasis. We aimed to conduct an in-depth review of current evidence linking psoriasis to personality traits and psychiatric comorbidities, as well as factors that put these patients at risk of psychopathology. Materials and Methods: A search of the PubMed database identified 1632 articles. We included articles studying psychological comorbidity in patients with psoriasis, looking especially at personality characteristics, and data linking psoriasis with increased risks of psychological distress, depression, anxiety and suicidality. In particular, we also evaluated subgroups in psoriasis found to be at risk. Results: Patients with psoriasis are more likely to be alexithymic, lack body awareness and possess a Type D personality. Alcohol, but not illicit drug use, disorders are also more common in patients with psoriasis. Patient groups who are especially at risk of psychological distress include women, younger patients, patients with a younger age of disease onset, those who self-assess their psoriasis to be severe, and those with lesions on visible or sensitive areas. Adopting motivational interviewing skills and incorporating the use of learning materials during consultations have been found to be useful. Conclusion: The knowledge of personality characteristics, "at-risk" groups, and early recognition of psychological distress among patients with psoriasis can help clinicians provide better holistic care and encourage a change in patients' behaviour.

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Key words: Alexithymia, Personality, Psychopathology, Suicidality

Introduction

Psoriasis is a chronic inflammatory skin condition that affects approximately 2% of the population worldwide.[1] The association between psoriasis and psychiatric disease is well documented and has been much better characterised in recent years. This has helped shed light on the intricate relationships between disease severity, personality and psychiatric comorbidity.

In many studies, psoriasis has been shown to be significantly associated with depression, anxiety and suicidal ideation.[2] Mechanisms connecting anxiety, depression and inflammation in psoriasis have been postulated and maladaptive cognitive and emotional patterns have been identified.[3,4] The use of psychotherapy such as cognitive behavioural therapy has been trialled, and found to be correlated with reduced disability, stress and interestingly even physical severity of psoriasis.[5,6]

Previous ethnographic research that studied patients with psoriasis in terms of disease impact and treatment satisfaction has identified key thematic categories of disappointment with treatments and confusion about psoriasis associated with a lack of direction from the treating physicians with regard to diagnosis and treatment regimens.[7] Evaluating and examining aspects of these patients' behaviours can aid healthcare professionals greatly in developing strategies to address the holistic management

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of patients with psoriasis, and to identify factors that predict the success of adherence to medication in such patients.

The body of literature examining the roles of personality, psychology, psychopathology and psychiatric comorbidity in psoriasis is vast. Individual studies focus on different aspects of this complex interplay of relationships, and this poses significant challenges for a single review to encompass the sheer breadth of knowledge in this vein. With this in mind, we felt that a review was timely, to provide an update and identify recommendations for clinical practice.

Materials, Methods and Results

We performed multiple searches on the PubMed database up to 11 November 2018 to identify articles investigating possible associations with the search term 'psoriasis and personality (or psychology or psychopathology or psychiatry)'. A total of 1632 articles dated from 1973 to 31 October 2018 were identified. Though this was not a systematic review, we analysed these articles to put together a picture of a psychological profile of patients with psoriasis, emphasising on clinically relevant aspects such as personality traits, psychological needs, psychopathology, suicidality, substance use and "at-risk" subgroups.

Personality Traits in Patients with Psoriasis

The concept of patients with psoriasis having a different personality profile is alluded to in the scientific literature. Martín-Brufau et al tested this hypothesis in a cross-sectional study involving 36 patients with psoriasis. Results demonstrated significant differences from healthy controls across various personality traits. Most remarkably, patients were found to favour practical over abstract thought, lacked innovation, and exhibited dependence and non-dominant personality styles.[8]

Later research that attempted to define this personality type has shown that patients with psoriasis are more likely to possess a Type D (D for "distressed") personality, characterised by high levels of negative affectivity (NA) and social inhibition (SI).[9] NA refers to the tendency to experience negative emotions across time and situations, whereas SI refers to the tendency to inhibit behaviours and the expression of emotions in social interactions.[10] In a more recent comparative pilot study, the prevalence of Type D personality was found to be 38.7% in patients with moderate to severe psoriasis, as compared to 23.7% in healthy controls (P <0.001).[11]

The combination of high NA and SI in individuals with Type D personality means that they experience strong negative emotions which they refrain from expressing, due to their fear of disapproval and rejection. This leads to discomfort, insecurity and a penchant for anxiety, stress and self-reproach.[10] Importantly, in patients with psoriasis, having a Type D personality has been found to be linked to increased perceived stigmatisation, with the SI aspect accounting for a greater component of this association.[12]

In a study of 185 adults, of whom 55 had psoriasis, Mizara et al found that psoriasis patients were also more likely to demonstrate early maladaptive schemas, namely emotional deprivation, social isolation, defectiveness, failure, vulnerability to harm, subjugation and emotional inhibition.[13] These were found to be significant predictors of psychological distress manifesting as anxiety and depression. Most importantly, the presence of emotional inhibition causes individuals to have difficulties communicating their emotions and needs, and is in keeping with a high prevalence of alexithymia in psoriasis patients.[14]

Alexithymia is a term first proposed by Sifneos in 1972, which literally means a lack of words for emotion (from the Greek a = lack, lexis = word, thymos = emotion).[15] Prevalence estimates of alexithymia in psoriasis patients vary, but have been reported to be as high as 40%, compared to 13.3% in controls in a recent study.[14] This term encapsulates elements of a Type D personality and decreased intuition, and is defined by a limited ability to identify and communicate emotions, and also difficulty distinguishing feelings from bodily sensations.[16] It is also characterised by restricted imagination and externally oriented cognition.[16] Of special relevance to the clinical context, the inability to describe emotions leads to individuals with alexithymia misinterpreting physical symptoms of emotional arousal as symptoms of somatic illness.[17] It has been proposed that alexithymia predisposes to ineffective coping and stress, which is a known triggering factor for psoriasis.[13]

Another pertinent personality characteristic that has been found in patients with psoriasis is the lack of body awareness, which is related to alexithymia.[18] The concept of body awareness is important in psoriasis, as self-care is important in preventing further worsening of the disease condition. Body ignorance (not recognising or ignoring bodily symptoms) was found to be associated with more itch, pain, fatigue, scratching, avoidant coping, neuroticism and helplessness in patients with psoriasis.[18] It was also associated with lower levels of extraversion and acceptance, as well as a decreased quality of life.[18]

All in all, these studies suggest that inherent personality traits play an important role in the holistic management of patients with psoriasis. A better understanding of the psychological profile allows for targeted approaches towards ameliorating the psychosocial disturbances associated with psoriasis.

Needs of Patients with Psoriasis

While healthcare professionals involved in the care of patients with psoriasis are aware that it can impact patients physically, emotionally and socially, patients commonly

feel that there is a lack of opportunities to discuss aspects of living with the disease during consultations.[19,20] Thus, it becomes important for doctors to examine the disabling impact of psoriasis from the patients' perspectives, or at least to proactively explore each individual's needs. If doctors are perceived to circumvent these topics or to lack expertise in managing psoriasis, this may adversely affect treatment adherence and overall patient care.[7,20]

A study exploring individual psychosocial support needs of psoriasis patients revealed significant confusion regarding psoriasis associated with a lack of direction from the treating physicians.[7] Key characteristics experienced by patients include substantial tangible and emotional costs, the hidden nature of psoriasis, having to bear the burden of psoriasis alone, and lack of patient direction and authority.[7] Issues raised included worry, hiding of symptoms and concerns about others' perception of hygiene and infectivity. Significant themes were related to isolation, stigmatisation, visible symptoms, hopelessness and impact on daily activities.[7]

In a qualitative study, Nelson et al looked at the needs of 29 patients with psoriasis, especially with regard to the clinical consult.[19] Key themes identified included a desire for the reality of living with psoriasis to be understood, and for professional engagement with the effects of psoriasis.[19]

Having identified the needs of patients with psoriasis, doctors must be additionally sensitive to any expression of distress by patients with psoriasis and should not give the impression that they are sidestepping patients' attempts at sharing their emotions. This highlights the need for a positive, sympathetic doctor-patient relationship where a non-judgemental approach is taken, and sufficient opportunity given for patients to explore their issues.

Psychopathology and Suicidality

The link of psoriasis with stress, depression and anxiety has been demonstrated.[21-26] The prevalence of depression has been shown to be as high as 33.7% in patients with psoriasis, compared to 22.7% of healthy controls.[26] Though there are less data on anxiety, the prevalence of anxiety in patients with psoriasis is also found to be consistently higher than that in normal controls.[26] It is clear that there is a significant mental health burden among patients suffering from psoriasis.

Depression has been theorised to aggravate inflammation in the setting of psoriasis via the induction of elevations in inflammatory cytokines and the abnormal activation of the hypothalamic-pituitary-adrenal axis, causing the stimulation of local cutaneous cytokines, and expression of immune-trafficking adhesion molecules. Increased activation of the sympathetic nervous system is hypothesised to be another factor, with noradrenaline as the main player in inducing cytokines in causing cutaneous inflammation.[3,27,28] The presence of inflammation has been theorised to cause depressive symptoms, possibly via the shunting of tryptophan and increasing the breakdown of serotonin, creating a functional serotonin deficit.[29-32]

Thoughts of self-harm and suicide are likewise more common in patients with psoriasis.[22-25,33,34] A meta-analysis evaluating the relationship between psoriasis and suicidality found that the pooled odds ratio (OR) for suicidal ideation and suicidal behaviours in patients with psoriasis—as compared to those without—was 2.05 (95% CI, 1.54-2.74) and 1.26 (95% CI, 1.13-1.40) respectively. Patients with psoriasis were more likely to attempt (pooled OR, 1.32; 95% CI, 1.14-1.54) and complete suicide (pooled OR, 1.20; 95% CI, 1.04-1.39) than those without psoriasis.[34] A greater likelihood of suicidality was found in patients with more severe disease, as well as in younger patients.[34]

Alcohol and Drug Use in Psoriasis

It is well established that the misuse of alcohol is more common in patients with psoriasis.[35-37] In a cross-sectional study conducted in the United Kingdom, 30.6% of study subjects were found to have alcohol use disorder compared to 14.3% in the control group with non-inflammatory skin lesions, representing the general population.[37] The physical severity of psoriasis has been associated with increased alcohol consumption.[38] This suggests the role of alcohol as a maladaptive coping strategy in psoriasis. Excess alcohol consumption is related not only to worsening of psoriasis, but also to depression, anxiety and poorer response to treatment.[39,40] Systemic drugs used commonly to treat psoriasis, including acitretin and methotrexate, may also be potentially hepatotoxic, limiting their suitability in patients with chronic alcohol misuse.[41] Additionally, patients with psoriasis have also been found to have an approximately 60% greater risk of dying from alcohol-related causes.[42]

In the few studies which evaluate the prevalence of illicit drug use in patients with psoriasis, it was not found to be significantly more common than in healthy controls.[43,44] Further studies on a larger scale may be needed to validate these results.

Looking at "At-Risk" subgroups in Psoriasis

Women

Female patients with psoriasis have been found to be at higher risk of psychological distress than males,[45] and are more likely to report a greater impact of the disease on their quality of life.[46] In a study involving 115 hospitalised patients with psoriasis, female patients also reported higher levels of stigmatisation, which was in turn also found to be the strongest predictor of quality of life impairment.[47]

When Type D personality traits were isolated, it was found that women with psoriasis demonstrated more SI and NA compared to healthy female individuals. While male patients with psoriasis also had higher levels of NA compared to healthy male controls, women with psoriasis demonstrated significantly higher NA compared to men with psoriasis.[12] Another study showed that males showed more phobic fears and depressiveness than women, who showed more neuroticism.[48]

Younger Patients

Younger patients with psoriasis have an increased risk of psychological distress compared to older patients,[29] and are more likely to experience suicidality compared to older patients.[34] A qualitative study exploring adolescents' lives with psoriasis identified main themes of physical symptoms, feeling different, psoriasis-related worry about the future, increased attention due to appearance, attempts to conceal skin, and treatment-related frustrations and worry.[49]

Younger Age of Disease Onset

A younger age of onset of psoriasis is associated with an increased risk of anxiety traits and depression, manifesting as somatic trait anxiety, psychic trait anxiety, stress susceptibility, embitterment, mistrust, trait irritability and verbal trait aggression.[50] This may be linked with the development of maladaptive schemas manifesting as psychological distress.[50] When compared to patients with adult onset of psoriasis, patients with pre-adult onset were also significantly more depressed and socially anxious, and reported higher levels of stigmatisation and negative body image emotions.[51]

Severity of Psoriasis

Some contention exists with regard to the association between disease severity and psychopathological morbidity. This is, in part, due to the different markers employed to gauge disease severity in various studies which may confound possible associations. The use of systemic treatment for psoriasis, the body surface area of involvement, Psoriasis Area Severity Index (PASI) and self-administered PASI have been used as markers of disease severity in different studies.[23,34,45,46,51-54]

It has been suggested that the patient's subjective assessment of severity of his psoriasis plays a significant role in psychopathology, as compared to objective measures. The perception of greater psoriasis severity has been associated with difficulties in emotional regulation, depression and a greater risk of suicidality.[34,51,52]

Surprisingly, when the use of systemic psoriasis treatment was employed as a marker of disease severity, there was no statistically significant difference in suicidality and anxiety between patients with mild and severe psoriasis.[23,53,54] Similarly, body surface area of involvement was not found to be related to psychological distress.[45] There was also no association found between PASI and alexithymia status.[55] One study, however, found a statistically significant increase in the risk of depression in patients on systemic psoriasis therapy, as compared to those who were not.[23] In fact, in a study involving 108 patients with psoriasis, acne and eczema, there was only a modest correlation between self-assessed and clinician-assessed severity measurements.[56] These seem to suggest that while clinician-assessed measurements are useful in assessing response to treatment, patients' self-assessments may be equally valuable in detecting underlying psychopathology.

The use of biologic treatments in patients with moderate to severe psoriasis also raises issues with regard to their safety profile, especially with regard to their psychiatric side-effects. Notably, there were reports of 6 patients with suicide attempts, of which 4 were completed, while on brodalumab, a human anti-interleukin-17 receptor A monoclonal antibody approved by the United States Food and Drug Administration in the treatment of moderate to severe plaque psoriasis.[57] However, the causal association between brodalumab and suicidal ideation and behaviour remains unestablished.[57] A recent study of 8272 patients with moderate to severe psoriasis previously given ustekinumab, infliximab, etanercept, or adalimumab found that biologic therapy was associated with a decreased risk of development of depressive symptoms compared to conventional systemic therapy. Adalimumab was most strongly associated with lower risk, with ustekinumab and infliximab trending towards lower risk but not achieving statistical significance.[58]

Location of Psoriasis Disease

There have been few studies to study the psychological impact of disease location. Different ways of categorising disease involvement, coupled with different outcome measures, also complicate direct comparison. Nail lesions were found to be associated with a large adverse effect on the quality of life,[46] whereas having lesions on the back of hands was found to be related to higher stigmatisation levels.[47] Inverse anatomical distribution of disease was found to be associated with depressive symptoms,[59] and the presence of psoriasis in a sensitive area (hands, scalp, face or genital areas) was found to be related to significantly higher levels of alexithymia.[55]

Conclusion

This review highlights the complex biopsychosocial interactions faced by patients with psoriasis. Given the visible nature of skin lesions, comorbidity and chronicity

in psoriasis, it is unsurprising that there is a significant psychological burden associated with the disease.

The research conducted into the effect of psoriasis on psychosocial aspects of living and vice versa has been extensive. However, the multifaceted aspects of patients' psychological profiles also mean that outside of clearly defined psychiatric diagnoses, many different outcome measures are employed in assessing the association of the disease with the patients' psychological states. This helps physicians and caregivers appreciate the ways that psoriasis impacts the lives of sufferers, yet at the same time may make direct comparison across different studies difficult, especially when there is significant overlap in outcome measures and variation in the way patients are categorised. Future studies could evaluate the role of psoriasis susceptibility genes, which are known to be associated with different phenotypic patterns of disease, in influencing the psychological profile of patients with psoriasis.[60]

Given the intricacy of the psychosocial factors in psoriasis, dermatologists and healthcare providers caring for patients with psoriasis should aid patients in developing strategies to deal with the impact of the disease on their physical, psychological and social well-being.[61] A systematic review found that psychosocial interventions, including cognitive behavioural therapy, psychoeducation, writing exercises, motivational interviewing, hypnosis, meditation and relaxation, demonstrated a small to medium effect on health-related quality of life, depression and anxiety.[62] Adopting motivational interviewing skills, which involves getting patients to compare where they are now with where they wish to be, can help practitioners manage patients holistically and support behavioural change.[63] High quality, theory-based psoriasis materials have proven to be useful to patients by helping them to improve their understanding and sense of control without increasing anxiety.[64] Combined psychology and dermatology services can also benefit this group of patients in providing much-needed support and access to community-based mental health services.[65]

Given the results of this review, we recommend the following: a) Routine and regular screening of patients for psychological distress, anxiety, depression, suicide risk and alcohol use; b) Equipping clinicians with listening and counselling skills; c) Giving patients the opportunities to express their needs, concerns and expectations; d) Referral of patients for appropriate psychosocial interventions, and ideally, a multidisciplinary approach with combined psychology and dermatology services; and e) Emphasis on "at-risk" groups identified i.e. women, younger patients, patients with younger age of onset, high-risk locations of psoriasis involvement. Above all, in their therapeutic approach, clinicians need to acknowledge and value the realities of living with psoriasis.

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Commentary

Making Clinical Practice Guidelines Pragmatic: How Big Data and Real World Evidence Can Close the Gap

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Abstract

Clinical practice guidelines (CPGs) have become ubiquitous in every field of medicine today but there has been limited success in implementation and improvement in health outcomes. Guidelines are largely based on the results of traditional randomised controlled trials (RCTs) which adopt a highly selective process to maximise the intervention's chance of demonstrating efficacy thus having high internal validity but lacking external validity. Therefore, guidelines based on these RCTs often suffer from a gap between trial efficacy and real world effectiveness and is one of the common reasons contributing to poor guideline adherence by physicians. "Real World Evidence" (RWE) can complement RCTs in CPG development. RWE—in the form of data from integrated electronic health records—represents the vast and varied collective experience of frontline doctors and patients. RWE has the potential to fill the gap in current guidelines by balancing information about whether a test or treatment works (efficacy) with data on how it works in real world practice (effectiveness). RWE can also advance the agenda of precision medicine in everyday practice by engaging frontline stakeholders in pragmatic biomarker studies. This will enable guideline developers to more precisely determine not only whether a clinical test or treatment is recommended, but for whom and when. Singapore is well positioned to ride the big data and RWE wave as we have the advantages of high digital interconnectivity, an integrated National Electronic Health Record (NEHR), and governmental support in the form of the Smart Nation initiative.

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Key words: Guideline adherence, Real world data, Physicians' practice patterns

The Role of Clinical Practice Guidelines and Their Limitations

Clinical practice guidelines (CPGs) have become ubiquitous in every field of medicine over the past few decades with thousands being published annually. Guidelines attempt to improve healthcare by: 1) guiding practitioners in the implementation of the latest research findings into practice, 2) promoting cost-effective treatments that are shown to reduce mortality and morbidity whilst discouraging ineffective, dangerous or wasteful practices; and 3) establishing standards so that patients receive consistent care regardless of where and by whom they are treated. Despite significant investment of resources in the development of guidelines yearly, there has been limited

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success in impacting health outcomes and low physician adherence to guidelines has been cited as an important factor.[1] It has been said that changing the behaviour of physicians is as difficult as that of patients, and simply informing physicians of the expected standards of care with guidelines alone is unlikely to achieve sustained adherence.[1]

Many barriers to adherence have been cited, such as the lack of awareness of the guidelines, lack of motivation to change, organisational constraints, and lack of time or resources.[2] However, it has been increasingly recognised that the lack of external generalisability is an important barrier towards the implementation of CPGs in routine clinical practice.[3] Guideline recommendations are preferentially based on data from well designed randomised controlled trials (RCTs) which are traditionally ranked at the apex of the evidence hierarchy.[4] While traditional RCTs are designed to demonstrate efficacy of an intervention, these "efficacy trials" are usually performed under ideal and controlled settings for drug registration purposes and adopt a highly selective process by which patients with any other pre-existing conditions or comorbidities are excluded. Often, less emphasis is placed on whether the treatment effect is achievable under real world conditions. For instance, RCTs in asthma typically exclude patients on the basis of age, smoking status, inadequate adherence, poor inhaler technique and other comorbidities. As a result, RCTs evaluating the efficacy of interventions in asthma and chronic obstructive pulmonary disease (COPD) have traditionally excluded up to 95% and 90% of routine care populations respectively.[5] Therefore, guideline recommendations based on these RCTs often suffer from a gap between trial efficacy and real world effectiveness. This has contributed partly to poor adherence by physicians to CPGs in many fields of medicine.[6]

How Real World Evidence Can Help CPGs Fulfil Their Intended Roles

Today, we are standing at the brink of a new era thanks to the proliferation and integration of electronic health records (EHRs) in both primary and tertiary care in Singapore. EHR contains a wealth of as-yet untapped real world data (RWD) that can be used to generate real world evidence (RWE), which is defined as the evidence derived from the synthesis and analysis of healthcare data outside of traditional clinical research settings.[7] Apart from EHR, RWD can be found in administrative claims and billing data, product and disease registries, health monitoring devices/wearables and even social media.[8]

The incorporation of RWE into guideline development and implementation has the potential to enable guideline developers to close the gap between mere knowledge of guidelines and translation to clinical practice in 4 methods.

Method 1: Incorporating Information on Both Treatment Efficacy and Real World Effectiveness Into Our CPGs

Demonstration of treatment efficacy does not necessarily equate to real world effectiveness and it is here that RWE can bridge the gap in our CPGs by helping guideline developers better understand treatment responses in the heterogenous patient populations of the real world with pragmatic trials. Interventional RWE studies like the Salford Lung Study[9] used a pragmatic RCT trial design where heterogenous patient cohorts were recruited under minimal selection criteria to test the real world effectiveness of an open label once-daily long-acting β agonist/inhaled corticosteroid dry powder inhaler in asthma and COPD. They were monitored under the routine care of physicians with no additional visits or attempts to change adherence in order to mimic true clinical practice by using EHR to capture real time data, track outcomes and minimise participant burden associated with trial visits. While such pragmatic studies sacrifice some internal validity, their results allow better approximation of real world practice than the traditional RCTs which are conducted under ideal conditions with high intensity of follow-up care that is often not economical or practical in real life. Trial pragmatism—which refers to the degree of matching between the care delivered in the trial setting and real world conditions—exists on a continuum and different study designs can make a trial more or less pragmatic.[10]

While pragmatic RCTs like the Salford Lung Study have improved the generalisability of research data, their findings are still nonetheless contextualised to the geographical setting where the trial was conducted and therefore may not be generalisable to other countries or healthcare settings due to various geographical, psychosocial and healthcare system differences (such as effect of climate and environment on the disease, health literacy and health-seeking behaviour of patients or quality or accessibility to health services). It is therefore imperative that there be international collaboration in the conduct of RWE studies to better understand how differences in geographic, psychosocial and healthcare system influence disease patterns and outcomes.

Method 2: Development and Incorporation of Precision Medicine (PM) into CPGs

Real world patient cohorts are heterogenous. However, most of our diagnostics and treatments have been developed for the "average patient" which may be effective for some but not all patients. In addition, international guidelines may not be contextualised for individual local practice settings in terms of local needs and resource availability. This has resulted in the proliferation of local CPGs with their varying interpretations of the available evidence. It is therefore difficult for frontline healthcare practitioners to apply CPGs to their real world patients who don't meet

the description of the "ideal" patient[11] but the emergence of PM may be a game changer.

Advances in genomic analysis have spurred the development of PM, which is defined as diagnostics and treatments that are targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic or psychosocial characteristics that distinguish an individual patient from other patients with similar clinical presentations.[12] Generating RWE from EHR would enable the creation of algorithms for the everyday patient that could assist the frontline healthcare provider in: 1) identifying patients with risk factors for aggressive disease prevention (e.g. prediabetes) and screening, 2) phenotyping and endotyping patients,[13] as well as 3) guiding individualised management in terms of medication selection and administration (Table 1).

Method 3: Enabling Continuous Performance Assessment of Guideline Quality and Conformance

Despite the proliferation in the number of CPGs over the years, the adherence to guidelines has remained low to moderate over the last 2 decades.[14] Poor quality guidelines may cause harm by promoting misuse or overuse of medical services and few, if any, guidelines are evaluated rigorously for efficacy and safety before implementation. RWE can meet this need for quality assurance by enabling post-implementation efficacy and safety analyses in the same way that pharmaceutical companies are required to conduct post-marketing surveillance.[15] This way, guideline developers are kept in a continuous feedback loop which keeps them informed about the impact of individual guideline recommendations on real world practice.

RWE can also facilitate guideline implementation by measuring guideline conformance. This may be performed by deconstructing the guidelines, identification of data elements required to assess each guideline recommendation and establishment of acceptable benchmarks for performance. Multidisciplinary interventions targeted at the patient, healthcare provider and local system are often needed to support guideline conformance and RWE can provide guideline implementation programmes with feedback on the efficacy of individual interventions.

Method 4: Increasing Healthcare System Efficiency and Cost Control by Identifying Gaps in Care and Areas of Low-Value Healthcare in Healthcare Systems for Quality Improvement (QI) and Health Technology Reassessment (HTR) Activities, Respectively

The increasing burden of chronic diseases and their ever-growing availability of diagnostic investigations and treatments has made healthcare today increasingly costly,[16] complex and often fragmented because patients have needs that exceed the temporal and informational capacity of any single healthcare provider.[17] By continuous collection and analysis of data on the health-seeking patterns of patients and prescribing patterns of physicians across primary, tertiary and acute care settings, RWE can support HTR and QI activities with real time data and evidence that: 1) identifies low-value healthcare practices for elimination and disinvestment by policymakers,[18] 2) promotes clinician adherence to high-value interventions, and 3) reduces costs and complexity of care by reducing service duplication and process variation across various healthcare providers.

The Challenges and Limitations of Real World Evidence and Big Data

RWE and big data, however, comes with its own set of strengths and challenges in the form of the 4 "V's," namely, Volume, Velocity, Variety and Veracity[19] (Table 2). The sheer volume and speed (velocity) in the generation of data can increase the potential for noise accumulation which may generate incorrect or unreliable (veracity) conclusions. In

Table 1. Examples of How Real World Data and Evidence Can Be Potentially Applied to Day-to-Day Routine Clinical Practice

Clinical decision support (CDS) tools: Integration of CDS tools with EHR can assist the physician in making prescriptive decisions for every patient encounter at multiple points from initial consultation to diagnosis to follow-up.* Recommendations by the Watson for Oncology CDS tool have been shown to be concordant with conventional tumour board treatment decisions in 93% of breast cancers.†
Telemedicine: The popularity of smart devices that track step count, heart rate, lifestyle habits (diet, physical activity and sleep) can be leveraged to enable the development of telemedicine where trackable health data is relayed to doctors for monitoring. This will also enhance patient engagement and facilitate self-management of chronic diseases such as hypertension and asthma.
Artificial intelligence (AI) and machine learning: Machine learning is an application of AI which allows a programme to learn and improve from reviewing a large amount of data without being explicitly programmed.‡ While the technology and application of machine learning in medicine is still nascent, it has been applied to mammography interpretation in radiology with a performance that was roughly equivalent to the bottom 10% of radiologists.¶

EHR: Electronic health record

*Castaneda C, Nalley K, Mannion C, Bhattacharyya P, Blake P, Pecora A, et al. Clinical decision support systems for improving diagnostic accuracy and achieving precision medicine. J Clin Bioinforma 2015;5:4.

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¶The Digital Mammography DREAM challenge. Available at: https://www.synapse.org/#!Synapse:syn4224222/wiki/401744. Accessed on 23 July 2018.

Table 2. The 4 "V's" of Big Data – Volume, Velocity, Veracity and Variety[*†]

The enormous volume of data being created daily is what gives big data its name. A total of 153 exabytes (1 exabyte = 1 billion gigabytes) of data were produced in 2013 and it has been estimated that 2314 exabytes of data will be produced in 2020.[‡]
Data velocity refers to the speed at which the data is generated, stored, analysed or refreshed. Data is being continuously produced by both human and machines in various networked systems such as emails, social media and electronic financial transactions. It has been estimated that rate of global internet traffic in 2018 is 50,000 GB per second of data.
Veracity refers to whether the data is accurate, reliable, representative and can be trusted. Datasets often come with inherent biases and lack of precision due to the limitations of data collection in the real world.
Variety refers to the different formats of data being generated daily. This can take the form of structured data formats such as financial statements which conform to a well defined set of norms on how the data is documented. However, the majority of all generated data is "unstructured" in contrast and come in the form of digital images, audio visual files, internet webpages and Twitter feeds and this poses challenges in data aggregation and interpretation.

[*]IBM Big Data & Analytics Hub. Available at: https://www.ibmbigdatahub.com/infographic/extracting-business-value-4-vs-big-data. Accessed on 23 July 2018.
[†]Williamson J. The 4 V's of Big Data. Available at: https://www.dummies.com/careers/find-a-job/the-4-vs-of-big-data/. Accessed on 7 November 2018.
[‡]MC Digital Universe with Research and Analysis by IDC. Vertical Industry Brief: The Digital Universe, Driving Data Growth in Healthcare. Available at: https://www.emc.com/analyst-report/digital-universe-healthcare-vertical-report-ar.pdf. Accessed on 25 November 2018.

addition, the large sample sizes that also give big data its strength may necessitate heavy computational resources and complex analytics to accurately aggregate and interpret the varied unstructured datasets acquired across various time points and sources into a collective dataset (Table 3). If big data is to be translated meaningfully into high quality RWE, it is important to have the necessary expertise in data analytics with trained data scientists and the application of standardised criteria[20] for data collection, analysis and reporting to minimise data "noise" and establish the quality of a RWE result. This is often resource and manpower-intensive. Finally, in light of high profile international occurrences of data breaches at the national level,[21] it is important to adequately address privacy concerns from the use of big data for research such as the distribution of sensitive data to third parties without consent and data security if we are to have the support and trust of the public.[22]

In addition, the quality and amount of data collected might be constrained when busy frontline healthcare workers are enlisted for data entry due to competing needs of patient care. While it is advantageous to collect as much data as possible now to answer research questions of the future, overburdening healthcare workers with the collection of data in a busy setting beyond what is collected for routine healthcare may result in fatigue, diminished participation in data entry and ultimately deterioration in data quality over time. Like any large projects, the balancing act between cost, quality and time is crucial and requires a multidisciplinary approach and innovations to overcome these constraints. In addition, key stakeholders (i.e. healthcare providers) should be engaged early to foster a sense of ownership of the RWE, to participate in the guideline development, implementation, evaluation and review processes generated from their daily practice.

Singapore's healthcare ecosystem is among the first in the world to have a seamless National Electronic Health Record (NEHR) that has connected primary and tertiary healthcare in the public sector since 2011.[23,24] Participation by private sector healthcare providers is currently voluntary and limited but this is soon to change should the government enact new legislation to mandate compulsory participation. In line with this, the government has established legislation such as the Human Biomedical Research Act[25] and Personal Data Protection Act[26] to further strengthen data governance in the era of big data. The time is therefore ripe for RWE studies to be performed in Singapore as we have the advantages of high digital interconnectivity, a truly integrated NEHR, and governmental support in the form of

Table 3. Big Data and Real World Evidence – Potential Benefits and Challenges

Potential Benefits
• Closing the gap between clinical trial efficacy and real world effectiveness in CPG recommendations
• Advancing the development of precision medicine in areas such as disease prevention, screening and treatment selection in the real world
• Facilitating guideline implementation by allowing continuous assessment of CPG conformance and performance
• Supporting quality improvement and health technology reassessment activities thereby increasing healthcare system efficiency and cost control
Challenges
• The reliable collection, aggregation, analysis, reporting and interpretation of big data is resource-intensive and requires specialised technical expertise
• Addressing data privacy and cybersecurity concerns
• Constraints on the amount and quality of big data that can be collected when busy frontline healthcare providers are enlisted for data collection

CPG: Clinical practice guidelines

the Smart Nation initiative.[27]

Conclusion

In conclusion, digital technologies, combined with RWE studies, complements the evidence generated by RCTs and have the potential to fill the gap in current CPGs which are predominantly based on efficacy studies from RCTs with limited generalisability. RWE can enhance the real world applicability of CPGs, incorporate PM into everyday practice, monitor guideline conformance and support clinical decision-making via artificial intelligence. Importantly, RWE allows doctors to take ownership of the data generated from their daily practice and provides them with the confidence to choose the right treatment options for the right patients.

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Effective Treatment of Paget's Disease of the Bone in a Chinese Woman

Dear Editor,

Paget's disease is caused by increased bone resorption and ineffective bone formation. Unrecognised and untreated disease can cause significant morbidity and reduced quality of life. Paget's disease is seen in 2.3% to 9% of the elderly population in Europe. Incidence is low in Scandinavian countries, Africa and Asia.[1] Only a few cases of Paget's disease in Asians have been reported in medical literature with the largest one describing 5 cases of Paget's disease diagnosed over an 8-year period in Singapore.[2] The incidence of Paget's disease is decreasing most possibly due to environmental changes such as improved nutrition, more sedentary lifestyle and reduced exposure to infections.[1] However, due to asymptomatic disease, the incidence of Paget's disease may be grossly underestimated.

Case Report

We describe a case of Paget's disease in a 63-year-old Singaporean Chinese woman with renal impairment, type 2 diabetes, hypertension and hyperlipidaemia. She was referred by her general practitioner for persistently elevated alkaline phosphatase levels which was initially found on routine testing. On questioning, the patient admitted to having vague bilateral lower limb aching. She denied having hearing loss. On examination (apart from very mild bowing of the left tibia), she did not have any other signs.

Her blood tests were normal except for an elevated alkaline phosphatase 312 U/L (normal 30-150). Heat fractionated alkaline phosphatase measurements showed increased levels of heat labile alkaline phosphatase indicating bone origin. Calcium, 25-hydroxy-vitamin D and phosphate levels were normal. She had chronic renal impairment with a creatinine clearance of 23 ml/min. Skeletal survey showed increased sclerosis and mild bone expansion associated with coarsening of the trabecular pattern affecting the left iliac and pubic bones (Fig. 1). There was also bowing of the left distal tibia shaft (Fig. 2).

As the patient was symptomatic, treatment was indicated. However, due to the renal impairment, bisphosphonates were contraindicated. After discussing the treatment options, she agreed to be started on denosumab. She was given denosumab 60 mg subcutaneously. The alkaline phosphatase levels normalised (118 U/L), within 3 months of starting treatment and the bilateral lower limb aching resolved. The patient refused bone scan due to financial constraints.

Her alkaline phosphatase levels and symptoms are being monitored in clinic. She is on 6-monthly denosumab injections.

Discussion

Interaction between genetic and environmental factors is thought to trigger the disease. Twelve percent to 40% of patients with Paget's disease have a positive family history.[3] The inheritance appears to be autosomal dominant with variable penetrance. Some recent observations have led to the hypothesis that viral infections such as measles virus, respiratory syncytial virus and canine distemper affecting osteoclasts may cause Paget's disease.[4] Further studies are needed to prove this hypothesis.

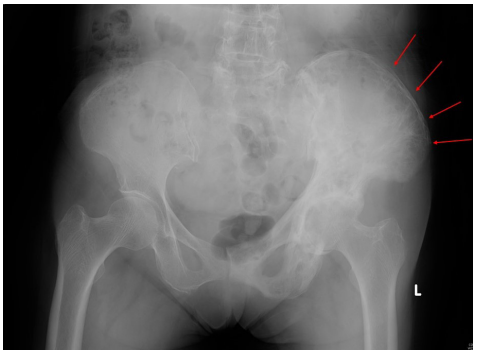

Fig. 1. Plain radiograph of pelvis.

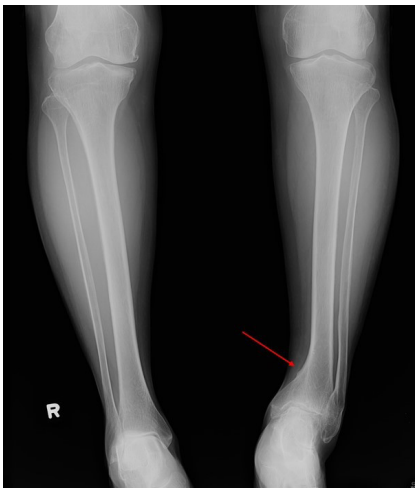

Fig. 2. Plain radiograph of bilateral tibia.

Most patients with Paget's disease are asymptomatic. The commonest symptom is pain but a survey of 863 patients indicated that pain is not a good index of the extent of disease.[5]

Biochemical markers of bone turnover can be tested in serum or urine to support the diagnosis and monitor response to treatment. Bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, C-telopeptide, urinary N-telopeptide, urinary pyridinoline and urinary deoxipyridinoline are usually elevated in active disease.[5] Total and bone alkaline phosphatase have the highest sensitivity (78% and 84%, respectively) and specificity (almost 100%) for diagnosis.[6] Nonetheless, a normal total alkaline phosphatase level does not rule out the diagnosis.[5] When the total alkaline phosphatase levels are normal, bone-specific alkaline phosphatase levels are elevated in 60% and urinary pyridinoline is increased in 40% of the patients with symptoms of Paget's disease.[7] Calcium and phosphate levels are normal in Paget's disease except when there is immobilisation.

Features of Paget's disease can be seen on plain radiograph. Bone scintigraphy is more sensitive compared to plain radiographs especially in early disease[7] and in patients with normal alkaline phosphatase levels, bone scintigraphy can be used to monitor the response to treatment.[7] Patients with osteolytic lesions should have repeat plain radiographs in about 1 year after diagnosis to determine whether there has been improvement.[7]

The aim of treatment is to prevent or minimise the complications of the disease. Nitrogen containing bisphosphonates (aminobisphosphonates) is the current mainstay of treatment. The recommended treatment by the guidelines published by the Endocrine Society is a single dose of intravenous zolendronic acid 5 mg.[8] A randomised controlled study showed that a single infusion of zolendronic acid produces more rapid, complete and sustained response compared to daily treatment with risendronate.[9] There was also significant improvement in quality of life, including pain relief in patients treated with zolendronic acid and remission of up to 6 years may be achieved.[9] Improvement is evidenced by normalisation of serum biochemical markers of bone turnover, reduced activity on bone scintigraphy and improvement of symptoms. Alkaline phosphatase levels start to drop 10 days after initiation of treatment and reach a nadir between 3 and 6 months.[10] Medications may need to be reinstated if there is a rise in bone turnover marker levels or if the symptoms return.

The PRISM (Paget's Disease Randomized Trial of Intensive versus Symptomatic Management) study compared symptomatic treatment against bisphosphonate treatment in 1324 patients with Paget's disease. As expected the bone turnover markers were lower in the bisphosphonate group; however, it did not translate to improvement in quality of life and symptoms.[11] Due to the lack of benefit of treatment in symptomatic patients, it was concluded that asymptomatic patients will not benefit from treatment. But the PRISM study has been criticised for its limitations such as high usage of bisphosphonates prior to enrolment in the study and short follow-up period.

Most authors and experts agree that symptomatic patients should be treated. Also young patients should have lower threshold for treatment in order to prevent future complications.[11] A clinical update from Mayo Clinic recommended asymptomatic patients with active disease of sites where complications are likely to develop such as the skull, spine and long bones to be initiated on treatment.

Bisphosphonates are contraindicated in patients with renal impairment with previous data showing incidences of nephrotic syndrome and acute tubular necrosis.[11] There are newer studies on the use of risendronate[12] and alendronate[13] in patients with estimated glomerular filtration rate (eGFR) as low as 15 ml/min which showed no significant change in serum creatinine concentration over a 2-year period. Due to the lack of consensus on the safety of bisphosphonates in renal impairment, they should be avoided, if possible.

Calcitonin can be used for the treatment of Paget's disease in the setting of renal impairment. It has been shown to reduce the biochemical markers of bone turnover by 40% to 50% and induce partial healing of lytic lesions on plain radiographs.[14] However, normalisation of bone turnover markers is not achieved in most patients. The use of calcitonin may result in neutralising antibodies, down regulation of calcitonin receptors and secondary hyperparathyroidism.[14] Given the limited efficacy and the inconvenience of injections, it is not an ideal choice for treatment.

There is some emerging evidence for using denosumab to treat Paget's disease, but it is not licensed for this indication yet. While there are case reports on denosumab being used to treat Paget's disease in the Caucasian population, there is none reported in the Asian population.

Denosumab is a monoclonal antibody which mimics osteoprotegerin (OPG). OPG is a basic glycoprotein, produced by the osteoblasts and marrow stromal cells which, as a decoy receptor, inhibits the binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to receptor activator of nuclear factor κ B (RANK).[15] RANK is a surface receptor on osteoclasts and osteoclast precursors which, when activated, increases the proliferation and differentiation of cells to form the osteoclast phenotype and inhibits osteoclast apoptosis.[16] The activation of bone remodelling therefore depends on the dynamic balance between RANKL and (OPG + denosumab). Denosumab is thus an antiresorptive agent.

There are case reports on denosumab being used successfully to treat juvenile Paget's disease.[17] Small

studies have shown denosumab result in more rapid normalisation of alkaline phosphatase in Paget's disease compared to bisphosphonates.[18]

However, several points should be considered before denosumab is used. A case report by Reid IR et al indicated that while denosumab lead to improvement in biochemical markers and symptoms, bone scintigraphy did not completely normalise. This led to the conclusion that denosumab only partially corrects Pagetic bone activity.[19] Larger studies are needed to further examine and validate this finding.

Also, unlike the prolonged action of bisphosphonates, the effectiveness of denosumab is short. Studies on the use of denosumab in osteoporosis showed that within 12 months of stopping denosumab, the bone mineral density returned to baseline.[20] The duration of remission of Paget's disease induced by denosumab is unknown. As such, patients treated with denosumab will need to be monitored closely for relapse. Patients with Paget's disease and osteoporosis will certainly require alternative therapy for osteoporosis if the Paget's disease is in remission and the denosumab is stopped.

Conclusion

As there are no long-term studies on the use of denosumab in Paget's disease, the relatively shorter duration of action and the absence of randomised controlled trial comparing denosumab against bisphosphonates, bisphosphonates should remain the first treatment choice. Denosumab can be considered when bisphosphonates are contraindicated and in those with treatment failure.

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