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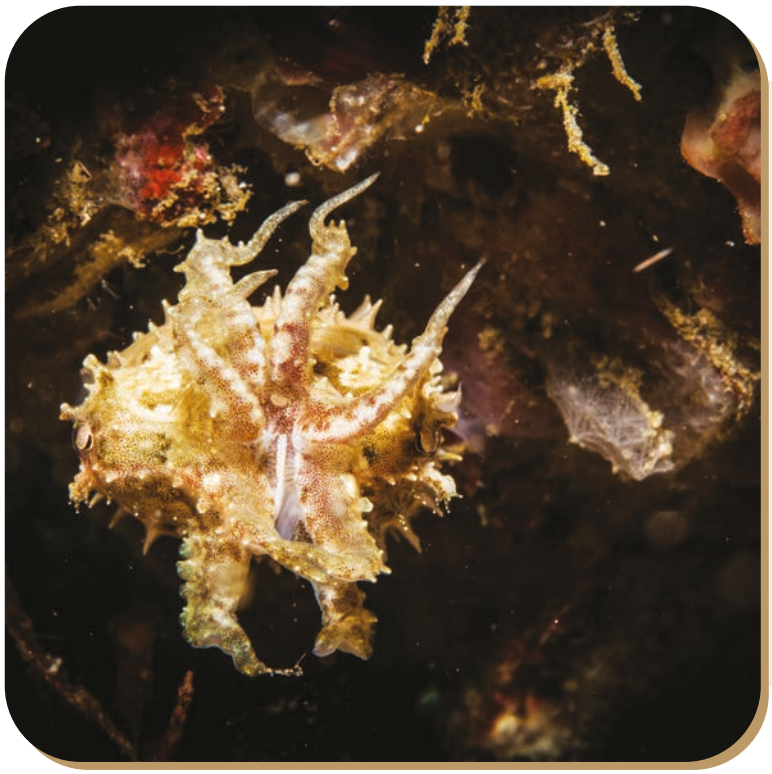

"Dwell on the beauty of life. Watch the stars, and see yourself running with them."

Marcus Aurelius (121 – 80)
Roman soldier

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Please see inside Contents for the full list of articles.

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Editorial

Hypertension Management and Prevention: The Devil is Ever in the Details of Targets

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Since the 1990s the development of the chemical treatment of human disorders, based on principles of human physiology, and clinical pharmaco-kinetics and -dynamics, has culminated in coherent sets of drug treatments that work reliably in most of the chronic non-communicable diseases affecting people worldwide. In the past 10-12 years the progressive refinement of antihypertensive drug treatment via well powered randomised clinical trials (RCTs) and meta-analyses thereof, has provided physicians with a core of blood pressure (BP) management knowledge which they can adapt easily across gender, ethnic groups, age bands, and coexisting disorders.

Even if the complex disorder-tailored management knowledge is not agglomerated into practice guidelines, the overall logic and workflow are simple enough to apply in urban communities without the use of a smartphone app. For instance, moderate hypertension, consisting of a sustained average blood pressure of 160/100 to 179/109 mmHg, usually responds within 2 months to a combination of angiotensin-converting enzyme inhibitor (AceI) and calcium ion-channel antagonist (calcium blocker, [CB]). However, some patients in the upper zone of this BP range might need a third drug, such as a ß1-selective ß-blocker or ß-blocker/α_1 blocker, a thiazide or thiazide-like diuretic, or an α_1-blocker—depending on their coexisting disease(s).

Upon such refinements depend the recommendations in practice guidelines, including the clinical practice guideline (CPG) for hypertension of the Ministry of Health, Singapore, which will soon appear after a prolonged gestation—the last guideline was published in 2005. The advices in the upcoming guideline were carefully weighed in the light of rigorously selected RCTs. Practitioners might regard the CPG as a comprehensive resource of sound and reliable advice for bespoke treatment for a particular patient, and indeed that is its basic purpose. Naturally, only time will tell to what extent the CPG succeeds in this broad objective.

It is always wise to reflect on the evolutionary nature of the RCT information from which CPG advices are derived. What is not broadly understood is that the vast majority of reviewed RCTs completed between 1986 and 2016 relied on several different instruments for BP measurement, the accuracy of which ultimately depended on unrecorded or non-implemented calibration with the gold-standard of directly measured intra-arterial blood pressure. The mercury column manometer (manual and analogue) and the aneroid manometer (semi-automatic and analogue) have been largely superseded by non-invasive arterial pressure technology, e.g. oscillometric wave algorithms yield numbers derived from pulse-wave forms.[1] From the latter design emerged the miniature "automated" oscillometric devices widely used in Singapore hospitals, polyclinics and many family medical centres. Strictly speaking, the latter are semi-automatic, but it is a matter of time before manometry becomes fully automated. The components retained from the earlier devices are only the pump and the inflatable cuff.

Why is BP measuring technology important? It matters because the physics of pulsatile and approximately laminar blood flow within human arteries is constant, but the BP values might not be measured linearly by all the current devices across the pressure range of, for instance, 115/75 to 220/120 mmHg (± 1 standard deviation [SD], covering 68.3% of a population), never mind an extreme range such as 80/50 to 280/160 mmHg (± 3 SD, or 99.7%). Secondly, assuming perfect size fitting of cuff-to-upper arm and well trained handlers, the mercury manometer needs calibration infrequently, and is better for accuracy of the systolic and diastolic BP, whereas digital oscillometric manometers produce BP values that are affected by heart rate, pulse pressure, arterial stiffness (the inverse of compliance), and atrial fibrillation.[2] Stiffer arteries in older persons blur the change in capacitance or in piezo-resistance, which constitutes the voltage signal translated by a microprocessor, via a simple algorithm, into numbers (viz. digits) of mmHg. Oscillometric BP estimation in older persons therefore tends to yield less accurate values of mean arterial pressure (= 2/3 diastolic BP + 1/3 systolic BP).

A blizzard of antihypertensive treatment trials has shown beyond reasonable clinical and statistical doubt that real and measurable cardiovascular (CVS) preventive benefit

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follows, within months in some persons, the reduction by single-digits of mmHg in the blood pressure below arbitrary but agreed thresholds. As the demographic load in many affluent countries expands for persons aged ≥70 years, any errors in measured BP clearly will affect many more people at very high CVS-event risk.

But, for measuring heart rate and the average BP simultaneously in many persons, digital meters—if calibrated often and applied consistently—are far ahead in speed and convenience.[1] Portable digital "monitors" applied on the upper arm are thus an epidemiologist's dream machine. It is no surprise that 24-hour ambulatory (brachial) BP monitoring has replaced mercury column manometry as the reference standard for determining an individual's BP status, i.e. for diagnosis and classification.

Crucially, however, the instantaneous BP varies hugely according to the individual's anxiety level, the extent of adrenergic nervous system activation (or recent exercise), ambient noise level, and the presence of other persons during the BP measurement. It goes without saying that the latter factor can greatly raise the measured BP, analogous to a nocebo effect[3]—the converse of the placebo effect. And yet this BP upsurge is widely ignored in both wards and clinics, and sometimes incompletely accounted for in RCTs.

Of the dozens of RCTs in the past 30 years, only the SPRINT and SPRINT-75 studies[4,5] were conducted using automated devices that measured the BP while the patient was sufficiently rested, and alone, in a quiet room. Moreover, none of the study patients had high pulse pressure. Experienced physicians know that about 1 in 5 persons will regularly show isolated clinic hypertension (e.g. 210/115 mmHg measured by an aide using an automatic oscillometric device), which settles towards 130+ mmHg systolic pressure, within about 10 minutes when the patient is alone. Yet most of the past 30 years' RCTs were conducted with manual non-automated, non-oscillometric manometers in the presence of one or more clinic or research staff. Careful studies have shown that the BP values recorded in non-rested persons under non-standardised, non-ideal, clinic conditions usually overestimate the actual systolic BP by about 10 or 12 mmHg.[6,7]

Admittedly such a difference is not critical for showing treatment-related changes in physiology so long as (i) BP changes due to drug treatment or other (e.g. device-related) interventions are not compared across different techniques of BP measurement, (ii) within-subject changes in the BP are consistently tracked across time (in cohort studies), and (iii) the lowest zone of BP is not linked to a paradoxical rise in CVS-event risk (the familiar J curve or J-shaped relation).

Debate continues on whether it matters that a clinician targets the patients' BP values at 120/80 mmHg (measured by a mercury manometer, for example), whereas the SPRINT target BP was measured by an automated oscillometric device.[4] Will the patient's mercury-manometric systolic pressure of 120 mmHg in the clinic actually represent an oscillometric BP of about 110 mmHg, which could be physiologically harmful to that patient in terms of arterial perfusion of the heart, brain and kidneys?

Due to physiological variation, an individual's home-at-rest systolic BP varies such that about 30 serial values can narrow the SD to 4 mmHg.[8] To decrease 95.5%, that is 2 SDs, of these averaged values below 130 mmHg would entail a true systolic BP of about 122 mmHg. By extension, to decrease 2 SDs of averaged values below 120 mmHg (the intensive treatment target) would require a true systolic of about 111 mmHg. The latter pressure, measured by mercury manometry, translates into a systolic pressure of about 100 mmHg by digital oscillometry. A physician faced with this requirement might well intensify the antihypertensive treatment—potentially causing postural hypotension, or physiological harm in terms of arterial perfusion of the heart, brain and kidneys, or both.

Natural caution in this area suggests that a new consensus might occur on systolic BP targets such as 130 mmHg rather than 120 mmHg.[9] However, a recent meta-analysis of 49 RCTs involving nearly 74,000 diabetic persons suggested that a systolic target of 139 mmHg or lower is linked to a rise in CVS death, "with no observed benefit".[10] This result is counterintuitive, as we would expect the largest clinical benefit in CVS-event prevention to occur in higher-risk patients,[11] as many earlier meta-analyses had shown.

Nonetheless, clinicians and bio-scientists will note that the SPRINT and SPRINT-75 studies of people at high CVS-event risk were funded and conducted by the National Institutes of Health USA, as opposed to the vast majority of pharmaceutical-company funded treatment trials, whose results produced the outcome interpretations within most or all practice guidelines to 2016. The publication of the two SPRINTs was a blast of fresh air. As usual, though, the fresh air contained some deficiencies: unlike the bulk of antihypertensive RCTs, they failed to decrease mortality from myocardial infarction, all CVS events, and from heart failure. Despite its early ending, SPRINT's outcomes might apply to about 7.6% of American adults, and 1 in 5 patients were aged 75 years or more.[5] Will the SPRINTs infer a scientific need to build up a pragmatic database of treatment outcomes using the strict evidential and methodological criteria applied?

It appears likely that some large-scale RCTs exceeding 4-5 year time-frames will be conducted to the exacting standards pioneered by SPRINT in subpopulations such as elderly people, and those with diabetes, chronic kidney disease, recent stroke, and any combination thereof. The effective numbers needed to benefit or to harm should be

fairly small in the multimorbid group. While the results of an early-wave meta-analysis of the latter kind supported the SPRINTs in terms of CVS-event reduction and the progression of albuminuria, between-group CVS mortality and all-cause deaths did not decrease with intensive BP reduction towards 118/75 mmHg.[12] Therefore, we await a comprehensive review in due time.

There is one bright spark on this horizon, viz. the bioscientific dynamos in China[13-16] might yet produce the evidential goods which should underpin the finetuning of the therapeutic BP targets and border posts that physicians heed to design minimum effective treatments for the best (net) benefits. One such in-progress RCT is the Chinese high normal blood pressure study (CHINOM) (Zhang Yuqing, personal communication at the 13th Asian Pacific Congress of Hypertension, Singapore, 6-8 October 2017). It promises to provide information on the biological value of multipronged pressure reduction in the approximate +1 SD of any human population, that is the Gaussian "hump" zone consisting of persons with BP of systolic 125-139 mmHg and diastolic 75-89 mmHg. The data from CHINOM could provide insights on pragmatic treatment targets in "relatively healthy" adults with borderline hypertension. Much will depend on the accuracy and consistency of that fundamental issue: pressure measurement.

REFERENCES

1. Wan Y, Heneghan C, Stevens R, McManus RJ, Ward A, Perera R, et al. Determining which automatic digital blood pressure device performs adequately: a systematic review. J Hum Hypertens 2010;24:431-8.
2. Selmyte-Besuspare A, Barysiene J, Petrikonyte D, Aidietis A, Marinskis G, Laucevicius A. Auscultatory versus oscillometric blood pressure measurement in patients with atrial fibrillation and arterial hypertension. BMC Cardiovas Disord 2017;17:87.
3. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet 2016;389:2473-81.
4. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. New Engl J Med 2015;373:2103-16.
5. Williamson JD, Supiano MA, Applegate WB, Berlowitz D, Campbell RC, Chertow GM, et al. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged ≥75 years: a randomized trial. JAMA 2016;315:2673-82.
6. Kjeldsen SE, Jund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurements in the Systolic Blood Pressure Intervention Trial: implications for entry and achieved blood pressure values compared with other trials. Hypertens 2016;67:808-12.
7. Bell KJ, Hayen A, Macaskill P, Craig JC, Neal BC, Fox KM, et al. Monitoring initial response to angiotensin-converting enzyme inhibitor-based regimens: an individual patient data meta-analysis from randomized, placebo-controlled trials. Hypertens 2010;56:533-9.
8. McManus RJ, Glasziou P, Hayen A, Mant J, Padfield P, Potter J, et al. Blood pressure self-monitoring: questions and answers from a national conference. BMJ 2008;337:a2732.
9. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-67.
10. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. BMJ 2016;352:1-10.
11. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:b1665.
12. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet 2016;387:435-43.
13. Zanchetti A, Liu L, Mancia G, Parati G, Grassi G, Stramba-Badiale M, et al; ESH-CHL-SHOT trial investigators. Continuation of the ESH-CHL-SHOT trial after publication of the SPRINT: rationale for further study on blood pressure targets of antihypertensive treatment after stroke. J Hypertens 2016;34:393-6.
14. Zanchetti A1, Liu L, Mancia G, Parati G, Grassi G, Stramba-Badiale M, et al; ESH-CHL-SHOT trial investigators. Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. J Hypertens 2014;32:1888-97.
15. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A; FEVER Study Group. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens 2005;23:2157-72.
16. Zhang Y, Zhang X, Liu L, Wang Y, Tang X, Zanchetti A; FEVER Study Group. Higher cardiovascular risk and impaired benefit of antihypertensive treatment in hypertensive patients requiring additional drugs on top of randomized therapy: is adding drugs always beneficial? J Hypertens 2012;30:2202-12.

Original Article

Gender-Specific Reference Charts of Fetal Head Circumference in a Singaporean Population

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Abstract

Introduction: With the global outbreak of Zika virus and its association with microcephaly, an up-to-date fetal head circumference (HC) nomogram is crucial to offer a reference standard in order to make an accurate diagnosis. This study was conducted to revise the local fetal HC nomogram. Materials and Methods: In this retrospective study, ultrasound data was used for construction of the fetal HC nomogram from a total of 6155 pregnancies in the ethnic Chinese population with low risk profile at KK Women's and Children's Hospital over a 10-year period. Regression model was fitted to calculate the mean and standard deviation of HC at each gestational age (GA). Comparison of HC between ethnic groups (no significant differences) and genders were made. The revised chart was compared with another commonly used reference chart (Hadlock). In an independent test population, different reference charts were used to estimate number of cases with microcephaly. Results: A statistically significant difference of HC between the genders was observed across all gestational ages. Gender-specific reference charts and equation were computed. Our revised fetal HC chart showed a different distribution from the Hadlock chart. Compared with the gender-specific charts, the Hadlock HC chart would significantly under-report microcephaly cases in male fetuses, and tend to over-report in female fetuses. Conclusion: This study provides a new set of gender-specific fetal HC charts in the Singaporean population for antenatal ultrasound surveillance of microcephaly.

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Key words: Microcephaly, Nomogram, Zika

Introduction

On 1 February 2016, the World Health Organization (WHO) declared the current Zika outbreak a Public Health Emergency of International Concern (PHEIC). On 31 March 2016, WHO announced that based on a growing body of research, there is scientific consensus that Zika virus is a cause of microcephaly and Guillain-Barre syndrome (GBS). More recently, the infection has also been associated with other clinical conditions and neuroimaging findings mainly relating to the central nervous system, including brain abnormalities, epilepsy, hearing and visual impairment, impairment of psychomotor development, and defects of the bones and joints. With a wide range of congenital abnormalities observed to be linked to Zika virus infection, WHO suggested the presence of new congenital syndrome and termed it Congenital Zika Syndrome.[1] Modelling analysis by Cauchemez et al and Johansson et al suggested that the estimated risk of microcephaly associated with maternal infection with the Zika virus is between 0.88% to 13.2%.[2,3] In Singapore, as of 13 November 2016, more than 400 cases of locally transmitted Zika have been confirmed, including a few who were pregnant women. To date, there is no published case of an affected fetus in Singapore.

Microcephaly is defined by WHO as an occipito-frontal head circumference (HC) ≥ 2 standard deviations below the mean for age and sex. Early diagnosis of microcephaly can be made by fetal ultrasound antenatally. WHO recommends an ultrasound of the fetus in the late second or early third trimester (preferably between 28 and 30 weeks) to identify fetal microcephaly and/or other brain abnormalities.[4] To diagnose microcephaly accurately, an appropriate reference standard of HC is of crucial importance. There being

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numerous different international and local fetal HC reference charts in use in different ultrasound machines, the number of microcephaly cases detected could theoretically vary depending on the charts used. Over- and under-detection of microcephaly during antenatal screening have important implications for clinical and public health response in view of the proven link between Zika virus and microcephaly. The current Singapore HC chart was published more than 2 decades ago.[5]

The primary aim of this paper was to update our local fetal HC nomogram to offer a national reference standard. We also investigated possible gender-specific and ethnicity-specific fetal HC nomogram. The secondary aim was to compare the updated fetal HC nomogram with another published reference chart.

Materials and Methods

Ultrasound data of fetal HC from ethnic Chinese women seen at the KK Women's and Children's Hospital (KKWCH) between 1 January 2005 and 31 December 2015 was selected from an existing fetal ultrasound database. One data point of any subject's multiple scans across the whole range of gestation between 11^{+0} and 39^{+6} weeks was randomly selected and used in this project. All included subjects were spontaneous singleton pregnancies, had first-trimester dating scan based on crown-rump length (CRL) and had term live births between 37-42 weeks. The exclusion criteria included abnormal fetal karyotype, congenital malformations, and maternal diseases that would affect the growth of the fetus (pre-eclampsia/eclampsia, diabetes mellitus, renal disease, and etc.). When there were excessive numbers of cases in a particular gestation week, subjects were randomly selected to ensure similar distribution throughout gestations (280-400 cases/week).

HC was measured by trained sonographers as previously published.[6-8] An intra- and inter-operator reproducibility study was conducted to establish the intra- and inter-observer variance (using technical error of measurement, TEM) in this centre. In the first trimester, electronic linear callipers should be used to measure the fetus in a neutral position. The biparietal diameter (BPD) and HC were measured on the largest true symmetrical axial view of the fetal head. From the second trimester onwards, fetal head was measured at the axial plane at the level where the continuous midline echo is broken by the cavum septum pellucidum in the anterior third. At this level, the anterior horns, the thalamus and posterior horns with the choroid plexus were visible. BPD was then measured from the proximal echo of the fetal skull to the distal side of the border deep to the ultrasound beam (outer-to-outer). The occipital-frontal diameter (OFD) was measured in the same plane between the leading edge of the frontal bone and the outer border of the occiput. The HC was calculated from the BPD and OFD measurements using the following formula:

$$HC = (BPD + OFD) \times 0.5 \times 3.14$$

Statistical analyses were performed using the R software and the data were analysed as recommended.[9] In brief, polynomial regression model was fitted to the measurement of HC as a function of gestational age (GA). The selected model was chosen based on adjusted r^2 value. Since the residuals were also dependent on GA, a polynomial regression analysis was performed between the absolute residuals and GA. The fitted values of this regression model were multiplied by $\sqrt{(\pi/2)}$ (= 1.253), to give gestation-specific standard deviations. Centiles were calculated using the formula: centile = mean + K x SD, where K is ±1.88 for 3rd and 97th centiles.

The differences of HC between the genders and a gender-specific equation were tested by applying multivariate regression fitted to the HC measurements, with GA as numeral variable and sex as categorical explanatory variable. The gender-specific equation was then used to estimate the number of microcephaly cases in a test population that comprised of all pregnant women seen in KKWCH from January to September 2016, and compared to the above unisex equation.

Another separate sample population comprised of ethnic Chinese (n = 2198), Indian (n = 1923) and Malay (n = 2668) were acquired, using the same criteria as the study population, from women seen at our centre from 2011 to 2015. Using this sample population, we compared differences of HC between the 3 ethnic groups, by applying multivariate regression fitted to the HC measurements, with GA as numeral variable, and race as categorical explanatory variable.

Comparison was also made between our updated charts with another published reference chart (Hadlock et al[10]). The study was approved by SingHealth Centralised Institutional Review Board (CIRB) on 16 October 2015 with reference number of 2015/2613.

Results

A total of 6155 low-risk pregnancies in ethnic Chinese population were evaluated between 11^{+0} and 39^{+6} weeks of gestation. In the intra- and inter-observer variability study, we established that the intra- and inter-observer variance (TEM) in this centre were 4.85 mm and 6.95 mm, respectively, with an inter-class correlation efficient (ICC) of 0.997 and 0.989.

The raw data of HC was fitted to the GA in weeks satisfactorily with a cubic polynomial model (Fig. 1). The corresponding formula for the regression model is as follows (with GA in weeks):

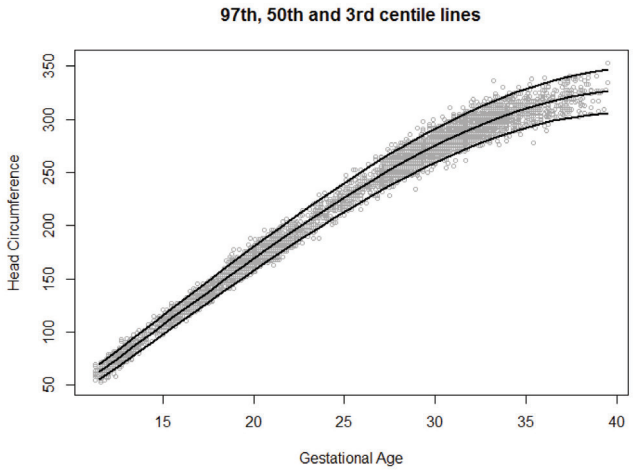

Fig. 1. The updated fetal head circumference (HC) by gestational age chart. The top line represents 97th percentile, middle line represents 50th percentile, and bottom line represents 3rd percentile.

$$Mean = -63.21 + 8.611*GA + 0.2072*GA^2 - 0.006036*GA^3$$

The absolute residuals for HC measurement across GA were fitted satisfactorily using a simple linear fit. The equation for the standard deviation (SD) is as follows (with GA in weeks):

$$SD = 0.988062 + 0.249153*GA$$

Table 1 shows the 3rd, 10th, 50th, 90th, and 97th percentile values and standard deviations as a function of GA for fetal HC.

Small but statistically significant differences in HC across all GAs (11^{+0} to 39^{+6} weeks) were observed between the genders. The HC of male fetuses is consistently larger than females, and the difference increases with GA. A gender-specific equation was computed as below,

$$Mean = -63.16 + 8.528*GA + 0.2711*GA^2 - 0.006051*GA^3 + 0.1309*sex*GA$$

Table 1. Revised Fetal Head Circumference (HC) Percentile Values by Gestational Age

Gestational Age (Week)	Head Circumference, mm					Standard Deviation
	3rd Centile	10th Centile	50th Centile	90th Centile	97th Centile	
$11^{+0} - 11^{+6}$	55.12	57.43	62.37	67.31	69.62	3.85
$12^{+0} - 12^{+6}$	67.14	69.60	74.86	80.11	82.57	4.10
$13^{+0} - 13^{+6}$	79.25	81.85	87.43	93.01	95.62	4.35
$14^{+0} - 14^{+6}$	91.40	94.16	100.06	105.95	108.71	4.60
$15^{+0} - 15^{+6}$	103.58	106.48	112.70	118.91	121.82	4.85
$16^{+0} - 16^{+6}$	115.73	118.78	125.32	131.85	134.91	5.10
$17^{+0} - 17^{+6}$	127.82	131.03	137.88	144.74	147.94	5.35
$18^{+0} - 18^{+6}$	139.82	143.18	150.35	157.53	160.88	5.60
$19^{+0} - 19^{+6}$	151.70	155.20	162.69	170.18	173.69	5.85
$20^{+0} - 20^{+6}$	163.40	167.05	174.87	182.68	186.33	6.10
$21^{+0} - 21^{+6}$	174.91	178.71	186.84	194.97	198.77	6.34
$22^{+0} - 22^{+6}$	186.17	190.12	198.57	207.02	210.97	6.59
$23^{+0} - 23^{+6}$	197.16	201.26	210.03	218.80	222.90	6.84
$24^{+0} - 24^{+6}$	207.84	212.09	221.18	230.27	234.52	7.09
$25^{+0} - 25^{+6}$	218.18	222.57	231.98	241.39	245.79	7.34
$26^{+0} - 26^{+6}$	228.13	232.67	242.40	252.13	256.68	7.59
$27^{+0} - 27^{+6}$	237.66	242.35	252.40	262.45	267.15	7.84
$28^{+0} - 28^{+6}$	246.73	251.58	261.95	272.31	277.16	8.09
$29^{+0} - 29^{+6}$	255.32	260.31	271.00	281.68	286.68	8.34
$30^{+0} - 30^{+6}$	263.37	268.52	279.52	290.53	295.67	8.59
$31^{+0} - 31^{+6}$	270.86	276.16	287.48	298.81	304.10	8.84
$32^{+0} - 32^{+6}$	277.75	283.20	294.84	306.49	311.93	9.09
$33^{+0} - 33^{+6}$	284.01	289.60	301.56	313.53	319.12	9.33
$34^{+0} - 34^{+6}$	289.59	295.33	307.62	319.90	325.64	9.58
$35^{+0} - 35^{+6}$	294.46	300.35	312.96	325.56	331.45	9.83
$36^{+0} - 36^{+6}$	298.59	304.63	317.55	330.47	336.51	10.08
$37^{+0} - 37^{+6}$	301.94	308.13	321.37	334.61	340.80	10.33
$38^{+0} - 38^{+6}$	304.46	310.80	324.36	337.92	344.26	10.58
$39^{+0} - 39^{+6}$	306.14	312.63	326.51	340.38	346.87	10.83

Table 2. Fetal Head Circumference Percentiles by Gestational Age and Gender

Gestational Age (Week)	Male (mm)			Female (mm)		
	3rd Centile	50th Centile	97th Centile	3rd Centile	50th Centile	97th Centile
$11^{+0} – 11^{+6}$	55.93	63.07	70.20	54.43	61.56	68.70
$12^{+0} – 12^{+6}$	68.03	75.62	83.21	66.39	73.98	81.57
$13^{+0} – 13^{+6}$	80.21	88.26	96.30	78.45	86.49	94.53
$14^{+0} – 14^{+6}$	92.45	100.95	109.44	90.55	99.05	107.54
$15^{+0} – 15^{+6}$	104.70	113.65	122.60	102.67	111.62	120.57
$16^{+0} – 16^{+6}$	116.94	126.34	135.74	114.78	124.18	133.58
$17^{+0} – 17^{+6}$	129.11	138.97	148.82	126.82	136.67	146.53
$18^{+0} – 18^{+6}$	141.19	151.50	161.81	138.77	149.08	159.39
$19^{+0} – 19^{+6}$	153.15	163.91	174.67	150.59	161.35	172.12
$20^{+0} – 20^{+6}$	164.93	176.15	187.36	162.25	173.46	184.68
$21^{+0} – 21^{+6}$	176.52	188.19	199.85	173.70	185.37	197.04
$22^{+0} – 22^{+6}$	187.86	199.98	212.11	184.92	197.04	209.16
$23^{+0} – 23^{+6}$	198.94	211.51	224.08	195.86	208.43	221.01
$24^{+0} – 24^{+6}$	209.70	222.72	235.75	206.49	219.52	232.54
$25^{+0} – 25^{+6}$	220.11	233.59	247.07	216.77	230.25	243.73
$26^{+0} – 26^{+6}$	230.14	244.07	258.01	226.67	240.61	254.54
$27^{+0} – 27^{+6}$	239.75	254.14	268.52	236.15	250.54	264.92
$28^{+0} – 28^{+6}$	248.90	263.74	278.58	245.17	260.01	274.85
$29^{+0} – 29^{+6}$	257.57	272.86	288.15	253.70	269.00	284.29
$30^{+0} – 30^{+6}$	265.70	281.44	297.19	261.71	277.45	293.20
$31^{+0} – 31^{+6}$	273.27	289.47	305.66	269.14	285.34	301.54
$32^{+0} – 32^{+6}$	280.23	296.88	313.54	275.98	292.63	309.28
$33^{+0} – 33^{+6}$	286.56	303.67	320.77	282.18	299.28	316.39
$34^{+0} – 34^{+6}$	292.21	309.77	327.33	287.70	305.26	322.82
$35^{+0} – 35^{+6}$	297.16	315.17	333.18	292.51	310.52	328.53
$36^{+0} – 36^{+6}$	301.36	319.82	338.28	296.58	315.04	333.51
$37^{+0} – 37^{+6}$	304.77	323.69	342.61	299.86	318.78	337.70
$38^{+0} – 38^{+6}$	307.36	326.74	346.11	302.32	321.70	341.07
$39^{+0} – 39^{+6}$	309.10	328.93	348.75	303.93	323.76	343.58

SD = 1.023236 + 0.240938*GA

Where sex = 1 for males and sex = 0 for females

Table 2 shows the 3rd, 50th, and 97th percentile values and standard deviations by GA and gender for fetal HC. Figures 2 and 3 show fetal HC charts with mean ± 2SD and ± 3SD for male and female fetuses, respectively.

To better understand the implication of gender-specific nomograms, we compared the numbers of microcephaly (below 2SD of mean) detected by using our revised unisex and gender-specific equations in the test population. Only ultrasound data from 20^{+0} to 39^{+6} weeks of gestation was studied. As shown in Table 3, using unisex chart would report significantly fewer cases as microcephaly in male fetuses than male-specific nomogram ($P<0.001$). Although not statistically significant, there is a trend that the unisex chart would define more microcephaly cases in females; the percentage of microcephaly in females is 4 times of that in males. Whereas, if using a gender-specific nomogram, the percentage of microcephaly remains similar in both male and female population.

When comparing the differences in HC measurements among the ethnic Chinese, Malay and Indian groups in the sample population, no statistical significances were observed among the 3 races (Chinese versus Malay, $P = 0.125$; Chinese versus Indian, $P = 0.122$).

Figure 4 compares our gender-specific HC charts with another commonly used chart – Hadlock et al,[10] and shows different distribution of fetal HC values, particularly at mean and +2SD.

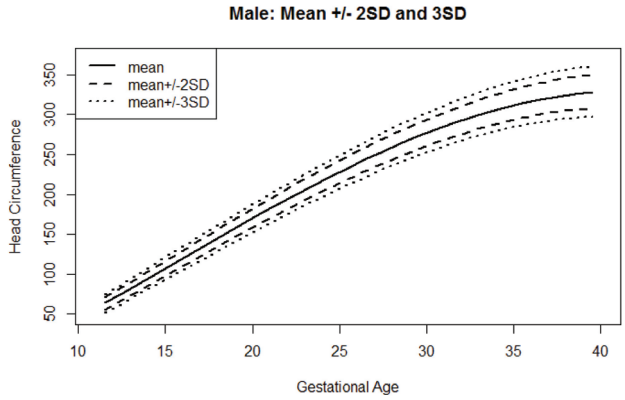

Fig. 2. Fetal head circumference (HC) of male fetuses with mean ± 2SD and ± 3SD.

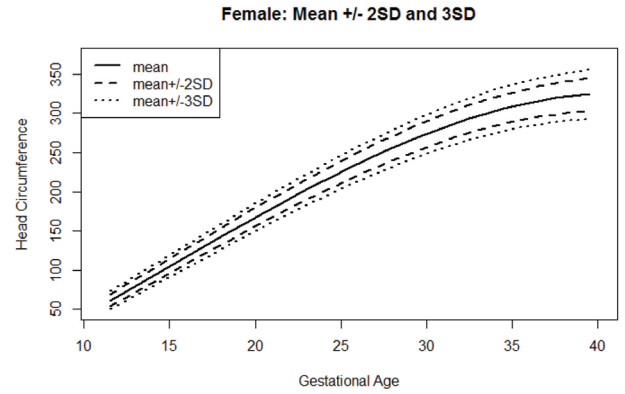

Fig. 3. Fetal head circumference (HC) of female fetuses with mean ± 2SD and ± 3SD.

Potential numbers of fetal microcephaly cases were estimated using Hadlock chart compared to our gender-specific charts. Using Hadlock's chart would report significantly fewer microcephaly cases in male fetuses (P <0.01). There is no statistical difference in female fetuses, but Hadlock tends to report more female fetuses as microcephaly (Table 3).

Discussion

Using data from the current sample of 6155 Chinese women locally, we have revised the existing fetal HC nomogram and equation.

A statistically significant and GA-dependent difference of HC was observed between the genders, with male fetal HC larger than females. Gender-related difference in fetal biometry has been previously reported.[11-15] In a large population, a small shift in the GA distribution might significantly affect rates of prematurity, intrauterine growth restriction and postdatism.

As the majority of people infected with Zika have no symptoms, infection during pregnancy may only manifest as fetal abnormalities, notably microcephaly. While universal testing is not recommended, antenatal HC monitoring is potentially an important part of surveillance in pregnancy in a Zika active area.[16] The use of unisex growth charts may make a pathologically small HC less obvious in a male fetus, potentially increasing the rate of false-negative diagnoses; vice versa, this may increase the false-positive of microcephaly in female fetuses, as shown in Table 3. Hence, in line with WHO definition of microcephaly by age and sex,[4] we produce a set of gender-specific HC nomograms with ±2SD and ±3SD for easy reference for prenatal surveillance of microcephaly.

As shown in our previous study,[6] there was no difference in HC measurements among Chinese, Indian and Malay. As Chinese is the largest component of the population in Singapore and allows completion of a large sample collection in a most reasonable time frame, in the current study, data from Chinese population was used to construct the reference chart. Again, comparison was made among the 3 ethnic groups in this study and showed no statistically significant difference in the mean values of fetal HC across all GAs.

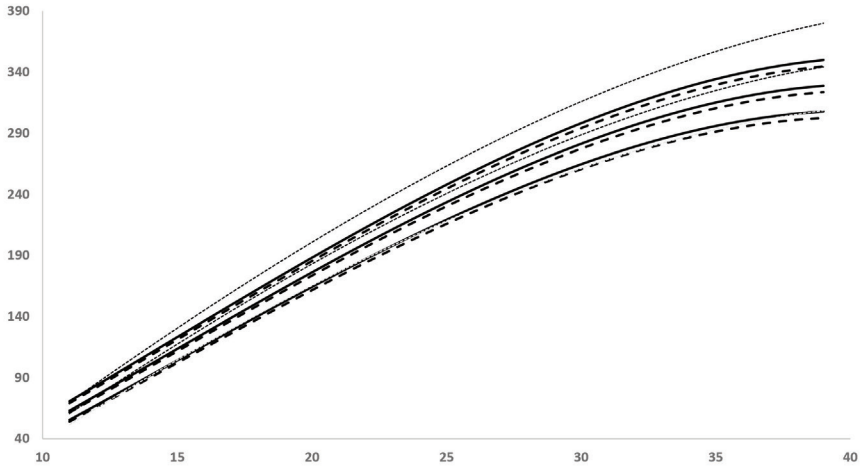

Fig. 4. Comparison of the revised gender-specific fetal head circumference charts (male – solid line, female – broken line) with Hadlock chart (dotted line), mean ± 2SD.

Table 3. Estimation of Microcephaly Using Gender-Specific, Unisex and Hadlock Equations

	Male Population			Female Population		
	Male-Specific Nomogram	Unisex Nomogram	Hadlock	Female-Specific Nomogram	Unisex Nomogram	Hadlock
Total number		1028			927	
Microcephaly	28	11	10	29	41	40
Percentage (%)	2.72	1.07	0.97	3.13	4.42	4.31
P value		0.00969	0.005376		0.1801	0.2199

Thus, the findings support the use of 1 set of gender-specific HC nomograms for all 3 races.

Comparison to Hadlock chart, a widely used formula which is incorporated in many ultrasound machines, was made with our new reference chart. In this study, we found that the present cohort of Singaporean fetuses had different HC measurements compared to the Hadlock's group. The population studied by Hadlock only consisted of Caucasian women from the Houston, Texas area. Geographical, ethnical and socioeconomic diversities may contribute to the difference. Of note, different techniques of HC measurement were used for the 2 studies. In Hadlock's study, HC was measured directly by using a hand-held map measurer or an electronic digitiser;[10] whereas, in the current study, HC were calculated from BPD and OFD. Although these methods have been shown to give equivalent results,[17] to establish a reference standard, a measuring method that is more compatible with current practice should be used. When we tested these 2 equations in the test population, significantly fewer male cases were defined microcephaly using Hadlock chart (P <0.01). This would have an impact on the incidence of microcephaly with the advent of Zika endemic. Therefore, we propose the use of this revised nomogram, which better fits the setting of our local requirement.

A key strength of our analysis was the large sample size which ensured greater precision was achieved when estimating centiles, especially the extreme ends.[8] In addition, meticulous standardisation and ongoing auditing of adherence to ultrasound measurement protocols have been in place since 1994[6,18-20] to ensure consistency and to minimise intra- and inter-observer variability. Our intra- and inter-observer study has shown excellent reliability of sonographers. A limitation of the study is its retrospective design with potential uncontrolled confounders. However, these data have been prospectively collected to build the database over the 10-year study period, and there is consistent use of the same standard of ultrasound practice in the same hospital where these data are acquired under the direction of the same maternal-fetal medicine sonologist.

Conclusion

There are statistical differences in female and male HC measurements throughout all GAs; with the ongoing outbreak of Zika virus infection, we recommend the use of 1 gender-specific nomogram for all ethnic groups in the Singaporean population for antenatal ultrasound surveillance of microcephaly.

Acknowledgements

The authors are grateful to the doctors and sonographers who have contributed to data collection. The study research was supported by departmental funding from the Department of Maternal Fetal Medicine, KK Women's and Children's Hospital.

REFERENCES

1. Costello A, Dua T, Duran P, Gülmezoglu M, Oladapo OT, Perea W, et al. Defining the syndrome associated with congenital Zika virus infection. Bulletin of the World Health Organization 2016;94:406-406A. Available at: http://dx.doi.org/10.2471/BLT.16.176990. Accessed on 13 November 2016.
2. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet 2016;387: 2125-32.
3. Johansson MA, Mier-Y-Teran-Romero L, Reefhuis J, Gilboa SM, Hills SL. Zika and the risk of microcephaly. N Engl J Med 2016;375:1-4.
4. WHO. Fact sheet – Microcephaly (updated 2 March 2016). Available at: http://www.who.int/mediacentre/factsheets/microcephaly/en/. Accessed on 13 November 2016.
5. Lai FM, Yeo GS. Reference charts of fetal biometry in Asians. SMJ 1995;36:628-36.
6. Yeo GS, Chan WB, Lun KC, Lai FM. Racial differences in fetal morphometry in Singapore. Ann Acad Med Singapore 1994;23:371-6.

7. Papageorghiou AT, Thilaganathan B, Bilardo CM, Ngu A, Malinger G, Herrera M, et al. ISUOG Interim Guidance on ultrasound for Zika virus infection in pregnancy: information for healthcare professionals. Ultrasound Obstet Gynecol 2016;47:530-2.
8. Napolitano R, Donadono V, Ohuma EO, Knight CL, Wanyonyi SZ, Kemp B, et al. Scientific basis for the standardization of fetal head measurements by ultrasound: a reproducibility study. Ultrasound Obstet Gynecol 2016;48:80-5.
9. Altman DG, Chitty LS. Charts of fetal size: 1. Methodology. Br J Obstet Gynaecol 1994;101:29-34.
10. Hadlock FP, Deter RL, Harrist RB, Park SK. Estimating fetal age: computer-assisted analysis of multiple fetal growth parameters. Radiology 1984;152:497-501.
11. Wald N, Cuckle H, Nanchahal K, Turnbull AC. Sex differences in fetal size early in pregnancy. Br Med J (Clin Res Ed) 1986;292:137.
12. Parker AJ, Davies P, Mayho AM, Newton JR. The ultrasound estimation of sex-related variations of intrauterine growth. Am J Obstet Gynecol 1984;149:665-9.
13. Bromley B, Frigoletto FD Jr, Harlow BL, Evans JK, Benacerraf BR. Biometric measurements in fetuses of different race and gender. Ultrasound Obstet Gynecol 1993;3:395-402.
14. Schwarzler P, Bland JM, Holden D, Campbell S, Ville Y. Sex-specific antenatal reference growth charts for uncomplicated singleton pregnancies at 15-40 weeks of gestation. Ultrasound Obstet Gynecol 2004;23:23-9.
15. Melamed N, Meizner I, Mashiach R, Wiznitzer A, Glezerman M, Yogev Y. Fetal sex and intrauterine growth patterns. J Ultrasound Med 2013;32:35-43.
16. World Health Organisation, Interim Guidance update. Pregnancy management in the context of Zika virus infection. Accessed on 13 May 2016. Available at: http://apps.who.int/iris/bitstream/10665/204520/1/WHO_ZIKV_MOC_16.2_eng.p df?ua=1. Accessed on 13 November 2016.
17. Hadlock FP, Kent WR, Loyd JL, Harrist RB, Deter RL, Park SK. An evaluation of two methods for measuring fetal head and body circumferences. J Ultrasound Med 1982;1:359-60.
18. Yeo GS, Lai FM, Wei X, Lata P, Tan DT, Yong MH, et al. Validation of first trimester screening for trisomy 21 in Singapore with reference to performance of nasal bone. Fetal Diagn Ther 2012;32:166-70.
19. Lai FM, Yeo GS. Down syndrome screening in Singapore--the effectiveness of a second trimester serum screening policy modelled on 29,360 pregnancies in KK Women's and Children's Hospital. Singapore Med J 1998;39:69-75.
20. Thia EW, Wei X, Tan DT, Lai XH, Zhang XJ, Oo SY, et al. Evaluation of an objective method of image assessment for first-trimester nasal bone. Ultrasound Obstet Gynecol 2011;38:533-7.

Review Article

Glycaemic, Blood Pressure and Low Density Lipoprotein Cholesterol Control in Adult Patients with Diabetes in Singapore: A Review of Singapore Literature Over Two Decades

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Abstract

Introduction: Diabetes mellitus is a burgeoning global health epidemic, with an estimated 422 million people living with diabetes in 2014. The number of adult diabetic patients in Singapore is expected to rise to 1 million in 2050. Despite advances made in the management of diabetes and improvements in healthcare accessibility and delivery, the rate and complications of diabetes (myocardial infarction, stroke, kidney failure and lower limb amputation) in Singapore have not decreased. Gaps between guidelines and practice have been reported in several parts of the world. In this narrative review, we aimed to describe the control of diabetes in Singapore over the past 20 years. Materials and Methods: We reviewed studies describing, or trials intervening in, the glycaemic, blood pressure (BP) and low density lipoprotein cholesterol (LDL-C) control of adult diabetic patients in Singapore published over the past 20 years (1997-2016). Studies selected from comprehensive electronic databases searches were reviewed by 4 reviewers (2 primary care physicians, 1 diabetologist and 1 public health epidemiologist). The GRADE approach was used to evaluate the quality of evidence. Results: We included 23 articles involving 257,097 subjects. There were 9 longitudinal, 12 cross-sectional and 2 case-control studies. All studies reported mean/median HbA1c between 7.2%-8.6%. BP ranged between 126.5-144 mmHg (systolic) and 70-84 mmHg (diastolic) in 9 studies. Nine studies reported LDL-C between 2.4-3.3 mmol/L. Conclusion: Mirroring global patterns, the glycaemic, BP and LDL-C control in adult diabetic patients in Singapore do not appear to be treated to target in the majority of patients.

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Key words: Glycated Haemoglobin (HbA1c), Hypertension, Lipid

Diabetes mellitus (DM) is a burgeoning global health epidemic, with an estimated 422 million people living with DM in 2014.[1] The prevalence of DM amongst Singaporean adults aged 18 to 69 years mirrors global trends, increasing from 8.2% in 2004[2] to 11.3% in 2010.[3] It is estimated that Singapore will have half a million people with diabetes by 2020, and this will rise to 1 million by 2050.[4]

According to figures from the Singapore National Registry of Diseases, 1 in 2 diabetics suffered from ischaemic heart disease; 2 in 3 who had newly diagnosed renal failure were diabetics; 2 in 5 with strokes suffered from DM; and about 1500 amputations per year arose as a complication of DM.[5] In Singapore, the total direct and indirect economic costs of diabetes for the entire working-age diabetes population was US$787 million in 2010. This is expected to increase to US$1867 million in 2050.[6]

It is well established that glycaemic control (measured by glycosylated haemoglobin, HbA1c) correlates with both microvascular and macrovascular complications.[7-10] Hypertension also contributes to the risk of DM complications. The coexistence of both hypertension and DM increases the risks of heart failure, nephropathy and

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other microvascular events.[11-12]

Low density lipoprotein cholesterol (LDL-C) is an important determinant in the atherogenic pathway leading to cardiovascular diseases[13] and is identified as a primary target of lipid treatment in all diabetic guidelines.[14]

Current international guidelines recommend management of patients with DM to HbA1c <7.0%, blood pressure (BP) <140/90 mmHg and 30%-50% reduction in LDL-C for most patients.[14-15] Singapore also adopts rather similar glycaemic, BP and LDL-C targets of <7.0% or <53 mmol/L, 140/80 mmHg and <2.6 mmol/L for the majority of non-pregnant diabetic adults.[16] The Singapore lipid clinical practice guidelines (CPG) stratifies patients according to risk of coronary artery disease and recommends a treat-to-target strategy for lipid control.[17]

Despite advances made in understanding the pathophysiology of diabetes and its management, as well as improvements in healthcare accessibility and delivery, the rates of cardiovascular endpoints and amputation in Singapore have not decreased, and in some cases, increased. Despite established guidelines, a gap between guidelines and practice in the management of diabetes has been reported in several parts of the world.[18-21] It is important to identify if such gaps also exist in Singapore. By reviewing the literature published over the past 20 years, we aimed to provide an overview of the glycaemic, BP and LDL-C control in adult patients with diabetes in Singapore. In this paper, we reviewed studies describing, or trials intervening in, the glycaemic, BP and LDL-C control of adult patients with diabetes in Singapore.

Materials and Methods

Search Strategy

Comprehensive searches of electronic databases including PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were made in October 2016 for relevant articles. The references of review articles and of included original publications were also screened for potentially relevant studies.

PubMed and CENTRAL database searches were conducted with a combination of 'Diabetes Mellitus', 'Glycaemic control', 'HbA1c', 'Haemoglobin A, glycosylated', 'Blood pressure/BP', 'Cholesterol, LDL' and 'Singapore' as search terms.

The initial search identified 2167 citations from PubMed and 38 from CENTRAL, respectively. After screening of the titles of the citations for relevance, 103 articles were accepted for further screening and abstracts of these articles were reviewed. Articles that did not discuss glycaemic, BP or lipid control in diabetic patients managed in Singapore were excluded.

Of these, a total of 28 studies were identified as potentially meeting the inclusion criteria and were included for the review. Another 3 studies were identified by hand search of bibliographic references of the 28 shortlisted studies. From these 31 articles, 8 were excluded due to similar study cohorts (3 studies), non-representative study (2 studies) and no relevant outcome parameters measured (3 studies). Eventually, 23 studies (9 longitudinal cohort, 12 cross-sectional and 2 case-control) were selected for review.

The selection process is shown in Figure 1. The following information was extracted from the 23 articles: type of study, grade of evidence, characteristics of study population, glycaemic control measured by glycosylated haemoglobin (HbA1c in %), BP readings (mmHg) and LDL-C (mmol/L).

Inclusion and Exclusion Criteria

Articles with adult diabetic cohorts managed in Singapore were included. Clinical parameters included HbA1c, BP and lipid control. Article types were restricted to clinical trials, cohort, case-control and cross-sectional studies involving human subjects, practice guidelines and review articles that were published within the past 20 years (1997 onwards). Studies focusing on paediatric and youth populations, gestational diabetes, surgical interventions, animal studies and non-English language articles were excluded.

Methods of Review

Members of the study team included 2 family physicians, a diabetologist and public health epidemiologist. One reviewer independently screened citations and abstracts to identify potentially suitable articles meeting the inclusion criteria. Full text articles were retrieved and data extraction of relevant study information of articles meeting the inclusion criteria was summarised. This was then reviewed by 3 other reviewers.

Validity Assessment

The GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach that is adopted by major international organisations including the World Health Organisation (WHO) and Cochrane Collaboration was used to evaluate the quality of evidence. The strength of evidence was graded as high, moderate, low, very low or insufficient.

Analyses

Descriptive statistics present the data from the selected articles tabulated by outcome parameters (HbA1c, BP and LDL-C) and methodology (longitudinal cohort studies, case-control studies, cross-sectional studies).

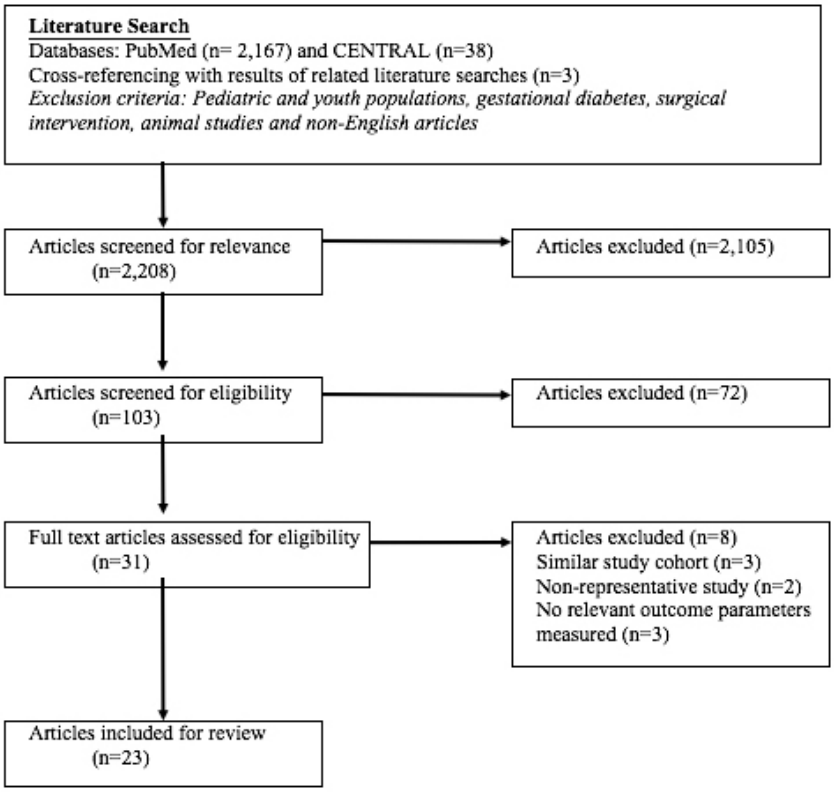

Fig. 1. Chart showing the selection process.

Results

A total of 23 studies that reported quantitative information about the glycaemic and/or BP and/or LDL-C control in Singaporean patients are included in this review.[2,3,22-42] We summarised the findings by individual outcomes of interest, study design and site of care.

Glycaemic Control

The level of glycaemic control measured by HbA1c (%) is presented in Tables 1-3. In general, the average HbA1c of 257,097 subjects studied across 23 studies ranged between 7.2% to 8.6%. Of the 23 studies, 9 were conducted in the primary healthcare setting, while 7 were in tertiary care. The remaining 7 cohorts had patients managed in both primary and tertiary care.

All except one were conducted on multiethnic cohorts, with Chinese being the predominant ethnic group. Chinese had consistently better glycaemic control compared to Malays and Indians. [2,3,23,25,26,30,32] In the Malay-only study, 3280 Malay diabetic adults aged 40-80 years had a mean HbA1c of 8.0% with only 26.9% having an optimal HbA1c <7%.[39]

The average age of subjects in the studies ranged between 46-62 years old. About 43.1%-92.7% of the subjects were reported to be on oral antidiabetic drugs (OADD), while 3.9%-38.8% were on insulin therapy. The reported average duration of diabetes ranged between 7.0-12.1 years.

In addition, elderly patients appeared to have better glycaemic control. Heng et al reported more than half of those aged 65-84 years, and about 2/3 of all aged 85 years and above achieved HbA1c <7%.[30] Toh et al reported the mean HbA1c among patients under Geriatric Medicine to be 6.9%. This was the lowest when compared to those managed in other subspecialties. Furthermore, significantly more patients in Geriatric Medicine had HbA1c <7% (65% vs 40.9%-52.5%, $P = 0.003$).[37] A similar finding was observed by Quah et al in their study based in the primary care setting.[31] When compared to patients aged <60 years, those aged between 60-69 years and >70 years were less likely to have HbA1c>8.0% (adjusted OR 0.42 and 0.38, respectively).[31]

Those with macro- and micro-albuminuria had poorer glycaemic control compared to those with normoalbuminuria (7.7% vs 7.4% vs 7.2%, $P<0.001$).[33] Also, Foo et al reported the intrapersonal mean HbA1c (iM-HbA1c) to be higher in multiethnic cohort of patients with moderate diabetic

Table 1. Longitudinal Studies

Managed in Primary Care Setting					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Ng et al, 2005[*] GRADE: low	Prospective cohort study (follow-up of 3 years) Sample size: 500	• Recruitment from 2 polyclinics in 1999 • Multiethnic/type 2 DM, not on insulin • Mean age: 53.9 ± 6.9 years • Median duration of DM: 7.0 years • Type of treatment: not reported	Baseline mean HbA1c (%) All 8.3 ± 1.7% Malay 8.7 ± 1.7%/Chinese 8.2 ± 1.7%/ Indian 8.2 ± 1.6% (P <0.032) Mean HbA1c at 3-year follow-up (%) All 7.6 ± 1.1 Chinese 7.4 ± 0.2/Malay 7.9 ± 1.3/Indian 7.8 ± 1.3 (P = 0.003)	Data not available	Data not available
Tan et al, 2015[†] GRADE: low	Longitudinal cohort study Sample size: 1256	• Recruited from single polyclinic in 2007 • Multiethnic/type 2 DM • Mean age: 57.5 ± 8.9 years • Duration of DM: not reported • Type of treatment: OADD (76%)/ insulin (15%); anti-hypertensive medications (85%); ACEI 252 (24%)	Baseline mean HbA1c (%) 7.7 ± 1.7	Baseline mean BP (mmHg) 131.9 ± 16.2 75.0 ± 9.7	

ACEI: Angiotensin converting enzyme inhibitor; BP: Blood pressure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; LDL: Low density lipoprotein; NHG: National Healthcare Group; OADD: Oral antidiabetic drugs; PCC: Primary care clinic; PHC: Primary health clinic; RH: Restructured hospital; SOC: Specialist outpatient clinic

[*]Ng TP, Goh LG, Tan Y, Tan E, Leong H, Tay EG, et al. Ethnic differences in glycemic control in adult type 2 diabetic patients in primary care: a 3-year follow-up study. Diabet Med 2005;22:1598-604.
[†]Tan NC, Barbier S, Lim WY, Chia KS. 5-Year longitudinal study of determinants of glycemic control for multi-ethnic Asian patients with type 2 diabetes mellitus managed in primary care. Diabetes Res Clin Pract 2015;110:218-23.
[‡]Wee SL, Tan CGP, Ng HS, Su S, Tai VU, Flores JV, et al. Diabetes outcomes in specialist and general practitioner settings in Singapore: challenges of right-siting. Ann Acad Med Singapore 2008;37:929-35.
[§]Hoe J, Koh WP, Jin A, Sum CF, Lim SC, Tavintharan S. Predictors of decrease in ankle-brachial index among patients with diabetes mellitus. Diabet Med 2012;29:e304-7.
[‖]Dalan R, Jong M, Choo R, Chew DE, Leow MK. Predictors of cardiovascular complication in patients with diabetes mellitus: a 5-year follow-up study in a multiethnic population of Singapore: CREDENCE II study. Int J Cardiol 2013;169:e67-9.
[¶]Liu JJ, Lim SC, Yeoh LY, Su C, Tai BC, Low S, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with type 2 diabetes. Diabet Med 2016;33:332-9.
[#]Low S, Lim SC, Yeoh LY, Liu JJ, Fun S, Su C, et al. Long-term diabetes outcomes in multi-ethnic Asians living in Singapore. Diabetes Res Clin Pract 2016;111:83-92.
[**]Lee WRW, Emmanuel S, Lim HS, Thai AC, Chew WL, Goh LG, et al. The status of diabetes mellitus in primary institution and restructured hospitals in Singapore. Singapore Med J 2001;42:508-12.
[††]Heng BH, Sun Y, Cheah JTS, Jong M. The Singapore National Healthcare Group diabetes registry – descriptive epidemiology of type 2 diabetes mellitus. Ann Acad Med Singapore 2010;39:348-52.

Table 1. Longitudinal Studies (Cont'd)

Managed in Tertiary Care					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Wee et al, 2008[‡] GRADE: very low	Retrospective cohort study Sample size: 383	• Recruited consecutive referrals to single tertiary DM clinic from January to March 2005 • Mean age: 57.5 ± 12.7 years • Duration of DM: not reported • Type of treatment: not reported	Baseline mean HbA1c (%) 8.43 ± 2.14	Baseline mean BP (mmHg) 134.9 ± 21.0 77.6 ± 10.6	Baseline mean LDL (mmol/L) 2.89 ± 1.05
Hoe et al, 2012[§] GRADE: low	Prospective cohort study Sample size: 87	• Recruited from tertiary care DM clinic between April to June 2007 • Multiethnic/type 2 DM patients • A total of 14.6% had a history of IHD and 4.9% had CVA • Mean age: 54.9 ± 13.0 years • Mean duration of DM: 8.8 ± 7.4 years • Type of treatment: not reported	Baseline median HbA1c (%) 7.7 (range 5.6 to 13.8)	Data not available	Data not available

ACEI: Angiotensin converting enzyme inhibitor; BP: Blood pressure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; LDL: Low density lipoprotein; NHG: National Healthcare Group; OADD: Oral antidiabetic drugs; PCC: Primary care clinic; PHC: Primary health clinic; RH: Restructured hospital; SOC: Specialist outpatient clinic

[*]Ng TP, Goh LG, Tan Y, Tan E, Leong H, Tay EG, et al. Ethnic differences in glycemic control in adult type 2 diabetic patients in primary care: a 3-year follow-up study. Diabet Med 2005;22:1598-604.

[†]Tan NC, Barbier S, Lim WY, Chia KS. 5-Year longitudinal study of determinants of glycemic control for multi-ethnic Asian patients with type 2 diabetes mellitus managed in primary care. Diabetes Res Clin Pract 2015;110:218-23.

[‡]Wee SL, Tan CGP, Ng HS, Su S, Tai VU, Flores JV, et al. Diabetes outcomes in specialist and general practitioner settings in Singapore: challenges of right-siting. Ann Acad Med Singapore 2008;37:929-35.

[§]Hoe J, Koh WP, Jin A, Sum CF, Lim SC, Tavintharan S. Predictors of decrease in ankle-brachial index among patients with diabetes mellitus. Diabet Med 2012;29:e304-7.

[‖]Dalan R, Jong M, Choo R, Chew DE, Leow MK. Predictors of cardiovascular complication in patients with diabetes mellitus: a 5-year follow-up study in a multiethnic population of Singapore: CREDENCE II study. Int J Cardiol 2013;169:e67-9.

[¶]Liu JJ, Lim SC, Yeoh LY, Su C, Tai BC, Low S, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with type 2 diabetes. Diabet Med 2016;33:332-9.

[#]Low S, Lim SC, Yeoh LY, Liu JJ, Fun S, Su C, et al. Long-term diabetes outcomes in multi-ethnic Asians living in Singapore. Diabetes Res Clin Pract 2016;111:83-92.

[**]Lee WRW, Emmanuel S, Lim HS, Thai AC, Chew WL, Goh LG, et al. The status of diabetes mellitus in primary institution and restructured hospitals in Singapore. Singapore Med J 2001;42:508-12.

[††]Heng BH, Sun Y, Cheah JTS, Jong M. The Singapore National Healthcare Group diabetes registry – descriptive epidemiology of type 2 diabetes mellitus. Ann Acad Med Singapore 2010;39:348-52.

Table 1. Longitudinal Studies (Cont'd)

Managed in Tertiary Care

Study, Year of Publication, and Quality of Study	Study Design and Sample Size	Study Population Characteristics	Glycaemic Control	BP Control	LDL-Cholesterol Control
Dalan et al, 2013[l] GRADE: low	Retrospective cohort study Sample size: 246	• Recruited from DM clinic from a single regional hospital between 2007 to 2008 • Multiethnic population/type 2 DM patients • Mean age: 55.8 ± 13 years • Mean duration of DM: not reported • Type of treatment: not reported	Baseline mean HbA1c (%) 8.1 ± 1.7	Baseline mean BP (mmHg) 135.0 ± 19.8 73.4 ± 10.3	Baseline mean LDL-C (mmol/L) 2.7 ± 0.9
Liu et al, 2015[¶] GRADE: low	Prospective cohort study Sample size: 2337	• Recruited from tertiary care DM clinics from a single regional hospital • Multiethnic/type 2 DM patients • Mean age at entry: 57.9 ± 11.9 years • Duration of DM: 10 years (range: 5.0 to 17.0) • Type of treatment: not reported	Baseline mean HbA1c (%) All 8.3 ± 1.8 Chinese 8.2 ± 1.8 Malay 8.5 ± 2.1 Indian 8.5 ± 1.5 *P* <0.0001	Baseline mean BP (mmHg) All 136 ± 20 Chinese 137 ± 19/ Malay 140 ± 23/ Indian 131±18 (*P* <0.0001) All 78 ± 11 Chinese 78 ± 11/ Malay 78 ± 12/ Indian 77 ± 10 (*P* = 0.383)	Baseline mean LDL (mmol/L) All 2.8 ± 0.9 Chinese 2.8 ± 0.9/ Malay 3.0 ±1.1/ Indian 2.9 ± 0.8 (*P* <0.0001)
Low et al, 2016[#] GRADE: low	Retrospective cohort study Sample size: 3006	• Recruited from DM clinic from single regional hospital managed between 2003 to 2011 • Multiethnic population/type 1 + 2 DM patients • Mean age: 46.1 ± 12.2 years • Mean duration of DM: 12.1 ± 8.8 years • Type of treatment: not reported	Baseline mean HbA1c (%) 8.6 ± 2.0 Indian 8.6 ± 2.0 Malay 8.5 ± 2.3 Chinese 8.2 ± 1.9 (*P* = 0.0001)	Baseline mean systolic BP (mmHg) 136.9 ± 20.7 Malay 139.6 ± 24.0 Chinese 137.0 ± 20.0 Indian 132.7 ± 18.7 (*P* = 0.0001)	Baseline mean LDL(mmol/L) 2.8 ± 1.0 Malay 3.0 ± 1.2 vs Indian 2.9 ± 0.9 vs Chinese 2.8 ± 1.0 (*P* = 0.050)

ACEI: Angiotensin converting enzyme inhibitor; BP: Blood pressure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; LDL: Low density lipoprotein; NHG: National Healthcare Group; OADD: Oral antidiabetic drugs; PCC: Primary care clinic; PHC: Primary health clinic; RH: Restructured hospital; SOC: Specialist outpatient clinic

[*]Ng TP, Goh LG, Tan Y, Tan E, Leong H, Tay EG, et al. Ethnic differences in glycemic control in adult type 2 diabetic patients in primary care: a 3-year follow-up study. Diabet Med 2005;22:1598-604.

[†]Tan NC, Barbier S, Lim WY, Chia KS. 5-Year longitudinal study of determinants of glycemic control for multi-ethnic Asian patients with type 2 diabetes mellitus managed in primary care. Diabetes Res Clin Pract 2015;110:218-23.

[‡]Wee SL, Tan CGP, Ng HS, Su S, Tai VU, Flores JV, et al. Diabetes outcomes in specialist and general practitioner settings in Singapore: challenges of right-siting. Ann Acad Med Singapore 2008;37:929-35.

[§]Hoe J, Koh WP, Jin A, Sum CF, Lim SC, Tavintharan S. Predictors of decrease in ankle-brachial index among patients with diabetes mellitus. Diabet Med 2012;29:e304-7.

[l]Dalan R, Jong M, Choo R, Chew DE, Leow MK. Predictors of cardiovascular complication in patients with diabetes mellitus: a 5-year follow-up study in a multiethnic population of Singapore: CREDENCE II study. Int J Cardiol 2013;169:e67-9.

[¶]Liu JJ, Lim SC, Yeoh LY, Su C, Tai BC, Low S, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with type 2 diabetes. Diabet Med 2016;33:332-9.

[#]Low S, Lim SC, Yeoh LY, Liu JJ, Fun S, Su C, et al. Long-term diabetes outcomes in multi-ethnic Asians living in Singapore. Diabetes Res Clin Pract 2016;111:83-92.

[**]Lee WRW, Emmanuel S, Lim HS, Thai AC, Chew WL, Goh LG, et al. The status of diabetes mellitus in primary institution and restructured hospitals in Singapore. Singapore Med J 2001;42:508-12.

[††]Heng BH, Sun Y, Cheah JTS, Jong M. The Singapore National Healthcare Group diabetes registry – descriptive epidemiology of type 2 diabetes mellitus. Ann Acad Med Singapore 2010;39:348-52.

Table 1. Longitudinal Studies (Cont'd)

Managed in Primary and Tertiary Care					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Lee et al, 2001[**] GRADE: low	Retrospective cohort study Sample size: 1697	• Recruited from 22 centres (1145 PHC, 552 RH) from 1 March 1998 to 30 April 1998 • Multiethnic/type 1 + 2 DM patients • Mean age: PHC 61.3 ± 11.2 years, RH 51.5 ± 17.7 years • Mean duration of DM: PHC 9.2 ± 6.8 years, RH 12.0 ± 8.5 years • Types of treatment: insulin (PHC – 6.4%, RH – 52.5%) OADD only (PHC – 83.5%, RH 43.1%)	Baseline mean HbA1c (%) 7.8 ±1.9 (PHC) 8.2 ± 1.9 (RH)	Baseline systolic BP >140 mmHg 31% (PHC) 26% (RH) Baseline diastolic BP >90 mmHg 4% (PHC) 7% (RH)	Data not available
Heng et al, 2010[††] GRADE: low	Retrospective cohort study Sample size: 170,513	• Recruited from the NHG chronic disease registry between 2005 to 2008 • Multiethnic population/type 2 DM patients • Patients managed at tertiary and primary care • Median age: males 59-61/females 63-64 • Duration of diabetes: not reported • Type of treatment: insulin (PCC – 13.8%, SOC – 31.3%, OADD (PCC – 86.2 to 89.2%, SOC 68.7 to 71.1%)	Baseline proportion of type 2 DM with HbA1c <7% Chinese males (highest in all age groups except 85+ year old) <45 year old – 36.4% 45 to 64 year old – 43.6% 65 to 84 year old – 55.7% Malay males (highest in 85+ year old age group) 85+ year old – 68.0% Chinese females (highest in all age groups except 85+ year old) <45 year old – 35.2% 45 to 64 year old – 42.6% 65 to 84 year old – 53.8% Malay females 85+ year old – 69.8% (highest in 85+ year old age group)	Data not available	Data not available

ACEI: Angiotensin converting enzyme inhibitor; BP: Blood pressure; CVA: Cerebrovascular accident; DM: Diabetes mellitus; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; HbA1c: Glycated haemoglobin; IHD: Ischaemic heart disease; LDL: Low density lipoprotein; NHG: National Healthcare Group; OADD: Oral antidiabetic drugs; PCC: Primary care clinic; PHC: Primary health clinic; RH: Restructured hospital; SOC: Specialist outpatient clinic

[*]Ng TP, Goh LG, Tan Y, Tan E, Leong H, Tay EG, et al. Ethnic differences in glycemic control in adult type 2 diabetic patients in primary care: a 3-year follow-up study. Diabet Med 2005;22:1598-604.

[†]Tan NC, Barbier S, Lim WY, Chia KS. 5-Year longitudinal study of determinants of glycemic control for multi-ethnic Asian patients with type 2 diabetes mellitus managed in primary care. Diabetes Res Clin Pract 2015;110:218-23.

[‡]Wee SL, Tan CGP, Ng HS, Su S, Tai VU, Flores JV, et al. Diabetes outcomes in specialist and general practitioner settings in Singapore: challenges of right-siting. Ann Acad Med Singapore 2008;37:929-35.

[§]Hoe J, Koh WP, Jin A, Sum CF, Lim SC, Tavintharan S. Predictors of decrease in ankle-brachial index among patients with diabetes mellitus. Diabet Med 2012;29:e304-7.

[‖]Dalan R, Jong M, Choo R, Chew DE, Leow MK. Predictors of cardiovascular complication in patients with diabetes mellitus: a 5-year follow-up study in a multiethnic population of Singapore: CREDENCE II study. Int J Cardiol 2013;169:e67-9.

[¶]Liu JJ, Lim SC, Yeoh LY, Su C, Tai BC, Low S, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with type 2 diabetes. Diabet Med 2016;33:332-9.

[#]Low S, Lim SC, Yeoh LY, Liu JJ, Fun S, Su C, et al. Long-term diabetes outcomes in multi-ethnic Asians living in Singapore. Diabetes Res Clin Pract 2016;111:83-92.

[**]Lee WRW, Emmanuel S, Lim HS, Thai AC, Chew WL, Goh LG, et al. The status of diabetes mellitus in primary institution and restructured hospitals in Singapore. Singapore Med J 2001;42:508-12.

[††]Heng BH, Sun Y, Cheah JTS, Jong M. The Singapore National Healthcare Group diabetes registry – descriptive epidemiology of type 2 diabetes mellitus. Ann Acad Med Singapore 2010;39:348-52.

Table 2. Cross-Sectional Studies

Managed in Primary Care Setting

Study, Year of Publication, and Quality of Study	Study Design and Sample Size	Study Population Characteristics	Glycaemic Control	BP Control	LDL-Cholesterol Control
Hong et al, 2004* GRADE: low	Cross-sectional study Sample size: 967	• Recruited from single polyclinic between April 1995 to June 1997 • Multiethnic/type 2 DM patients • Mean age: Chinese 61.6 + 10.6 years, Malay 56.0 + 11.0 years, Indian 59.9 + 10.6 years (P <0.001) • Median duration of diabetes: Chinese 7.0 years (IQR 9.0), Malay 4.0 years (IQR 8.0), Indian 6.5 years (IQR 11.0) P = 0.11 • Type of treatment: OADD(%): Chinese 82.6, Malay 89.9, Indian 83.0 Insulin (%): Chinese 4.7, Malay 4.3, Indian 5.0	Mean HbA1c (%) Chinese 7.65, Malays 8.18, Indians 8.36 (P <0.01) Age and mean HbA1c <50 – 8.7% 50 to <70 – 8.1% 70 and above – 7.4% P <0.01	Data not available	Data not available
Narayanan et al, 2010† GRADE: low	Cross-sectional study Sample size: 521	• Recruited in 9 polyclinics over 5 consecutive working days in January 2004 • Multiethnic/type 2 DM patients • Patients with PAD were older (66.8 vs 59.1 years; P <0.001) • Patients with PAD had longer duration of DM: 13.92 ± 9.7 years vs 9.81 vs 8.32 years (P <0.001) • More patients with PAD were on insulin (24.4% vs 10.2%; P <0.001)	Mean HbA1c (%) PAD 8.19 ± 1.48 No PAD 7.89 ± 1.43 P = ns	Data not available	LDL-C (mmol/L) PAD 3.04 ± 0.85 No PAD 3.14 ± 1.08 P = ns

ACEI: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; BP: Blood pressure; CAD: Coronary artery disease; CV: Cardiovascular; DM: Diabetes mellitus; DR: Diabetic retinopathy; GM: General Medicine; GP: General practitioner; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; GRM: Geriatric medicine; HbA1c: Glycated haemoglobin; IQR: Interquartile range; LDL: Low-density lipoprotein; NHGP: National Healthcare Group Polyclinics; OADD: Oral anti-diabetic drug; PAD: Peripheral arterial disease

*Hong CY, Chia KS, Hughes K, Ling SL. Ethnic differences among Chinese, Malay and Indian patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2004;45:154.

†Narayanan RML, Koh WP, Phang J, Subramaniam T. Peripheral arterial disease in community-based patients with diabetes in Singapore: results from a primary healthcare study. Ann Acad Med Singapore 2010;39:525-31.

‡Shim YT, Lee J, Toh MP, Tang WE, Ko Y. Health-related quality of life and glycaemic control in patients with type 2 diabetes mellitus in Singapore. Diabet Med 2012;29:e241-8.

§Quah JHM, Liu YP, Luo N, How CH, Tay EG. Younger adult type 2 diabetic patients have poorer glycaemic control: a cross-sectional study in a primary care setting in Singapore. BMC Endocrine Disorders 2013;13:18.

‖Lee ES, Tang WE. The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore. Singapore Med J 2015;56:681-6.

¶Loh PT, Toh MP, Molina JA, Vathsala A. Ethnic disparity in prevalence of diabetic kidney disease in an Asian primary healthcare cluster. Nephrology (Carlton) 2015; 20:216-23.

#Toh MP, Heng BH, Sum CF, Jong M, Chionh SB, Cheah JT. Measuring the quality of care of diabetic patients at the specialist outpatient clinics in public hospitals in Singapore. Ann Acad Med Singapore 2007;36:980-6.

**National Health Survey 2004. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

††Wu AY, Tan CB, Eng PH, Tan KT, Lim SC, Tan EK. Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2006;47:315-20.

‡‡National Health Survey 2010. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

§§Huang OS, Lamoureux EL, Tay WT, Tai ES, Wang JJ, Wong TY. Glycemic and blood pressure control in an Asian Malay population with diabetes and diabetic retinopathy. Arch Ophthalmol 2010;128:1185-90.

‖‖Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB, et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164-71.

Table 2. Cross-Sectional Studies (Cont'd)

Managed in Primary Care Setting					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Shim et al, 2012‡ GRADE: low	Cross-sectional study Sample size: 282	• Recruited from 2 polyclinics between September to December 2009 • Multiethnic/type 2 DM patients/diet control excluded • Mean age: 58.1 ± 8.8 years • Duration of diabetes: 1 to <5 years (26.2%), 5 to <10 years (28.7%), 10 to <15 years (17.4%), 15 to <20 years (14.2%), >20 years (13.5%) • Type of treatment: insulin (30.1%) • Presence of end-organ damage: 31.6%	Mean HbA1c (%) 8.0 ± 1.6 HbA1c >8.0% 39.7%	Data not available	Data not available
Quah et al, 2013§ GRADE: low	Cross-sectional study Sample size: 688	• Recruited from 8 polyclinics in January 2009 • Multiethnic/type 2 DM patients • Mean age: 62.2 ±11.1 years • Duration of DM: <5 years (32.8%), 5 to 9.9 years (21.6%), 10 to 14.9 years (17.5%), 15 to 19.9 years (9.6%), >20 years (18.5%) • Type of treatment: OHA 92.7%, insulin 10.8%	Mean HbA1c (%) 7.6 ± 1.35 Median HbA1c (%) 7.3 (5.0 to 14.0) 25.4% had HbA1c >8.0% ≥70 years HbA1c ≤8.0% (32.5%) vs HbA1c >8% (20.6%) (P <0.001) <60 years HbA1c ≤8.0% (30.7%) vs HbA1c >8% (51.4%) (P <0.001)	Data not available	Data not available

ACEI: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; BP: Blood pressure; CAD: Coronary artery disease; CV: Cardiovascular; DM: Diabetes mellitus; DR: Diabetic retinopathy; GM: General Medicine; GP: General practitioner; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; GRM: Geriatric medicine; HbA1c: Glycated haemoglobin; IQR: Interquartile range; LDL: Low-density lipoprotein; NHGP: National Healthcare Group Polyclinics; OADD: Oral anti-diabetic drug; PAD: Peripheral arterial disease

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†Narayanan RML, Koh WP, Phang J, Subramaniam T. Peripheral arterial disease in community-based patients with diabetes in Singapore: results from a primary healthcare study. Ann Acad Med Singapore 2010;39:525-31.

‡Shim YT, Lee J, Toh MP, Tang WE, Ko Y. Health-related quality of life and glycaemic control in patients with type 2 diabetes mellitus in Singapore. Diabet Med 2012;29:e241-8.

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Table 2. Cross-Sectional Studies (Cont'd)

Managed in Primary Care Setting					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Lee et al, 2015[l] GRADE: low	Cross-sectional cohort study Sample size: 786	• Recruitment from single polyclinic from 1August 2010 to 28 February 2011 • Multiethnic/type 2 DM patients • Mean age: 63.95 ± 10.36 years • Mean DM duration years: 7.04 ± 5.16 years • Hypertensives (83.1%) • Hypertension duration years: 7.45 ± 4.90 years • Type of treatment: 55.7% on ACEI and/or ARB	Mean HbA1c (%) 7.2 ± 1.0	Systolic BP (mmHg) 126.5 ±19 Diastolic BP (mmHg) 70 ± 13	LDL (mmol/L) 2.40 ± 0.75
Loh et al, 2015[¶] GRADE: low	Cross-sectional cohort study Sample size: 57,594	• Recruited from 11 NHGP polyclinics between 1 January 2006 to 31 December 2009 • Multiethnic/type 2 DM patients • Mean age: 65.7 ± 11.5 years • Mean duration of DM: 8.4 ± 5.3 years • Type of treatment: not reported	Mean HbA1c (%) 7.5 ± 1.3 HbA1c <7% 36.9% HbA1c >8% 25.2%	Data not available	Data not available

ACEI: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; BP: Blood pressure; CAD: Coronary artery disease; CV: Cardiovascular; DM: Diabetes mellitus; DR: Diabetic retinopathy; GM: General Medicine; GP: General practitioner; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; GRM: Geriatric medicine; HbA1c: Glycated haemoglobin; IQR: Interquartile range; LDL: Low-density lipoprotein; NHGP: National Healthcare Group Polyclinics; OADD: Oral anti-diabetic drug; PAD: Peripheral arterial disease

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[†]Narayanan RML, Koh WP, Phang J, Subramaniam T. Peripheral arterial disease in community-based patients with diabetes in Singapore: results from a primary healthcare study. Ann Acad Med Singapore 2010;39:525-31.

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[‡‡]National Health Survey 2010. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

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Table 2. Cross-Sectional Studies (Cont'd)

Study, Year of Publication, and Quality of Study	Study Design and Sample Size	Study Population Characteristics	Glycaemic Control	BP Control	LDL-Cholesterol Control
Managed in Tertiary Care Setting					
Toh et al, 2007[#] GRADE: low	Cross-sectional study Sample size: 575	• Recruited from 6 medical specialties at 3 acute hospitals • Patients on continuous care for minimum of 15 months from October 2003 to April 2005 • Multiethnic/type 2 DM patients • Excluded if co-managed by diabetes centres or primary clinics • Age: <55 years – 20.2%, 55 to 64 years – 24.0%, 65 to 74 years – 27.0%, 75 to 84 years – 21.6%, >85 years – 7.3% • Duration of diabetes: not reported • Type of treatment: not reported	Mean HbA1c (%) 7.3 ± 1.5 Cardio 7.5 ±1.4 GM 7.5 ± 1.6 GRM 6.9 ± 1.3 Others 7.3 ± 1.6 *P* = 0.016	Mean BP (mmHg) 137.1 ± 19.4 77.6 ± 9.0	LDL-C (mmol/L) 2.72 ± 0.85 Cardio 2.56 ± 0.83 GM 2.88 ± 0.92 GRM 2.6 ± 0.94 Others 2.75 ± 0.68 *P* = 0.011
Managed in Primary and Tertiary Care Setting					
Epidemiology & Disease Control Division, Ministry of Health, Singapore 2004[**] GRADE: very low	Population-based national health survey Sample size: 7275 (57.3% response rate, 4168 responders)	• National cross-sectional survey done 10 September to 4 December 2004 • Multiethnic/type 1+2 DM patient aged 18 to 74 years old • Patients managed at tertiary and primary care • Mean/median age: not reported • Duration of diabetes: not reported	Mean HbA1c 7.6% Proportion of known diabetic patients with HbA1c >8.0% 27.6% Proportion of patients on treatment with HbA1c >8.0% 28.7% Proportion of HbA1c >8.0% by ethnicity Indian (36.8%), Malay (31.1%), Chinese (24.2%)	Data not available	Data not available

ACEI: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; BP: Blood pressure; CAD: Coronary artery disease; CV: Cardiovascular; DM: Diabetes mellitus; DR: Diabetic retinopathy; GM: General Medicine; GP: General practitioner; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; GRM: Geriatric medicine; HbA1c: Glycated haemoglobin; IQR: Interquartile range; LDL: Low-density lipoprotein; NHGP: National Healthcare Group Polyclinics; OADD: Oral anti-diabetic drug; PAD: Peripheral arterial disease

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[§]Quah JHM, Liu YP, Luo N, How CH, Tay EG. Younger adult type 2 diabetic patients have poorer glycaemic control: a cross-sectional study in a primary care setting in Singapore. BMC Endocrine Disorders 2013;13:18.

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[#]Toh MP, Heng BH, Sum CF, Jong M, Chionh SB, Cheah JT. Measuring the quality of care of diabetic patients at the specialist outpatient clinics in public hospitals in Singapore. Ann Acad Med Singapore 2007;36:980-6.

[**]National Health Survey 2004. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

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[‡‡]National Health Survey 2010. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

[§§]Huang OS, Lamoureux EL, Tay WT, Tai ES, Wang JJ, Wong TY. Glycemic and blood pressure control in an Asian Malay population with diabetes and diabetic retinopathy. Arch Ophthalmol 2010;128:1185-90.

[‖‖]Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB, et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164-71.

Table 2. Cross-Sectional Studies (Cont'd)

Managed in Primary and Tertiary Care Setting					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Wu et al, 2006[‡‡] GRADE: low	Cross-sectional study Sample size: 499	• Recruited from 5 diabetes and 15 GP clinics between May to December 2002 • Multiethnic/type 2 DM patients • Mean age: 58.26 ± 11.48 years • Mean duration of hypertension: 7.54 ± 7.67 years • Mean duration of DM: 8.64 ± 7.61 years • A total of 97.2% were receiving antihypertensive therapy • Type of treatment: not reported • A total of 16.8% of patients had known CV complications	Mean HbA1c (%) 7.9	Mean BP (mmHg) 144 ± 19 84 ± 9 Systolic/diastolic BP <130/85 mmHg 22.2%	Data not available
Epidemiology & Disease Control Division, Ministry of Health, Singapore, 2010[††] GRADE: very low	Population-based national health survey Sample size: 7512 (57.7% response rate, 4337 responders)	• National cross-sectional survey done from 17 March to 13 June 2004 • Multiethnic/type 1+2 DM patient aged 18 to 79 years old • Patients managed at tertiary and primary care • Mean/median age: not reported • Duration of diabetes: not reported	Mean HbA1c 7.7% Proportion of known diabetic patients with HbA1c >8.0% 32.0% Proportion of patients on treatment with HbA1c >8.0% 28.6% Proportion of HbA1c >8.0% by ethnicity Malay (47.6%), Indian (37.9%), Chinese (24.9%)	Data not available	Data not available

ACEI: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; BP: Blood pressure; CAD: Coronary artery disease; CV: Cardiovascular; DM: Diabetes mellitus; DR: Diabetic retinopathy; GM: General Medicine; GP: General practitioner; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; GRM: Geriatric medicine; HbA1c: Glycated haemoglobin; IQR: Interquartile range; LDL: Low-density lipoprotein; NHGP: National Healthcare Group Polyclinics; OADD: Oral anti-diabetic drug; PAD: Peripheral arterial disease

[*]Hong CY, Chia KS, Hughes K, Ling SL. Ethnic differences among Chinese, Malay and Indian patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2004;45:154.

[†]Narayanan RML, Koh WP, Phang J, Subramaniam T. Peripheral arterial disease in community-based patients with diabetes in Singapore: results from a primary healthcare study. Ann Acad Med Singapore 2010;39:525-31.

[‡]Shim YT, Lee J, Toh MP, Tang WE, Ko Y. Health-related quality of life and glycaemic control in patients with type 2 diabetes mellitus in Singapore. Diabet Med 2012;29:e241-8.

[§]Quah JHM, Liu YP, Luo N, How CH, Tay EG. Younger adult type 2 diabetic patients have poorer glycaemic control: a cross-sectional study in a primary care setting in Singapore. BMC Endocrine Disorders 2013;13:18.

[‖]Lee ES, Tang WE. The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore. Singapore Med J 2015;56:681-6.

[¶]Loh PT, Toh MP, Molina JA, Vathsala A. Ethnic disparity in prevalence of diabetic kidney disease in an Asian primary healthcare cluster. Nephrology (Carlton) 2015; 20:216-23.

[#]Toh MP, Heng BH, Sum CF, Jong M, Chionh SB, Cheah JT. Measuring the quality of care of diabetic patients at the specialist outpatient clinics in public hospitals in Singapore. Ann Acad Med Singapore 2007;36:980-6.

[**]National Health Survey 2004. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

[††]Wu AY, Tan CB, Eng PH, Tan KT, Lim SC, Tan EK. Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2006;47:315-20.

[‡‡]National Health Survey 2010. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

[§§]Huang OS, Lamoureux EL, Tay WT, Tai ES, Wang JJ, Wong TY. Glycemic and blood pressure control in an Asian Malay population with diabetes and diabetic retinopathy. Arch Ophthalmol 2010;128:1185-90.

[‖‖]Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB, et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164-71.

Table 2. Cross-Sectional Studies (Cont'd)

Managed in Primary and Tertiary Care Setting					
Study, Year of Publication, and Quality of Study	**Study Design and Sample Size**	**Study Population Characteristics**	**Glycaemic Control**	**BP Control**	**LDL-Cholesterol Control**
Huang et al, 2010[§§] GRADE: low	Cross-sectional study Sample size: 3280	• Population-based survey between 2004 to 2006 • Only Malays aged 40 to 80 years old surveyed • Mean age: 62.5 ± 9.4 years • Mean duration of DM: 12.1 ± 8.7 years • Type of treatment: OADD (58.3%), insulin (10.5%), antihypertensives (41.5%)	Mean HbA1c (%) 8.0 ± 2.0 No DR 8.2 ± 2.0 vs DR 8.9 ± 2.0 (*P* <0.001) Optimal HbA1c 26.9% No DR 31.9% vs DR 17.4% (*P* <0.001)	Mean systolic BP (mmHg) 154.6 ± 23.7 No DR 152.1± 22.8 vs DR 159.4 ±24.5 (*P* <0.001) Mean diastolic BP (mmHg) 79.2 ± 11.0 BP <130/80 mmHg 13.4%	LDL (mg/dL) 127.4 ± 38.6 No DR 131.3 ± 38.6 DR 123.6 ± 38.6 *P* = 0.02
Low et al, 2015[‖] GRADE: low	Cross-sectional study Sample size: 1861	• Recruited from 1 tertiary care DM clinic and 1 polyclinic from August 2011 to November 2013 • Multiethnic/type 2 DM patients • HbA1c >12% excluded • Mean age: 57.5 ± 10.7 years • Mean duration of DM: 10 years (range: 4 to 16) • Type of treatment: insulin (29%), use of statins (81.2%) • Cardiovascular complications: PAD 10.1%, neuropathy 9.6%, CAD 9.7%, stroke 3.3%	Mean HbA1c (%) 7.5 (6.8 to 8.5) HbA1c <7% – 30.9% 7% to 7.9% – 31.6% 8% to 8.9% – 19.6% 9% to 12% – 17.9% HbA1c <7% 30.9%	Mean systolic BP (mmHg) 139 (127 to152) Mean diastolic BP (mmHg) 79.1 ± 9.6 BP <140/80 mmHg 53.4%	LDL (mmol/L) 2.6 (2.2 to 3.2) LDL <2.6 mmol/L 48.5%

ACEI: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; BP: Blood pressure; CAD: Coronary artery disease; CV: Cardiovascular; DM: Diabetes mellitus; DR: Diabetic retinopathy; GM: General Medicine; GP: General practitioner; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; GRM: Geriatric medicine; HbA1c: Glycated haemoglobin; IQR: Interquartile range; LDL: Low-density lipoprotein; NHGP: National Healthcare Group Polyclinics; OADD: Oral anti-diabetic drug; PAD: Peripheral arterial disease

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[†]Narayanan RML, Koh WP, Phang J, Subramaniam T. Peripheral arterial disease in community-based patients with diabetes in Singapore: results from a primary healthcare study. Ann Acad Med Singapore 2010;39:525-31.

[‡]Shim YT, Lee J, Toh MP, Tang WE, Ko Y. Health-related quality of life and glycaemic control in patients with type 2 diabetes mellitus in Singapore. Diabet Med 2012;29:e241-8.

[§]Quah JHM, Liu YP, Luo N, How CH, Tay EG. Younger adult type 2 diabetic patients have poorer glycaemic control: a cross-sectional study in a primary care setting in Singapore. BMC Endocrine Disorders 2013;13:18.

[‖]Lee ES, Tang WE. The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore. Singapore Med J 2015;56:681-6.

[¶]Loh PT, Toh MP, Molina JA, Vathsala A. Ethnic disparity in prevalence of diabetic kidney disease in an Asian primary healthcare cluster. Nephrology (Carlton) 2015; 20:216-23.

[#]Toh MP, Heng BH, Sum CF, Jong M, Chionh SB, Cheah JT. Measuring the quality of care of diabetic patients at the specialist outpatient clinics in public hospitals in Singapore. Ann Acad Med Singapore 2007;36:980-6.

[**]National Health Survey 2004. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

[††]Wu AY, Tan CB, Eng PH, Tan KT, Lim SC, Tan EK. Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2006;47:315-20.

[‡‡]National Health Survey 2010. Epidemiology & Disease Control Division. Ministry of Health, Singapore.

[§§]Huang OS, Lamoureux EL, Tay WT, Tai ES, Wang JJ, Wong TY. Glycemic and blood pressure control in an Asian Malay population with diabetes and diabetic retinopathy. Arch Ophthalmol 2010;128:1185-90.

[‖‖]Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB, et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164-71.

Table 3. Case-Control Studies

Study, Year of Publication, and Quality of Study	Study Design and Sample Size	Study Population Characteristics	Glycaemic Control	BP Control	LDL-Cholesterol Control
Managed in Primary Care Setting					
Foo et al, 2016* GRADE: low	Retrospective case-control Sample size: 172 diabetic patients with moderate retinopathy, with 226 matched controls	• Recruited at single polyclinic between 2012 to 2013 • Multiethnic/type 2 DM with moderate DR • Controls = type 2 DM without DR • Mean age (cases vs controls): 59.7 ± 11.5 years vs 62.0 ± 10.6 years (P = 0.04) • Duration of DM (cases vs controls): 10.9 ± 10.1 years vs 7.3 ± 9.0 years (P = 0.53) • Hypertensives and hyperlipidaemia (cases vs controls): no significant differences • Type of treatment: antihypertensive treatment (cases vs controls): 29.8% vs 60.4% (P = 0.06) • Lipid-lowering treatment (83%) • Antidiabetic treatment (cases vs controls): 91.8% vs 74.3% (P <0.001) • OADD (cases vs controls): 88.3% vs 74.3% (P = 0.002) • OADD + insulin (cases vs controls): 18.7% vs 6.8% (P = 0.002)	HbA1c (%) intrapersonal (iM) mean DR 8.2 ± 1.8 Controls 7.3 ± 1.2 (P = 0.001)	iM SBP (mmHg) DR 136.8 ± 16.2 vs controls 129.6 ±13.6 (P = 0.001) iM DBP (mmHg) DR 73 ± 9.4 vs controls 73.0 ± 10.2 (P = 0.99)	LDL-C (mmol/L) DR 2.4 ± 0.8 vs controls 2.4 ± 0.7 (P = 0.70)
Managed in Primary and Tertiary Care Setting					
Puar et al, 2012† GRADE: low	Retrospective case-control Sample size: 558 diabetic patients admitted with hip fracture with 558 matched controls	• Cases and controls recruited at acute hospital between 1 January 2005 to 31 December 2010 • Controls selected from a registry of diabetics managed in the same hospital's DM clinic • Cases were managed at both primary and tertiary care • Mean age (cases vs controls): no significant difference • Duration of diabetes (cases vs controls): 11.9 ± 7.9 years vs 12.5 vs 10 years (P = 0.30) • Type of treatment (cases vs controls): insulin 12.1% vs 14.5%	Median HbA1c (%) Cases 6.8 (range 6.2 to 7.8) Controls 7.4 (range 6.7 to 8.5) HbA1c <6% Cases 19.4%, controls 10.4% HbA1c 6.1% to 7.0% Cases 40.1%, controls 27.4% HbA1c 7.1% to 8.0% Cases 20.4%, controls 28.5% HbA1c >8% Cases 20.1%, controls 33.7%	Data not available	Data not available

DBP: Diastolic blood pressure; DM: Diabetes mellitus; DR: Diabetic retinopathy; GRADE: Grade of Recommendation, Assessment, Development and Evaluation; HbA1c: Glycated haemoglobin; OADD: Oral anti-diabetic drug; SBP: Systolic blood pressure

*Foo V, Quah J, Cheung G, Tan NC, Ma Zar KL, Chan CM, et al. HbA1c, systolic blood pressure variability and diabetic retinopathy in Asian type 2 diabetics. J Diabetes 2017;9:200-7.

†Puar TH, Khoo JJ, Cho LW, Xu Y, Chen YT, Chuo Am, et al. Association between glycemic control and hip fracture. J Am Geriatr Soc 2012;60:1493-7.

retinopathy (DR) compared to matched controls who were managed in the primary care setting (8.2% vs 7.3%; $P = 0.001$).[41] There was no significant difference in diabetic control between those with peripheral arterial disease (PAD) and those who did not.[33]

Blood Pressure Control

The BP control is presented in Tables 1-3. The average systolic and diastolic BP in 12 studies range between 126.5-144.0 mmHg and 70-84 mmHg, respectively.[22,24-27,29,35,37-41] The mean duration of hypertension was 6.7-7.54 years. Overall, the results for BP control were mixed. Lee et al observed that the proportion of patients whose BP were treated to target were 69% in the primary health clinic and 74% in restructured hospitals.[29]

However, Toh et al reported 26.2% achieving optimal BP in a multiethnic cohort managed in various medical subspecialists,[37] while Low et al reported that nearly half (46.6%) had BP >140/80.[40] The only Malay cohort reported an average systolic and diastolic BP of 154.6 mmHg and 79.2 mmHg respectively.[39] Indians had significantly better BP control compared to Chinese and Malays.[25,26] A similar trend was also reported by Dalan et al.[27]

The prevalence of kidney disease (including micro- and macro-albuminuria) in 4 studies was between 19.9%-72%.[35,36,38,40] There were between 24%-73% who were on angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB).

Foo et al reported significantly higher intrapersonal mean systolic blood pressure (iM-SBP) in patients with moderate DR compared to matched controls (136.8 mmHg vs 129.6 mmHg; $P = 0.001$). There was no difference in diastolic BP (iM-DBP) at about 73.0 mmHg in both groups.[41]

LDL-Cholesterol (LDL-C) Control

The mean LDL-C control is presented in Tables 1-3. The mean LDL-C in 9 studies was between 2.4 and 3.3mmol/L.[24-27,35,37,39-41] The use of statin in 1 study was 81.2%. However, 51.5% in this study did not achieve optimal LDL-C (<2.6 mmol/L).[40] Liu et al reported Malays to have significantly poorer LDL-C control compared to Chinese and Indians.[25]

Amongst various medical subspecialists, those managed under Cardiology and Geriatric Medicine had lower LDL-C at 2.56 mmol/L and 2.60 mmol/L, respectively. A higher proportion of patients in these 2 disciplines also achieved LDL-C control <2.6 mmol/L (56.8% and 62.0%, respectively), when compared to other medical specialties (44.8%-45.2%).[37] The LDL-C control was not significantly different between those with PAD and those without.[33]

The mean LDL-C in those with moderate DR and matched controls were similar at 2.4 mmol/L (note: LDL reported in mg/dL converted to mmol/L by multiplying 0.02586). Although 90.1% and 92.4% had hyperlipidaemia in both arms, only 83.0% and 83.3% were on any form of lipid-lowering treatment in the cases and control groups, respectively.[41]

Discussion

To the best of our knowledge, this is the first study reviewing the glycaemic, BP and LDL control of adult diabetic patients in Singapore. This qualitative review demonstrates that achievement of these cardiovascular risk factor targets has generally been suboptimal over the past 20 years in Singaporean patients with diabetes, and are comparable to several parts of the world including the United States of America, Australia and Asia.[43-47]

With the advent of new and novel antidiabetic treatment as well as advances in models of diabetic care programmes over the past 10 years, it is reasonable to expect significant strides in achieving diabetic targets in a developed nation such as Singapore where healthcare is easily accessible. Despite the availability of published guidelines, translation of guidelines into practice to achieve recommended diabetes management and targets, still fall short globally.

Although the heterogeneity of the various cohorts reviewed does not permit a quantitative assessment of the data, there appears to be marginal improvements since the last large study of 12 Asian countries including Singapore that documented poor achievement of glycaemic targets nearly 20 years ago.[47] The lower rates of progression to proliferative DR and visual loss due to diabetes provides further indirect evidence to the improvement of risk factor control.[48] This observation, however, requires further validation. Suffice to say, diabetes care remains challenging and its complexity cannot be underestimated. In fact, diabetes continues to be a challenging healthcare problem in Singapore, and was made a healthcare priority by the Minister of Health when he declared "war on diabetes" in a Parliamentary sitting in April 2016.[49]

In Singapore, private general practitioners (GPs) are the main provider of primary care services, seeing 81% of primary care attendances. The remaining 19% are seen by polyclinic doctors. However, private GPs look after only 55% of chronically ill patients, while the rest are managed by polyclinic doctors.[50]

From the epidemiological viewpoint and based on the local healthcare resource allocation, it may be postulated that those with early and uncomplicated disease are managed in the private sector. Due to cost and availability of healthcare resources, those with more complex comorbidities and higher pill burden are managed in the public primary healthcare setting, while those with advanced end-organ

complications are managed at tertiary care.

This may be particularly so in Singapore even though the costs of many chronic diseases may be defrayed using governmental subsidies such as the Pioneer Generation (PG) and Community Health Assist Scheme (CHAS) for eligible patients. Given the difference in drug costs between the public and private healthcare, those who require multiple medications for complex comorbidities will have lesser out-of-pocket payment in public healthcare compared to private care even after utilising these subsidies, as well as their Medisave account (a national medical savings scheme that helps individuals put aside part of their income for future medical expenses). Anecdotally, these patients tend to transfer their care from the private to the public sector once the out-of-pocket payment becomes unmanageable.

It has been shown that diabetes management programmes and resource allocation such as the extension of Medisave coverage to outpatient treatment increased compliance to processes of diabetes care, reduced hospitalisation risk and total healthcare cost, albeit only in the first 2 years.[51]

Apart from a single study that included patients managed in the private sector,[38] the remaining studies reviewed in this article were all conducted in the public polyclinics and hospitals. There remains a dearth of information regarding the glycaemic, BP and LDL-C targets of the majority of diabetic patients in Singapore. Due to the aforementioned reasons, the glycaemic, BP and LDL control from public sector data may be an overestimation of how Singapore is performing nationally.

It is well established that a target-driven, long-term and intensive multifactorial intervention reduces risk of cardiovascular and microvascular complications.[52] Potential factors that may hinder the attainment of these targets include time and resource constraints faced by doctors during consultation, as well as patient's variable knowledge of these targets as a result of poor concordance between managing doctors, especially when the patient consults more than 1 primary doctor.[53] Furthermore, such intensity can be resource-intensive to sustain.

We find it interesting that the elderly population appeared to have better glycaemic control compared to younger patients.[30,37] This may have been due to shorter duration of diabetes in older individuals. However, the duration of diabetes in these 2 studies were not reported. The elderly are also less likely to benefit from tight glycaemic control in the long-term, and treatment has to be individualised.[54] In addition to the U-shaped HbA1c mortality relationship,[55] older patients with lower HbA1c levels may also suffer from poor nutritional status, frailty or sarcopaenia, that may all contribute to a higher mortality risk.[56] Similar to the local American Heart Association (AHA) and American Diabetes Association (ADA) guidelines, the American Geriatrics Society recommends a less stringent HbA1c target of 8% or less in frail older adults or those with a short life expectancy.[57] However, with much of the focus on treating to target, more is needed to identify a threshold of de-escalating treatment, those at risk and how to safely de-escalate treatment.

Finally, the unique multiethnic Singapore population demands special attention. The profile of the diabetic population in Singapore has changed dramatically because of socioeconomic transformation in the last 2 decades. For example, the age-standardised prevalence of diabetes in the Malay population had increased from 11.3% to 16.6% between 1992 and 2010, whereas it did not change very much in the Chinese population (10.8% to 9.7%) during the same period. Among the 3 main racial groups, Indians ranked first in the prevalence of DM, followed by Malays and Chinese. On the other hand, hypertension and hyperlipidaemia was most prevalent in Malays, followed by Chinese and Indians.[3] In order to be effective, chronic disease management programmes have to be specifically tailored to meet the changing needs and profiles of these racial groups.

As alluded to, the limitations of this study include the lack of data from the private primary care setting. All but one study is from public primary and tertiary care settings, and do not adequately represent the entire diabetes cohort in Singapore. Apart from ethnicity, factors such as socioeconomic status, patient education, patient knowledge about diabetes and availability of healthcare facilities are also known to affect control of diabetes.[58,59] In addition, all the studies included in the analysis were assessed to be of either low or very low quality. Furthermore, the heterogeneity of the studies also does not facilitate quantitative meta-analysis to be performed. Finally, the primary limitation of this review is the lack of longitudinal follow-up data on control of these indices.

These limitations notwithstanding, this review provides the first overview of glycaemic, BP and LDL-C control in adult patients with diabetes in Singapore over the past 20 years.

Conclusion

This 20-year overview of the glycaemic, BP and LDL-C control in adult diabetic patients in Singapore mirrors global trends, as these indices do not appear to be treated to target in the majority of patients. There appears to be marginal improvements reported in the studies over the past 20 years, although this requires further validation. There are gaps in translating guidelines into practice in the management of diabetes in Singapore. Data from the private primary care setting is urgently required.

REFERENCES

1. Global report on diabetes. World Health Organisation, Geneva, 2016.
2. National Health Survey 2004. Epidemiology & Disease Control Division. Ministry of Health, Singapore.
3. National Health Survey 2010. Epidemiology & Disease Control Division. Ministry of Health, Singapore.
4. Phan TP, Alkema L, Tai ES, Tan KH, Yan Q, Lim WY, et al. Forecasting the burden of type 2 diabetes in Singapore using a demographic epidemiological model of Singapore. BMJ Open Diabetes Res Care 2014;2:e000012.
5. National Registry of Disease Office. Ministry of Health, Singapore. Available at: https://www.nrdo.gov.sg/?AspxAutoDetectCookieSupport=1. Accessed on 2 November 2016.
6. Png ME, Yoong J, Phan TP, Wee HL. Current and future economic burden of diabetes among working-age adults in Asia: conservative estimates for Singapore from 2010-2050. BMC Public Health 2016;16:153.
7. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405-12.
8. Diabetes Control and Complications Trial Research Group: the effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-86.
9. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53.
10. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560-72.
11. Deedwania PC. Diabetes and hypertension, the deadly duet: importance, therapeutic strategy, and selection of drug therapy. Cardiol Clin 2005;23:139-52.
12. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;321:412.
13. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117-25.
14. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al on behalf of the American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777-803.
15. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in Circulation 2014;129:S46-8]. Circulation 2014;129:S1-45.
16. Clinical Practice Guidelines on Diabetes Mellitus. March 2014. Ministry of Health, Singapore.
17. Clinical Practice Guidelines on Lipids. December 2016. Ministry of Health, Singapore.
18. Koro CE, Bowlin SJ, Bourgeois N, Fedder DO. Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes: a preliminary report. Diabetes Care 2004;27:17-20.
19. Amod A, Riback W, Schoeman HS. Diabetes guidelines and clinical practice: is there a gap? The South African cohort of the International Diabetes Management Practices Study. JEMDSA 2012;17:85-90.
20. Jenssen TG, Tonstad S, Claudi T, Midthjell K, Cooper J. The gap between guidelines and practice in the treatment of type 2 diabetes: a nationwide survey in Norway. Diabetes Res Clin Pract 2008;80:314-20.
21. Eliasson B, Cederholm J, Nilsson P, Gudbjörnsdóttir S: Steering Committee of the Swedish National Diabetes Register. The gap between guidelines and reality: type 2 diabetes in a national diabetes register 1996-2003. Diabet Med 2005;22:1420-6.
22. Tan NC, Barbier S, Lim WY, Chia KS. 5-Year longitudinal study of determinants of glycemic control for multi-ethnic Asian patients with type 2 diabetes mellitus managed in primary care. Diabetes Res Clin Pract 2015;110:218-23.
23. Ng TP, Goh LG, Tan Y, Tan E, Leong H, Tay EG, et al. Ethnic differences in glycemic control in adult type 2 diabetic patients in primary care: a 3-year follow-up study. Diabet Med 2005;22:1598-604.
24. Wee SL, Tan CGP, Ng HS, Su S, Tai VU, Flores JV, et al. Diabetes outcomes in specialist and general practitioner settings in Singapore: challenges of right-siting. Ann Acad Med Singapore 2008;37:929-35.
25. Liu JJ, Lim SC, Yeoh LY, Su C, Tai BC, Low S, et al. Ethnic disparities in risk of cardiovascular disease, end-stage renal disease and all-cause mortality: a prospective study among Asian people with type 2 diabetes. Diabet Med 2016;33:332-9.
26. Low S, Lim SC, Yeoh LY, Liu JJ, Fun S, Su C, et al. Long-term diabetes outcomes in multi-ethnic Asians living in Singapore. Diabetes Res Clin Pract 2016;111:83-92.
27. Dalan R, Jong M, Choo R, Chew DE, Leow MK. Predictors of cardiovascular complication in patients with diabetes mellitus: a 5-year follow-up study in a multiethnic population of Singapore: CREDENCE II study. Int J Cardiol 2013;169:e67-9.
28. Hoe J, Koh WP, Jin A, Sum CF, Lim SC, Tavintharan S. Predictors of decrease in ankle-brachial index among patients with diabetes mellitus. Diabet Med 2012;29:e304-7.
29. Lee WRW, Emmanuel S, Lim HS, Thai AC, Chew WL, Goh LG, et al. The status of diabetes mellitus in primary institution and restructured hospitals in Singapore. Singapore Med J 2001;42:508-12.
30. Heng BH, Sun Y, Cheah JTS, Jong M. The Singapore National Healthcare Group diabetes registry – descriptive epidemiology of type 2 diabetes mellitus. Ann Acad Med Singapore 2010;39:348-52.
31. Quah JHM, Liu YP, Luo N, How CH, Tay EG. Younger adult type 2 diabetic patients have poorer glycaemic control: a cross-sectional study in a primary care setting in Singapore. BMC Endocrine Disorders 2013;13:18.
32. Hong CY, Chia KS, Hughes K, Ling SL. Ethnic differences among Chinese, Malay and Indian patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2004;45:154.
33. Narayanan RML, Koh WP, Phang J, Subramaniam T. Peripheral arterial disease in community-based patients with diabetes in Singapore: results from a primary healthcare study. Ann Acad Med Singapore 2010;39:525-31.
34. Shim YT, Lee J, Toh MP, Tang WE, Ko Y. Health-related quality of life and glycaemic control in patients with type 2 diabetes mellitus in Singapore. Diabet Med 2012;29:e241-8.
35. Lee ES, Tang WE. The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore. Singapore Med J 2015;56:681-6.
36. Loh PT, Toh MP, Molina JA, Vathsala A. Ethnic disparity in prevalence of

diabetic kidney disease in an Asian primary healthcare cluster. Nephrology (Carlton) 2015;20:216-23.

37. Toh MP, Heng BH, Sum CF, Jong M, Chionh SB, Cheah JT. Measuring the quality of care of diabetic patients at the specialist outpatient clinics in public hospitals in Singapore. Ann Acad Med Singapore 2007;36:980-6.
38. Wu AY, Tan CB, Eng PH, Tan KT, Lim SC, Tan EK. Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore. Singapore Med J 2006;47:315-20.
39. Huang OS, Lamoureux EL, Tay WT, Tai ES, Wang JJ, Wong TY. Glycemic and blood pressure control in an Asian Malay population with diabetes and diabetic retinopathy. Arch Ophthalmol 2010;128:1185-90.
40. Low SK, Sum CF, Yeoh LY, Tavintharan S, Ng XW, Lee SB, et al. Prevalence of chronic kidney disease in adults with type 2 diabetes mellitus. Ann Acad Med Singapore 2015;44:164-71.
41. Foo V, Quah J, Cheung G, Tan NC, Ma Zar KL, Chan CM, et al. HbA1c, systolic blood pressure variability and diabetic retinopathy in Asian type 2 diabetics. J Diabetes 2017;9:200-7.
42. Puar TH, Khoo JJ, Cho LW, Xu Y, Chen YT, Chuo AM, et al. Association between glycemic control and hip fracture. J Am Geriatr Soc 2012;60:1493-7.
43. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. JAMA 2004;291:335-42.
44. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB. Is glycemic control improving in U.S. adults? Diabetes Care 2008;31:81-6.
45. Macisaac RJ, Jerums G, Weekes AJ, Thomas MC. Patterns of glycaemic control in Australian primary care (NEFRON 8). Intern Med J 2009;39:512-8.
46. Chan GC. Type 2 diabetes mellitus with hypertension at primary healthcare level in Malaysia: are they managed according to guidelines? Singapore Med J 2005;46:127-31.
47. Chuang LM, Tsai ST, Huang BY, Tai TY; Diabcare-Asia 1998 Study Group. The status of diabetes control in Asia: a cross-sectional survey of 24 317 patients with diabetes mellitus in 1998. Diabet Med 2002;19:978-85.
48. Wong TY, Mwamburi M, Klein R, Larsen M, Flynn H, Hernandez-Medina M, et al. Rates of progression in diabetic retinopathy during different time periods. A systematic review and meta-analysis. Diabetes Care 2009;32:2307-13.
49. Ministry of Health, Singapore. Speech by Minister for Health, Mr Gan Kim Yong, at the MOH Committee of Supply Debate 2016. Available at: https://www.moh.gov.sg/content/moh_web/home/pressRoom/speeches_d/2016/speech-by-minister-fo-health--mr-gan-kim-yong--at-the-moh-commit.html. Accessed on 24 January 2017.
50. Sng QS. Primary Care Survey 2010. Profile of Primary Care Patients. Ministry of Health Singapore. Available at: https://www.moh.gov.sg/content/moh_web/home/Publications/information_papers/2011/primary_care_survey2010profileofprimarycarepatients.html. Accessed on 30 December 2016.
51. Tan WS, Ding YY, Xia WC, Heng BH. Effects of a population-based diabetes management program in Singapore. Am J Manag Care 2014;20:e388-98.
52. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003;348:383-93.
53. Tan NC, Ho SC. Treat-to-target approach in managing modifiable risk factors of patients with coronary heart disease in primary care in Singapore: what are the issues? Asia Pac Fam Med 2011;10:12.
54. Abbatecola AM, Paolisso G. Diabetes care targets in older persons. Diabetes Res Clin Pract 2009;86:S35-40.
55. Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients. Diabetes Care 2011;34:1329-36.
56. Kim TN, Park MS, Yang SJ, Yoo HJ, Jang HJ, Song W, et al. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care 2010;33:1497-9.
57. Brown AF, Mangione CM, Saliba D, Sarkisian CA; California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. J Am Geriatr Soc 2003;51:S265-80.
58. Weng C, Coppini DV, Sonksen PH. Geographic and social factors are related to increased morbidity and mortality rates in diabetic patients. Diabet Med 2000;17:612-7.
59. Ismail IS, Nazaimoon WM, Mohamad WB, Letchuman R, Singaraveloo M, Pendek R, et al. Sociodemographic determinants of glycaemic control in young diabetic patients in peninsular Malaysia. Diabetes Res Clin Pract 2000;47:57-69.

Commentary

Is the Human Organ Transplant Act (HOTA) to Blame? Addressing Our Organ Shortage from a Public Policy Perspective

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In 1906, Jaboulay performed the first transplant surgery in the history of mankind. He transplanted a goat and porcine kidney into 2 different patients, who unfortunately did not survive.[1] Later in 1952, John Merrill, Joseph Murray and Hartwell Harrison performed the first successful kidney transplant at the Brigham Hospital in Boston, United States.[2] Since then, transplant medicine has progressed significantly and is now recognised as a life-saving and cost-efficient treatment for patients.

Despite the availability of transplant teams and technology, the main barrier to accessing this life-saving treatment is the scarcity of organs worldwide. To increase the rates of cadaveric organ procurement, a presumed consent system was adopted in Singapore through the legislation of the Human Organ Transplant Act (HOTA) in 1987.[3] Under this policy, Singaporeans and permanent residents are organ donors unless they opt-out (by registering their objection with the National Organ Transplant Unit).[4] Despite the adoption of this system, Singapore has not achieved the expected increase in the number of actualised organ donors. In 2013, the national cadaveric transplant rates for kidney, liver and heart were 7.97 per million of population (pmp), 3.52 pmp and 0.74 pmp, respectively.[5] These figures pale in comparison to countries like Croatia that boast national cadaveric transplant rates of 48.4 pmp for kidneys and 32.3 pmp for livers.[6]

A logical question that follows is whether our low donation rate stems from of a lower number of brain deaths. We assume that with better car safety technology, improved legislation (e.g. ban on mobile phone usage while driving and mandatory seat belt laws) and a lower traffic speed, there would be a low number of traffic-related deaths, a correspondingly low incidence of brain death and hence, fewer organ donors. Indeed, based on data from the Singapore Department of Statistics, there was a 25% decline in the absolute number of traffic-related deaths between 1987 and 2016, despite an increase in the total population of the country.[7] The traffic death rate in Singapore now stands at 3.6 per 100,000. Although this rate is low, some countries that have a high donation rate (e.g., Spain and Croatia) have similarly low traffic accident rates (3.6 and 9.2 per 100,000, respectively).[8] Taken together, we believe that there is potential for an increase in the number of organs that can be retrieved.

Is Mandated Consent a Silver Bullet for Singapore?

In response to the shortage of transplantable organs, both the public and parliamentarians have asked the government to consider a mandated consent over a presumed consent policy.[9,10] To provide a background for readers not familiar with these terms, there are 3 types of consent policies that countries adopt with respect to organ donation: explicit, presumed and mandated consent. For explicit consent, a person is an organ donor only if he/she voluntarily goes to an agency and signs up for it; for presumed consent, all residents are donors unless they have explicitly opted-out; and for mandated consent, all residents are required to state their organ donation preference without a default being shown (this is carried out during common tasks such as driver license renewals or income tax filing).[11] In Singapore, the presumed consent policy has been in force since HOTA was first enacted in 1987.[3]

The call to consider mandated consent in Singapore is not without basis. Even with a hard opt-out system (where families cannot decide against organ donation when a patient has been declared brain dead), there are ways that families have circumvented donation.[12] For example, families can end life support for their relatives before brain death is even certified.[12] This decision is sometimes carried out because family members have little knowledge of the deceased relative's views on organ donation; consequently, they act conservatively and are less willing to accept organ donation for relatives than they are for themselves.[13] In such cases, a mandated consent system could reduce the premature

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termination of life support. If all residents were made to state their organ donation preferences explicitly, there would be no ambiguity about what the deceased patient desires, resulting in a higher rate of donor actualisation. The switch to mandated consent seems even more attractive because it appears to come without costs. In a seminal publication, Johnson and Goldstein reported that: 1) both presumed and mandated consent increased the number of organ donors compared to explicit consent; and 2) no significant difference was observed in consent rates between presumed and mandated consent policies.[4]

Although mandated consent appears promising, we suggest that it may not be Singapore's magic bullet. First, we know of no country that has changed its policy from presumed to mandated consent; any such move would need to be taken very cautiously. Second, and perhaps more importantly, we recently published the first local study comparing organ donation rates as a function of policy type.[14] In a group of 157 university students, we examined willingness to enlist as organ donors when presented with either an explicit, mandated or presumed consent policy. In stark contrast to the findings of Johnson and Goldstein, our findings suggested that switching to a mandated consent policy could potentially decrease the pool of donors in Singapore (with 79.85% of students donating if a mandated consent policy was in place, compared to 92% under a presumed consent policy).

Beyond Mandated Consent: The Need for a Holistic Approach

Moving beyond policy types, it is important to recognise that donation rates vary significantly even amongst countries with a presumed consent policy. Croatia is an interesting case in point. In 1988, Croatia adopted a presumed consent policy for organ donation. Like Singapore today, this policy did not yield the expected increase in organ donation and by the year 2000, the donation rate in Croatia was a mere 2.7 pmp. Since then, however, Croatia has developed its transplant programme by adopting a multipronged approach. The measures they adopted included appointing hospital transplant coordinators, establishing 24-hour duty desks, adopting new legislation, developing a new financial model, organising public awareness campaigns and starting a donor assurance programme.[15] These measures yielded great dividends and by 2014, the donation rate had increased thirteenfold to 35 pmp[6] – one of the highest in the world (Fig. 1).

The case of Croatia suggests that Singapore's presumed consent policy may not be a key reason for her low organ donation rate. Instead of abandoning presumed consent, we should direct our efforts at improving the transplant

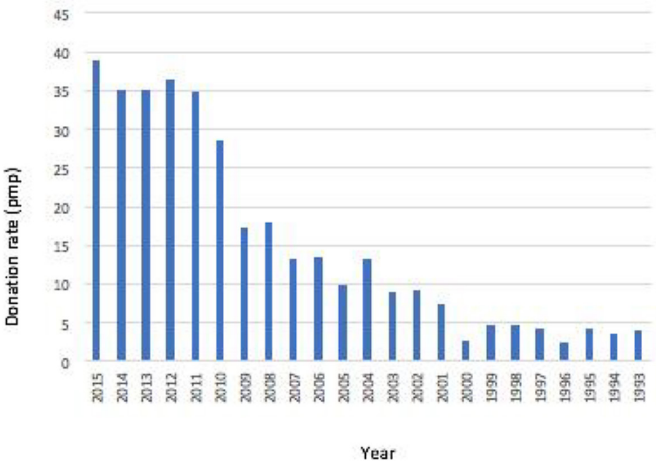

Fig. 1. Deceased donor rates in Croatia from 1993 to 2015 (International Registry in Organ Donation and Transplantation).

infrastructure and workflow, aiming at increasing referral rates, improving donor management, decreasing family objection and improving public perception of the programme.

Additionally, as part of a holistic approach, it is notable that HOTA only covers Singapore citizens and permanent residents. This represents a missed opportunity, as 3 out of 10 people who reside in Singapore are foreigners on long-term passes.[16] Currently, foreigners can become organ donors only if they have explicitly consented under the Medical (Therapy, Education and Research) Act. The inclusion of foreigners in HOTA's presumed consent scheme or an alternate mandated consent scheme could significantly increase the nation's donation rates, a move that has been implemented in countries with both presumed consent (e.g., Spain, Portugal) and mandated consent policies (e.g., Canada).[17]

As a further avenue for growth, donation after cardiac death (DCD) programmes have gained traction worldwide and could be pursued within Singapore. Although the majority of organ transplants arise from living-related donors and donation after brainstem death (DBD),[17] the first kidney transplant programmes involved donors who had sustained circulatory death.[18] Compared to DBD, organs harvested from DCD sustain a longer warm ischaemia time and are therefore, of inferior quality and more prone to failure.[19,20] However, this is partially mitigated through the use of extracorporeal membrane oxygenators in controlled DCD, such that DCD is increasingly being explored to address organ shortage. Indeed, in 2016, DCD represented nearly half of all deceased organ donors in the United

Kingdom (UK).[21] This statistic suggests that a similar DCD programme could increase the total yield of organ donations in Singapore, although mounting such a programme will likely require not only technical expertise but also debates in Parliament to overcome the ethical, professional and legislative challenges that UK has faced.

Conclusion

Our transplant policies have come a long way since we performed our first kidney transplant in 1970. The introduction of the Medical (Therapy, Education and Research) Act and HOTA have resulted in significant increases in donor rates, and many patients with failing kidneys, livers and hearts have benefitted from organ transplantation. Until xenografts and artificial organs become a reality, patients on the transplant waitlist will continue to die unless organs can be found. To optimise the number of organs harvested, public policies need to be continually modified. We need to enhance our infrastructure and workflow to improve organ donation rates, supported by research (e.g., feasibility of financial reimbursement models, cultural barriers) to inform us about the direction of future public policies.

REFERENCES

1. Morris PJ. Transplantation – a medical miracle of the 20th century. N Engl J Med 2004;351:2678-80.
2. Merrill JP, Murray JE, Harrison JH, Guild WR. Successful homotransplantation of the human kidney between identical twins. J Am Med Assoc 1956;160:277-82.
3. Ministry of Health, Singapore. Human Organ Transplant Act. Available at: https://www.moh.gov.sg/content/moh_web/home/legislation/legislation_and_guidelines/human_organ_transplantact.html. Accessed on 8 February 2017.
4. Johnson EJ, Goldstein D. Medicine. Do defaults save lives? Science 2003;302:1338-9.
5. International Registry in Organ Donation and Transplantation Database (Singapore). IRODaT 2013. Available at: http://www.irodat.org/?p=database&c=_S - data. Accessed on 8 February 2017.
6. International Registry in Organ Donation and Transplantation (Croatia). IRODaT 2014. Available at: http://www.irodat.org/?p=database&c=_S - data. Accessed on 8 February 2017.
7. Singapore Department of Statistics. M651281 – Road Traffic Accident Casualties, Annual. Available at: http://www.tablebuilder.singstat.gov.sg/publicfacing/createDataTable.action?refId=5513. Accessed on 10 February 2017.
8. World Health Organization. Road traffic accidents. Data by country. Available at: http://apps.who.int/gho/data/node.main.A997. Accessed on 10 February 2017.
9. Ministry of Health, Singapore. Increasing Singapore's Organ Transplant Rate. Available at: https://www.moh.gov.sg/content/moh_web/home/pressRoom/Parliamentary_QA/2016/increasing-singapore-s-organ-transplant-rate.html. Accessed on 8 February 2017.
10. The Straits Times. Organ donation: consider mandated consent. 25 May 2016. Available at: http://www.straitstimes.com/opinion/organ-donation-consider-mandated-consent. Accessed on 8 February 2017.
11. No authors listed. Strategies for cadaveric organ procurement. Mandated choice and presumed consent. Council on Ethical and Judicial Affairs, American Medical Association. JAMA 1994;272:809-12.
12. Kwek TK, Lew TW, Tan HL, Kong S. The transplantable organ shortage in Singapore: has implementation of presumed consent to organ donation made a difference? Ann Acad Med Singapore 2009;38:346-8.
13. Sanner M. A comparison of public attitudes toward autopsy, organ donation, and anatomic dissection. A Swedish survey. JAMA 1994;271:284-8.
14. Liu CW, Lai CKY, Lu BZ, Thangavelautham S, Ho VK, Liu JCJ. A comparison of mandated, presumed, and explicit consent systems for deceased organ donation among university students in Singapore. Ann Acad Med Singapore. In press.
15. Zivcic-Cosic S, Busic M, Zupan Z, Pelcic G, Anusic Juricic M, Jurcic Z, et al. Development of the Croatian model of organ donation and transplantation. Croat Med J 2013;54:65-70.
16. Population.sg. Who is in our population 2017? Available at: https://population.sg/articles/who-is-in-our-population. Accessed on 25 June 2017.
17. Rudge C, Matesanz R, Delmonico FL, Chapman J. International practices of organ donation. Br J Anaesth 2012;108 Suppl 1:i48-55.
18. Manara AR, Murphy PG, O'Callaghan G. Donation after circulatory death. Br J Anaesth 2012;108 Suppl 1:i108-21.
19. Weber M, Dindo D, Demartines N, Ambühl PM, Clavien PA. Kidney transplantation from donors without a heartbeat. N Engl J Med 2002;347:248-55.
20. Chan EY, Olson LC, Kisthard JA, Perkins JD, Bakthavatsalam R, Halldorson JB, et al. Ischemic cholangiopathy following liver transplantation from donation after cardiac death donors. Liver Transpl 2008;14:604-10.
21. Organ Donation and Transplant. Donation after circulatory death. Available at: http://www.odt.nhs.uk/donation/deceased-donation/donation-after-circulatory-death/. Accessed on 22 June 2017.

A Comparison of Once- and Thrice-Weekly Erythropoietin Dosing for the Treatment of Anaemia of Prematurity

Dear Editor,

Globally, 1 in 10 infants are born prematurely according to reports by the World Health Organisation (WHO).[1] Anaemia of prematurity (AOP) is a common complication in preterm very low birth weight (VLBW) infants. The need for multiple blood transfusions may expose these infants to increased risk of infections and related adverse reactions.

The Cochrane Systematic Review surmised that erythropoietin (EPO) given later in the postnatal period to stable growing preterm infants is effective therapy for AOP in reducing the number of blood transfusions.[2] However, significant variations were noted in the EPO dosing regimen and the duration of treatment in these studies.[3,4] EPO at a dose of 250 IU/kg thrice-weekly for 6 weeks is a commonly practised regimen based on previous larger trials and is the current treatment protocol for infants with AOP in our neonatal intensive care unit (NICU).

There were several recent studies reporting comparable effectiveness between once- and thrice-weekly EPO dosing with no significant differences in the frequency of adverse events.[5,6] Simplification of the dosing regimen is attractive and may help improve in the compliance with therapy with the reduction in the number of injections, therefore reducing the frequency of pain inflicted, and decreased hospital revisits, staff workload and risk of medication errors. Aiming towards service improvement, we studied whether once-weekly dosing of EPO was comparable to thrice-weekly dosing in treating AOP.

This is a non-randomised comparative study that used a non-inferiority analysis technique. This study was approved by the Universiti Kebangsaan Malaysia (UKM) Research Ethics Committee and registered in the Malaysian National Medical Research Trial Registry (NMRR-13-866-17373). Preterm infants included in this study were of gestational ages of <33 weeks; birthweight <1500 g; tolerating full enteral feeding of at least120 mL/kg/day and with haemoglobin (Hb) levels of <12 g/dL. Parental informed consent was obtained before enrolling the infants who met these study inclusion criteria. The determination of the non-inferiority margin was done based on the principle of the 95-95 approach.[7,8] Based on only one available study as reference,[9] the margin of non-inferiority was calculated to be -0.125 g/dL. The sample size thus comprised 35 patients per group by using -12.5% as the margin of non-inferiority, significance level of 0.05 and 0.8 as the power of the study.[10]

We compared 2 back-to-back periods of therapeutic intervention. A historical cohort group comprised infants receiving EPO at the conventional dose of 250 IU/kg thrice-weekly between October 2012 and March 2013. Several more infants were prospectively enrolled to receive this regimen when this study was commenced to make up the numbers required in this arm as determined by the sample size calculation followed by the comparison treatment group comprising prospectively enrolled infants who were given the new alternative regimen of 750 IU/kg/dose once-weekly (similar cumulative dose of 750 IU/kg weekly for both groups). Treatment with subcutaneous EPO with either of the assigned dosing regimen was administered for a period of 6 weeks as per unit protocol. All patients received Erythropoietin-beta (Recormon®) (Roche Diagnostics GMBH, Germany). In addition, patients in both groups received oral ferrous ammonium citrate at a treatment dose of 6 mg/kg/day upon initiation of EPO therapy. The Hb change from pre-therapy baseline level was the primary outcome measure. For the intention-to-treat (ITT) analysis, all infants who fulfilled the selection criteria were included, whereby any missing Hb readings were adjusted by the "Last Observation Carried Forward" method. The changes in absolute reticulocyte count (ARC) and serum ferritin levels were monitored following the commencement of EPO before the subjects were discharged home. Data were collected weekly until the first 2 months of post-discharge from the NICU.

A total of 68 VLBW infants had sufficiently available data for comparative analysis; n = 35 in the control group (conventional thrice-weekly regimen) and n = 33 in the treatment group (alternative once-weekly regimen), as shown in Figure 1. The characteristics of infants before EPO therapy were comparable except for a significantly lower pre-treatment Hb in the once-weekly than thrice-weekly (10.5 ± 1.06 g/dL vs 11.5 ± 1.76 g/dL, respectively; P = 0.01) group (Table 1). The mean corrected gestational age when EPO was commenced was similar, 32.3 ± 2.3 weeks vs 32.6 ± 2.6 weeks (P = 0.64), which translated to an average postnatal age of 25.1 ± 6.5 days vs 23.3 ± 10.4 days in the once-weekly and thrice-weekly group, respectively. There was no difference in the respiratory status of the infants in

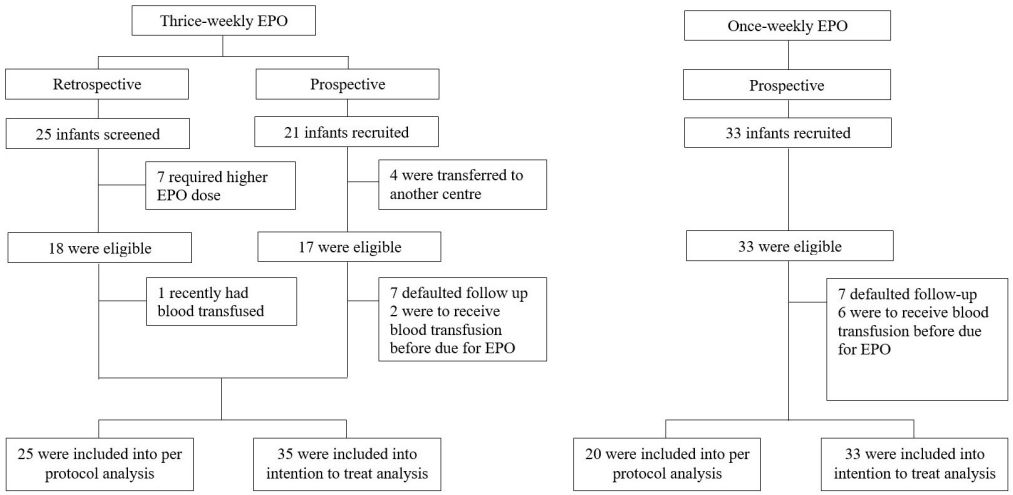

Fig. 1. Charts showing enrolment and outcomes.

Table 1. Subject Characteristics and Treatment Outcomes

Variables	**Thrice-Weekly EPO n = 35**	**Once-Weekly EPO n = 33**	***P* Value**
Gender, male, n (%)	16 (45.7)	15 (45.5)	0.90
Gestational age, weeks	29.3 (2.31)	28.7 (2.14)	0.27
Corrected gestational age at the commencement of EPO, weeks	32.6 (2.6)	32.3 (2.3)	0.64
Birth weight, kg	1.2 (0.27)	1.1 (0.26)	0.06
Body weight at the commencement of EPO, kg	1.4 (0.31)	1.3 (0.32)	0.31
Hb level, g/dL	11.5 (1.76)	10.5 (1.06)	0.01*
Serum ferritin at entry, µmol/L	370 (280)	415 (445)	0.71
Body weight at 5th week, kg	2.2 (0.50)	2.0 (0.49)	0.02*
†Hb level at 5th week, g/dL	11.0 (1.71)	10.0 (1.73)	0.02*
†Hb increment from baseline by 5th week, %	-2.1 (17.3)	-4.3 (14.7)	0.57
†ARC at 5th week, $\times 10^9$/L	247 (109)	174 (77)	<0.01*
†Serum ferritin at 5th week of EPO, µmol/L	169 (117)	170 (119)	0.96
Mechanical ventilator support, median [IQR] (day)	0.0 [0.00 – 0.00]	0.0 [0.00 – 0.00]	0.08
CPAP support, median [IQR] (day)	5.0 [0.00 – 27.00]	1.0 [0.0 – 17.88]	0.30
Highest FiO_2, median [IQR] (%)	21.0 [21.0 – 25.0]	21.0 [21.0 – 25.0]	0.92
Infants requiring blood transfusion, n (%)	3 (8.6)	6 (18.2)	0.30‡
Pre-transfusion Hb level, g/dL	8.3 (0.35)	8.4 (0.65)	0.75
Cumulative EPO dose received prior to blood transfusion, IU/kg	1500.0 (1561.25)	2125.0 (876.78)	0.20
IVH and resolution on cranial ultrasound, n (%)	23 (88.5)	18 (100.0)	0.12§
Chronic lung disease, n (%)	8 (22.9)	5 (15.6)	0.45‖
Retinopathy of prematurity, n (%)	2 (5.9)	3 (10.0)	0.66¶

Comparisons between groups are on intention-to-treat basis; Values are expressed as mean (SD) unless specified otherwise.
ARC: Absolute reticulocyte count; CPAP: Continuous positive airway pressure; EPO: Erythropoietin; FiO_2: Fractional inspired oxygen; Hb: Haemoglobin; IVH: Intraventricular haemorrhage
*Statistically significant at $P < 0.05$.
†Missing values handled using the "Last Observation Carried Forward" method. Refer to Figure 2 for the available data for each variable and time-point.
‡RR (95% CI) = 0.47 (0.13-1.73).
§RR (95% CI) = 0.89 (0.77-1.02).
‖RR (95% CI) = 1.46 (0.53-4.01).
¶RR (95% CI) = 0.59 (0.11-3.30).

both groups at and after EPO treatment. Specifically, the duration of mechanical ventilation support, continuous positive airway pressure (CPAP) therapy and the highest FiO_2 required were not different between the groups. These implied that the 2 groups of infants were comparable in terms of baseline characteristics. The severity of intraventricular haemorrhage (IVH) and rates of resolution were similar between groups.

There was no significant difference in the percentage of Hb increment from pre-treatment baseline between the groups (-4.3 ± 14.7 % vs -2.1 ± 17.3 %; $P = 0.57$). The mean in ARC peaked after 3 weeks of EPO treatment in both groups (Fig. 2) and it was significantly higher in the thrice-weekly ($247 \pm 109 \times 10^9$/L) than once-weekly ($174 \pm 77 \times 10^9$/L) group with $P < 0.01$ when analysed under ITT (Table 1). However, there were many missing data after the initial 4-week period and based on per protocol (PP) analysis, mean ARC was not significantly different between EPO once- and thrice-weekly at the 5th week of treatment ($196 \pm 90 \times 10^9$/L vs $253 \pm 80 \times 10^9$/L, respectively; $P = 0.20$). There was also no significant difference in serum ferritin of infants who received once-weekly EPO compared to those who received the thrice-weekly regimen (170 ± 119 μmol/L vs 169 ± 117 μmol/L; $P = 0.96$) (Table 1).

In clinical outcomes, the increment in weight was significantly lower resulting in a lower mean body weight in the once-weekly group (2.0 ± 0.49 kg) as compared to the thrice-weekly group (2.2 ± 0.50 kg) ($P = 0.02$). The need for blood transfusion when on EPO, although was twice more frequent in the once-weekly group, was not statistically significant (RR = 0.47, 95% CI [0.13 to 1.73]; $P = 0.30$). In all these infants, blood transfusion was administered after 3 weeks of EPO therapy (mean cumulative dose of 2125 ± 877 IU/kg) and when the mean Hb had decreased by 2.4 ± 1.13 g/dL. Hence, there was no significant difference between the groups and the indications were in abiding with the unit transfusion guideline which involves transfusing growing VLBW infants only when the Hb level is below 8 g/dL, or higher if the infant is symptomatic with increased oxygen supplementation or elevated baseline heart rate and poor weight gain. The trend in weekly changes of Hb and ARC for the 2 groups are shown in Figure 2.

Although several studies have associated exogenous EPO therapy with the incidence and severity of retinopathy of prematurity (ROP), a recent meta-analysis indicated insufficient evidence for such a relationship.[11-14] Our study did not show a significant difference in the ROP rates between groups and these cases were all non-threshold diseases. The incidence of ROP in our unit has remained low despite an active EPO use policy for AOP when benchmarked against most of the centres in the Vermont-Oxford Neonatal Network.

Subcutaneous EPO has a relatively short half-life, ranging from10 to 22 hours at a steady state in premature infants.[15]As such, the pharmacokinetics of EPO in preterm infants may necessitate a more frequent dosing. Our study which showed that once-weekly EPO did not result in a more rapid rise in the reticulocyte count compared to the thrice-weekly is supportive of a more frequent dosing. We speculate that a more constant steady state EPO receptor saturation or stimulation may be required for an increased and more sustained bone marrow response for a Hb rise. Higher erythropoietic activity with the thrice-weekly dosing regimen has also been reported in previous studies.[5,6] There was no significant difference in ferritin level between the groups, similar to other reports.[5,6] In comparing the 2 dosing regimen, our study showed that EPO dosing of 750 IU/kg once-weekly was inferior to EPO 250 IU/kg thrice-

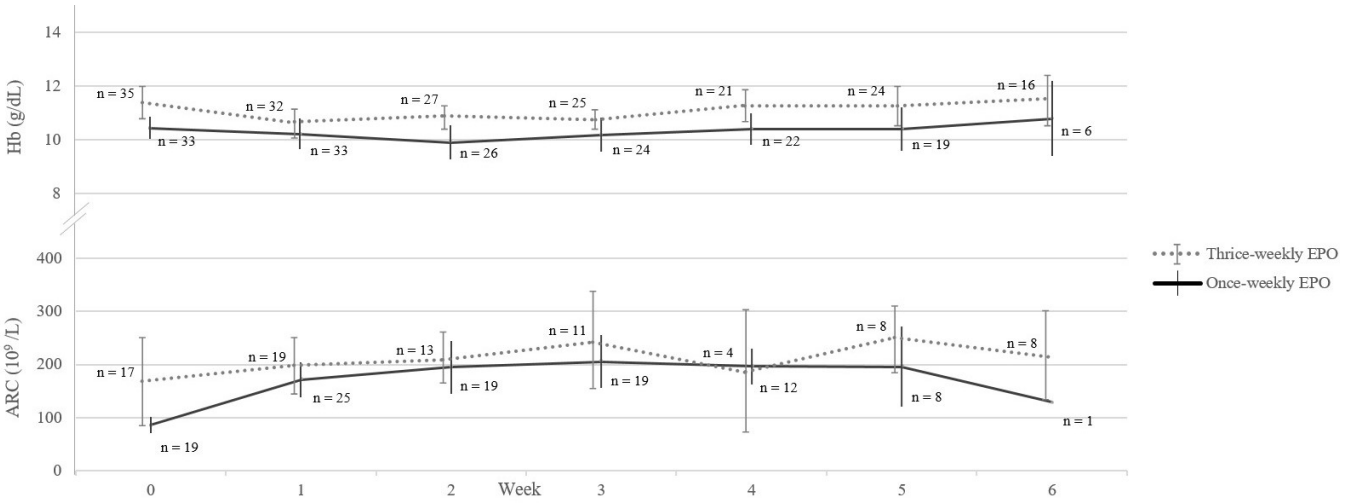

Fig. 2. Graphs showing weekly changes of haematological parameters for thrice-weekly versus once-weekly erythropoietin dosing.

weekly, based on the crossing below of the predetermined non-inferiority margin of -0.125 and the lower bounds of the 95% CI for both PP (d = -0.24; lower bound 95% CI = -1.27) as well as ITT analyses (d = -0.05; lower bound 95% CI = -0.93).

There were several limitations in this study such as phlebotomy blood losses that were not recorded, missing data due to patient lost to follow-up after discharge and the study design was not a true randomised trial, with infants recruited from 2 different periods and they were not matched in characteristics. These may be improved together with the inclusion of pain scores or local site reactions relating to the dosing frequency in future larger controlled trials in determining the optimal use and dosage of EPO in the treatment of AOP.

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REFERENCES

1. World Health Organization. Preterm birth. Available at: http://www.who.int/mediacentre/factsheets/fs363/en/. Accessed on 13 March 2016.
2. Aher SM, Ohlsson A. Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2012 Sep 12;(9):CD004868.
3. Rocha VLL, Benjamin AC, Procianoy RS. The effect of recombinant human erythropoietin on the treatment of anemia of prematurity. J Pediatr 2001;77:75-83.
4. Kotto-Kome AC, Garcia MG, Calhoun DA, Christensen RD. Effect of beginning recombinant erythropoietin treatment within the first week of life among very-low-birth-weight neonates, on "early" and "late" erythrocyte transfusions: a meta-analysis. J Perinatol 2004;24:24-9.
5. Ohls RK, Roohi M, Peceny HM, Schrader R, Bierer R. A randomized, masked study of weekly erythropoietin dosing in preterm infants. J Pediatr 2012;160:790-5.
6. Vazquez-Lopez MA, Llamas MA, Galera R, Sanchez AR, Lendinez F, Gonzalez-Ripoll M, et al. Comparison between one and three doses a week of recombinant erythropoietin in very low birth weight infants. J Perinatol 2011;31:118-24.
7. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials 2011;12:106.
8. Rothmann MD, Tsou HH. On non-inferiority analysis based on delta-method confidence intervals. J Biopharm Stat 2003;13:565-83.
9. Maier RF, Obladen M, Scigalla P, Linderkamp O, Duc G, Hieronimi G, et al. The effect of epoetin beta (recombinant human erythropoietin) on the need for transfusion in very-low-birth-weight infants. N Engl J Med 1994;330:1173-8.
10. Zhong B. How to calculate sample size in randomized controlled trial? J Thorac Dis 2009;1:51-4.
11. Brown MS, Baron AE, France EK, Hamman RF. Association between higher cumulative doses of recombinant erythropoietin and risk for retinopathy of prematurity. J AAPOS 2006;10:143-9.
12. Aher SM, Ohlsson A. Early versus late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants. Cochrane Database of Syst Rev 2012;10:CD004865.pub3.
13. Suk KK, Dunbar JA, Liu A, Daher NS, Leng CK, Leng JK, et al. Human recombinant erythropoietin and the incidence of retinopathy of prematurity: a multiple regression model. J AAPOS 2008;12:233-8.
14. Xu XJ, Huang HY, Chen HL. Erythropoietin and retinopathy of prematurity: a meta-analysis. Eur J Pediatr 2014;173:1355-64.
15. Ohls RK, Veerman MW, Christensen RDJ. Pharmacokinetics and effectiveness of recombinant erythropoietin administered to preterm infants by continuous infusion in total parenteral nutrition solution. Pediatr1996;128:518-23.

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Health-related Quality of Life of Home Ventilated Patients (HoMe V) from a Tertiary Hospital in Singapore

Dear Editor,

Home mechanical ventilation (HMV) is an established treatment of severe chronic respiratory failure from neuromuscular disorders, restrictive thoracic disease, obesity hypoventilation syndrome and chronic obstructive pulmonary disease. Life prolongation, symptom control, and improvement of patient well-being and function are some of the treatment goals. Hospitalisation rate is reduced once HMV is established.[1] HMV patients, however, face unique challenges. HMV may affect a variety of physical and psychological health domains such as respiratory symptoms, limited mobility, anxiety, compromised social interaction and depression. The effects of non-invasive positive pressure ventilation (NIPPV) on patient reported outcomes (PRO) varied depending on the underlying disorder.[2] However, study quality in this area is poor and there remains many uncertainties as to which patient may benefit from HMV and how they may benefit.

Health-related quality of life (HRQoL) is a psychological construct describing the subjectively experienced health status based on various components of health including physical state, psychological well-being, social relations and functional capacities. As an important component of health surveillance, HRQoL has steadily become essential in evaluating the costs and benefits of modern treatment modalities, and a valid indicator of service needs.[3]

International multicentre studies have reported improvement in HRQoL following HMV establishment.[1] An evaluation of HRQoL in HMV patients is timely as multiethnic Singapore is seeing a growing number of HMV patients. A better understanding of HRQoL and factors influencing it is crucial in improving quality of care and optimising clinical outcomes.

The aim of the HoMe V (HRQoL of home mechanical ventilated patients) study is to describe the HRQoL among HMV patients and to evaluate if local outcome measures are comparable to those reported overseas.[1,4] The secondary objective is to determine factors associated with HRQoL.

Materials and Methods

Tan Tock Seng Hospital (TTSH) Home Ventilation and Respiratory Support Service (HVRSS)[5] is the first service in Singapore dedicated to support ventilator-assisted and ventilator-dependent patients in the community. We invited clinically stable patients from TTSH HVRSS who were well adapted to HMV to participate in the study. Participants with cognitive impairment, psychiatric disorders, communication barriers or disabilities, and those unable to comprehend English were excluded.

We conducted phone calls to obtain initial verbal consent and to schedule an appointment for questionnaire administration. Participants were reassessed for medical stability prior to proceeding with written consent. Participants were deemed medically unstable if they had evidence of acute respiratory failure,[6] defined as worsening of symptoms, signs of respiratory infection (any 2 of the following: increasing cough, purulent sputum or fever) or SpO_2 <90 mmHg. Written consent was obtained from medically stable participants on the day of the survey appointment. Participants were withdrawn from the study if they voluntarily dropped out or if their condition deteriorated.

The study was approved by the Domain Specific Review Board (National Healthcare Group).

Questionnaire

The English version of the Severe Respiratory Insufficiency (SRI) questionnaire,[7] a disease-specific, multi-dimensional, self-administrated HRQoL instrument, was used to measure HRQoL. It has good psychometric properties, consisting of 49 questions across 7 domains covering respiratory complaints (RC), physical functioning (PF), attendant symptoms (such as cough and expectoration, headache, dizziness and neck ache) and sleep (AS), social relationship (SR), anxiety (AX), psychological well-being (WB), and social functioning (SF). Subscales are aggregated into one summary score (SS) where higher values indicate higher HRQoL. For data evaluation, values obtained from the questionnaire were scaled from 0 to 100, analogous to computation of percentages. We also included a question, "In view of your experience thus far, would you agree to be on ventilator support if you could decide on your treatment all over again?"

Statistical Analysis

Statistical computation was performed with Statistical

Package for Social Sciences (SPSS Inc., Chicago, IL), version 21. Continuous variables were reported as mean ± standard deviation, unless otherwise stated. Absolute numbers and percentages of each category were used for categorical data. Unpaired student's t-test compared continuous variables. Chi-square test analysed differences between categorical variables. ANOVA test evaluated study differences in continuous variables between categorical variables with more than 2 categories. *P* values <0.05 were considered significant.

Results

We approached 38 eligible participants. Six refused participation. Eight were unable to complete the survey for various reasons: 1 relocated, 3 were unable to schedule, 1 died, and 3 were deemed medically unstable to proceed. Twenty-four (63.2%) gave written consent and completed the questionnaire. Questionnaires were administered in 33.2 ± 13.7 minutes, with 100% response rate for all items. Characteristics of the study population are shown in Table 1. Respiratory complaints scored highest while physical functioning scored lowest. Among the psychosocial domains, social relationships scored highest while social functioning had the lowest score.

Psychometric subscale values and SRI-SS were not significantly different between age groups, genders and ethnic groups. No difference in psychometric scales was observed for educational level, monthly household income, caregiver groups, Charlson-age comorbidity index and HMV duration. Emergency department attendance (25%) and admission rates (37.5%) were low. Modifiable factors associated with HRQoL subscales were route of ventilation. Tracheostomy group (50.69 ± 17.75) scored lower than non-tracheostomy (70.83 ± 15.59) group in terms of social relationship, $P = 0.01$. Tracheostomy group (30.99 ± 15.68) also scored lower in social functioning than non-tracheostomy (61.35 ± 7.48) group, $P = 0.02$.

Participants on HMV for less than 14 hours (59.09 ± 30.76) scored higher than those ventilated for 14 hours or more (37.50 ± 15.53) in social functioning.

Choosing Ventilator Support Again

Thirteen out of 24 (54%) indicated that they would choose ventilator support again if given a second chance. Three (12.5%) were unsure.

Discussion

Generally, a moderate global HRQoL was observed. SS, AS and WB scores for our cohort were comparable with international multisite studies.[1,4,7] Our cohort scored higher for RC and AX as a whole (Table 2). Our holistic and structured delivery of HVRSS with co-interventions such as access to telephone support and home visits could have positively influenced some of the PRO measures.[2]

Nonetheless, differences in patients' characteristics prevailed between our study and previous studies. Our cohort had a predominance of males and Chinese, was younger (mean age 53.2 ± 16.2 years), and spent more time on ventilator (mean duration 15 hours daily) compared to Windisch's cohort[1] of predominantly chronic obstructive pulmonary disease (COPD) and restrictive thoracic disease (RTD) patients with mean age ranging from 53 to 63 years, and who spent 7.3 ± 2.7 hours daily on NIPPV. Ghosh's cohort[7] of inpatients with COPD, RTD and obesity hypoventilation syndrome (OHS) had a mean daily duration of ventilation from 7 to 8 hours; higher (11 hours) for neuromuscular disorders patients who were younger.

In contrast, HVRSS supports largely patients with respiratory muscular dysfunction from neuromuscular dystrophy (NMD), Duchene muscular dystrophy (DMD), and amyotrophic lateral sclerosis (ALS). The local practice where patients tend to be referred for ventilator support later in the disease's trajectory could partly explain the observed differences in daily ventilation time. Research into the knowledge, attitudes and practices of both physicians and patients towards HMV would add to the knowledge to this emerging intervention.

Our PF and SF scores were poor; in keeping with previous reports where scores in these 2 domains were low in neuromuscular disease due to the accompanying disability and handicap from limb weakness.[1] Problems of social integration[8] and perceived stigmatisation[9]—known issues that trouble patients with tracheostomy—could account for the lower SF and SR scores. Non-invasive ventilation may be preferred over invasive support (tracheostomy).[10] However, patients with more severe illnesses are more likely to require invasive ventilation. Hence, the mode of ventilation may not solely account for poorer SF and SR scores.

It is well documented that HRQL is strongly influenced by the underlying disease. In our study, association between daily ventilation time and SF domain was borderline significant after stratifying for primary diagnostic groups. This is likely that our study was underpowered. Notwithstanding, we noted that the associations and trends were largely preserved. Our study's finding was in concordance to Hannan et al[2] where a beneficial PRO is seen in patients with amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). Interestingly, we did not see the same benefit in the RTD group, as reported in systematic review. Our cohort had only 2 participants in the RTD category, and they seemed to have a poorer in in SS score. We speculate that this apparent lack of benefit could be a result of the very small sample in that group.

Table 1. Characteristics of the Study Participants

Continuous Variables	**n**	**%**
Gender		
Male	19	79.2
Female	5	20.8
Age (years)		
<40	7	29.2
40 to 60	8	33.3
>60	9	37.5
Ethnicity		
Chinese	21	87.5
Non-Chinese	3	12.5
Highest education		
Basic (primary, secondary, ITE & equivalent)	16	66.7
Tertiary education (polytechnic & university)	7	29.2
Marital status		
Never married	11	45.8
Ever married (married & divorced)	12	50.0
Employment status		
Employed	18	75.0
Unemployed	5	20.8
Monthly household income		
Less than $1000	9	37.5
$1000 to $4000	12	50.0
$4000 and above	3	12.5
Housing type		
HDB 1- & 3-room	6	25.0
HDB 4-room	6	25.0
HDB 5-room	5	20.8
Maisonette, executive flats/condominium/landed	2	8.3
Others (nursing home)	3	12.5
Main caregiver		
Family members (parents, siblings, spouse, children, daughter-in-law)	6	25.0
Domestic helper	7	29.2
Family & helper	6	25.0
Others (self, friend, nursing home [n = 3])	5	20.8
Primary diagnosis		
Ventilatory muscle disorders*	14	58.4
Tetraplegia	2	8.3
Restrictive lung disease	2	8.3
Others†	6	25.0
Route of ventilation		
Tracheostomy	12	50.0
Non-tracheostomy	11	45.8

ED: Emergency department; HDB: Housing and Development Board; HMV: Home mechanical ventilation; ITE: Institute of Technical Education; SD: Standard deviation

*Neuromuscular disorder (n = 7); Duchene muscular dystrophy (n = 3); Amyotrophic lateral sclerosis (n = 4).

†Anterior spinal cord infarct (n = 1); Becker's musculodystrophy (n = 1); Congenital hypomyelinating disease (n = 1); Mitochondrial myopathy (n = 1); Prolonged ventilation for aspiration pneumonia (n = 1); Spinal muscular atrophy (n = 1).

‡High SRI values indicate better health-related quality of life (HRQoL).

Table 1. Characteristics of the Study Participants (Cont'd)

Categorical Variables	**Mean (SD)**	**Range**
Age	53.2 (16.2)	27 – 78
Charlson-Age Comorbidity Index (CACI)	1.7 (1.5)	0 – 6
Duration of HMV (months)	22.3 (31.5)	0.6 – 116
Hours of HMV per day	15.1 (9.8)	1 – 24
ED attendance past 6 months	0.23 (0.5)	0 – 1
Admissions past 6 months	0.4 (0.6)	0 – 2
Severe Respiratory Insufficiency (SRI) Domain Score‡	**Mean (SD)**	**Range**
Summary score (SS)	56.3 (15.3)	21.8 – 83.5
Respiratory complaints (RC)	70.7 (19.4)	31.3 – 100.0
Physical functioning (PF)	38.5 (20.7)	0.00 – 75.0
Attendant symptoms and sleep (AS)	62.2 (18.2)	35.7 – 100
Social relationship (SR)	61.5 (19.7)	16.7 – 95.8
Anxiety (AX)	60.6 (20.7)	15.0 – 100.0
Psychological well-being (WB)	53.4 (22.8)	5.6 – 86.1
Social functioning (SF)	47.4 (26.3)	9.4 – 100.0

ED: Emergency department; HDB: Housing and Development Board; HMV: Home mechanical ventilation; ITE: Institute of Technical Education; SD: Standard deviation

*Neuromuscular disorder (n = 7); Duchene muscular dystrophy (n = 3); Amyotrophic lateral sclerosis (n = 4).

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‡High SRI values indicate better health-related quality of life (HRQoL).

Table 2. Comparison of SRI

Authors, Place of Care	**Disease Type**	**Sample Size**	**Mean Age**	**Average Use Per Night (Hour)**	**SRI Scores [Mean (SD)]**							
						Biophysical Domain			**Psychosocial Domain**			
					SS	**RC**	**PF**	**AS**	**SR**	**AX**	**WB**	**SF**
Windisch et al,* home	All	82	-	7.3 (2.7)	61 (16)	-	-	-	-	-	-	-
Lopez et al,† home	All	115	62 (14)	8.6 (3.2)	57.8 (18.5)	61.2 (22.1)	43.2 (26.7)	60.9 (21.6)	76.7 (17.2)	55.9 (24.8)	58.3 (22.7)	54.9 (25.8)
Ghosh et al,‡ hospital	All	152	-	8.4 (3.8)	55.9 (18.9)	52.7 (20.9)	42.2 (22.3)	56.8 (20.5)	70.6 (21.4)	52.3 (27.2)	59.5 (21.3)	60.6 (24.4)
HVRSS, home	All	24	53	15	56.3 (15.3)	70.7 (19.4)	38.5 (20.7)	62.2 (18.2)	61.5 (19.7)	60.6 (20.7)	53.4 (22.8)	47.4 (26.3)

AS: Attendant symptoms and sleep (of SRI); AX: Anxiety (of SRI); HVRSS: Home ventilation and respiratory support service; PF: Physical functioning (of SRI); RC: Respiratory complaints (of SRI); SD: Standard deviation; SF: Social functioning (of SRI); SR: Social relationship (of SRI); SRI: Severe respiratory insufficiency; SS: Summary score (of SRI); WB: Psychological well-being (of SRI)

*Windisch W; Quality of life in home mechanical ventilation study group. Impact of home mechanical ventilation on health-related quality of life. Eur Respir J 2008;32:1328-36.

†López-Campos JL, Failde I, Masa JF, Benítez-Moya JM, Barrot E, Ayerbe R, et al. Factors related to quality of life in patients receiving home mechanical ventilation. Respir Med 2008;102:605-12.

‡Ghosh D, Rzehak P, Elliott MW, Windisch W. Validation of the English Severe Respiratory Insufficiency Questionnaire. Eur Respir J 2012;40:408-15.

A systematic review[11] reported that fewer than half of ventilator-assisted individuals (VAIs) were actively employed, and many caregivers had to reduce or quit work hours to enable care for VAIs. It also highlighted burden in the domains of financial strain, negative impact on employment, and insufficient time for oneself and personal relationships. Despite this, if given a second chance, 80% of caregivers would choose HMV again for their loved ones. In our cohort, 75% were unemployed. Slightly more than half (54%) indicated that they would choose to go on HMV again if they were to be given a second chance.

Strengths and Limitations

To our knowledge, this is the first study of its kind in multiethnic Asian patients. Our study suffered from a lack of statistical power due to its small sample size. Our small sample may not be representative of the population of patients managed by HVRSS. Clinically stable patients who were well adapted to HMV were invited to participate in our study. Sampling and responder bias could potentially confound the results as those who responded to the survey may be different to the rest of the study population. Caution should be exercised in generalising the data.

The inclusion of a concomitant generic HRQoL instrument, such as the SF-36, would have allowed for comparison to other chronic disease groups. However, we felt that its inclusion may add unnecessary burden on the study participants in a cohort with high degrees of disability, and compromise the feasibility this pilot study.

Given the low prevalence of HMV, future studies could look into collaboration with other Asian centres to improve statistical power. HRQoL changes over time could be tracked using longitudinal data.

Conclusion

HMV patients have fairly good overall HRQoL and optimal medical care. Non-invasive ventilation was associated with better social relationship and social functioning. More could be done about psychosocial well-being to enhance HRQoL.

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REFERENCES

1. Windisch W; Quality of life in home mechanical ventilation study group. Impact of home mechanical ventilation on health-related quality of life. Eur Respir J 2008;32:1328-36.
2. Hannan LM, Dominelli GS, Chen YW, Darlene Reid W, Road J. Systematic review of non-invasive positive pressure ventilation for chronic respiratory failure. Respir Med 2014;108:229-43.
3. Budweiser S, Hitzl AP, Jörres RA, Schmidbauer K, Heinemann F, Pfeifer M. Health-related quality of life and long-term prognosis in chronic hypercapnic respiratory failure: a prospective survival analysis. Respir Res 2007;8:92.
4. López-Campos JL, Failde I, Masa JF, Benítez-Moya JM, Barrot E, Ayerbe R, et al. Factors related to quality of life in patients receiving home mechanical ventilation. Respir Med 2008;102:605-12.
5. Low LL, Adrian Tan KH, Farhad F Vasanwala. Collaboration between Two Restructured Hospitals' Family Physician-led Transitional Home Care Teams in the Provision of Home Ventilation Respiratory Support. Proceedings of Singapore Healthcare 2014;23:Number 2.
6. Testa MA, Simonson DC. Assessment of quality of life outcomes. N Engl J Med 1996;334:835-40.
7. Ghosh D, Rzehak P, Elliott MW, Windisch W. Validation of the English Severe Respiratory Insufficiency Questionnaire. Eur Respir J 2012;40:408-15.
8. Akenroye MI, Osukoya AT. Permanent tracheostomy: its social impacts and their management in Ondo State, Southwest, Nigeria. Niger J Clin Pract 2013;16:54-8.
9. Singer S, Danker H, Bloching M, Kluge A, Schwenke J, Oeken J, et al. Perceived stigmatisation following laryngectomy. Psychother Psychosom Med Psychol 2007;57:328-33.
10. Hess DR. The growing role of non-invasive ventilation in patients requiring prolonged mechanical ventilation. Respir Care 2012;57:900-18.
11. MacIntyre EJ, Asadi L, Mckim DA, Bagshaw SM. Clinical outcomes associated with home mechanical ventilation: a systematic review. Can Respir J 2016;2016:6547180.

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Occult Acetabular Fractures in the Elderly: A Report of Three Cases and Review of Literature

Dear Editor,

Occult acetabular fractures are uncommon injuries.[1] Whilst acetabular fractures are often the result of high-energy trauma,[2] injuries of varying energy may result in occult acetabular fractures. In the elderly with osteoporosis, they can present with such fractures from low-energy injuries[3] or even in situations with no discernible history of trauma. The elderly may also present with pre-existing arthritis of the hip joint and this can confound the clinical presentation of an occult acetabular fracture. In patients with persistent hip pain especially on weight-bearing, radiographic imaging is indicated. Despite the efficacy of radiographs in the detection of acetabular fractures, occult acetabular fractures are not visible on radiographs and require further imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) scans for diagnosis.[4,5] In addition, advanced imaging can serve to differentiate exacerbated arthritic pain from that of an occult fracture. Occult acetabular fractures are often not displaced and therefore non-surgical treatment can be considered.

For the purpose of this review, we defined occult acetabular fractures to be those that cannot be diagnosed with plain radiographs (including specialised radiograph views such as Judet's view), even on retrospective viewing. We describe 3 cases of occult acetabular fractures in the elderly (65 years and above) as a result of varying mechanisms of injury and reviewed existing literature. Of the 15 cases of occult acetabular fractures found in existing literature, only 10 met our definition (Table 1). The remaining 5 fractures were seen on retrospective viewing of initial radiographs. These injuries are often difficult to diagnose and require a high degree of suspicion as well as judicious use of advanced imaging. This paper thus seeks to discuss the clinical presentation, imaging findings, treatment modalities and outcomes of occult acetabular fractures.

Case Reports

Case 1

An 82-year-old male with hypertension and hyperlipidaemia presented with sudden onset of left hip pain for 2 days. Prior to presentation, the patient was community-ambulant without aid. There was no history of trauma. The hip pain occurred on weight-bearing but resolved on rest. On examination, there was full range of motion of the left hip. Axial loading reproduced the pain. Pelvic and hip radiographs (Fig. 1a) did not reveal any fractures. In view of the persistent pain, an MRI of the left hip (Fig. 1b) was performed on post admission day 2. The MRI revealed a non-displaced fracture of the anterior column of the left acetabulum. His bone mineral density was measured using dual energy X-ray absorptiometry (DEXA), which showed a T-score of -2.3 (femur) and -0.6 (lumbar spine). His vitamin D levels were low at 17.7 g/dl.

As the acetabular fracture was non-displaced and over a non-weight-bearing portion of the acetabulum, the patient was treated non-surgically. He was advised not to weight bear on the left lower limb for 1 month. A Judet's view of his pelvis (Figs. 1c and 1d) was performed 1 month after the MRI of his pelvis and since no definite fracture line was seen, he was subsequently allowed to weight bear as tolerated. For his osteopaenia, he was treated with vitamin D replacement and bisphosphonate therapy. One year after the injury, the patient was well and ambulating without aid.

Case 2

A 65-year-old lady with multiple comorbidities such as diabetes mellitus type 2, hypertension, hyperlipidaemia and hypothyroid on thyroxine replacement, presented to the emergency department after a road traffic accident. She was the front seat passenger of a car that collided into a pillar. After the accident, the patient complained of persistent left hip pain. Whilst she was still able to ambulate, the hip pain was exacerbated on weight-bearing.

On examination, there was full range of motion of the left hip. There was palpable tenderness over the posterior aspect of the left hip. Pelvic radiographs did not reveal any fractures. An MRI of her left hip (Fig. 2a) showed a non-displaced fracture of the posterior column of the acetabulum and a non-displaced Pipkin classification type IV femoral head fracture. She was managed non-surgically with wheelchair mobilisation. At the 2-month follow-up, the pelvic radiograph (Fig. 2b) showed sclerosis over the posterior acetabulum, suggestive of a healing fracture. She eventually recovered fully and was able to ambulate independently.

Table 1. Existing Literature for Occult Acetabular Fractures

References (Country/ Year of Publication)	Demographics (Age/Gender)	Mechanism of Injury	Fracture Configuration	Diagnostic Modality	Treatment	Outcome
Guerado et al* (Spain/2012)	75/F	No trauma	Transverse	Healing fracture seen on interval X-ray (2 months)	Cemented THA	Ambulation with aids
	83/F	No trauma	Anterior column	Healing fracture seen on interval X-ray (2 months)	Non-surgical with non-weight bear for 2 weeks	Ambulation with aids
Mouzopoulous et al† (Greece/2008)	28/M	RTA	Anterior column	CT	Non-surgical with traction for 6 weeks	Return to premorbid
Kakar et al‡ (UK/2007)	85/F	Fall	Anterior column and posterior wall	CT	Non-surgical with non-weight bear for 6 weeks	Ambulation with aids
	69/F	Fall	Transverse	MRI	Weight bear as tolerated with aids	Ambulation with aids
	69/F	Fall	Medial wall fracture	Healing fracture seen on interval X-ray	No information available	No information available
Thomas et al§ (USA/2006)	79/M	Jogging	Supra-acetabular fracture	MRI and CT	Cemented THA	Return to premorbid
Schachter et al‖ (USA/2003)	65/F	RTA	Transverse	CT	Non-surgical with traction for 6 weeks	Ambulation with aids
Olive et al¶ (USA/1989)	71/F	RTA	Anterior column	Central fracture dislocation seen on interval X-ray	Cemented THA	Satisfactory hip at 1-year
Rogers et al# (USA/1975)	23/F	RTA	Central	Tomography	No information available	No information available

CT: Computed tomography; F: Female; M: Male; MRI: Magnetic resonance imaging; RTA: Road traffic accident; THA: Total hip arthroplasty; UK: United Kingdom; USA: United States of America

*Guerado E, Cano JR, Cruz E. Occult acetabular fracture in elderly patients. The Open Orthop J 2012;6:582-6.

†Mouzopoulos G, Lasanianos N, Mouzopoulos D, Tzurbakis Mathaios, Georgilas I. Occult acetabular fracture. A case report. Emerg Radiol 2008;15:437-9.

‡Kakar R, Sharma H, Allcock P, Sharma P. Occult acetabular fractures in elderly patients: a report of three cases. J Orthop Surgery (Hong Kong) 2007;15:242-4.

§Thomas M. Occult acetabular fracture in an elderly runner. J Orthop Sports Phys Ther 2006;36:415-24.

‖Schachter AK, Roberts CS, Seligson D. Occult bilateral acetabular fractures associated with high-energy trauma and osteoporosis. J Orthop Trauma 2003;17:386-9.

¶Olive RJ Jr, Marsh HO. Occult central acetabular fracture resulting in fracture-dislocation. A case report. Clin Orthop Relat Res 1989;248:240-5.

#Rogers LF, Novy SB, Harris NF. Occult central fractures of the acetabulum. AJR Am J Roentgenol 1975;124:96-101.

Case 3

A 76-year-old nursing home resident with known hypertension and a previous lumbar 1 and 2 compression fracture (but not on bisphosphonates), fell whilst trying to transfer from the bed to wheelchair. He had right hip pain and was unable to ambulate thereafter. His right hip was tender on examination and range of motion was limited by pain. Plain radiographs of the hip did not show any fracture. MRI of the right hip (Fig. 3) was performed in view of the persistent pain and revealed a non-displaced right subcapital neck of femur fracture as well as a non-displaced fracture of the anterior column of the acetabulum. He was treated conservatively in view of his premorbid status with wheelchair mobilisation for 6 weeks. After being discharged back to his nursing home, he defaulted any subsequent follow-up, hence no repeat radiographs were taken after admission. On phone consultation with his son 2 years after his injury, the patient's right hip was pain-free and he was able to return to his premorbid state.

Discussion

Occult acetabular fractures can result from varying mechanisms of injury, ranging from high-impact trauma to low-energy injuries. Low-energy injuries can result in occult acetabular fractures in the elderly, on the background of osteoporosis.[6] Whilst the literature review revealed 15 occult acetabular fractures in 8 published English literature, only 10 of these cases were truly occult.[7-13] It is important

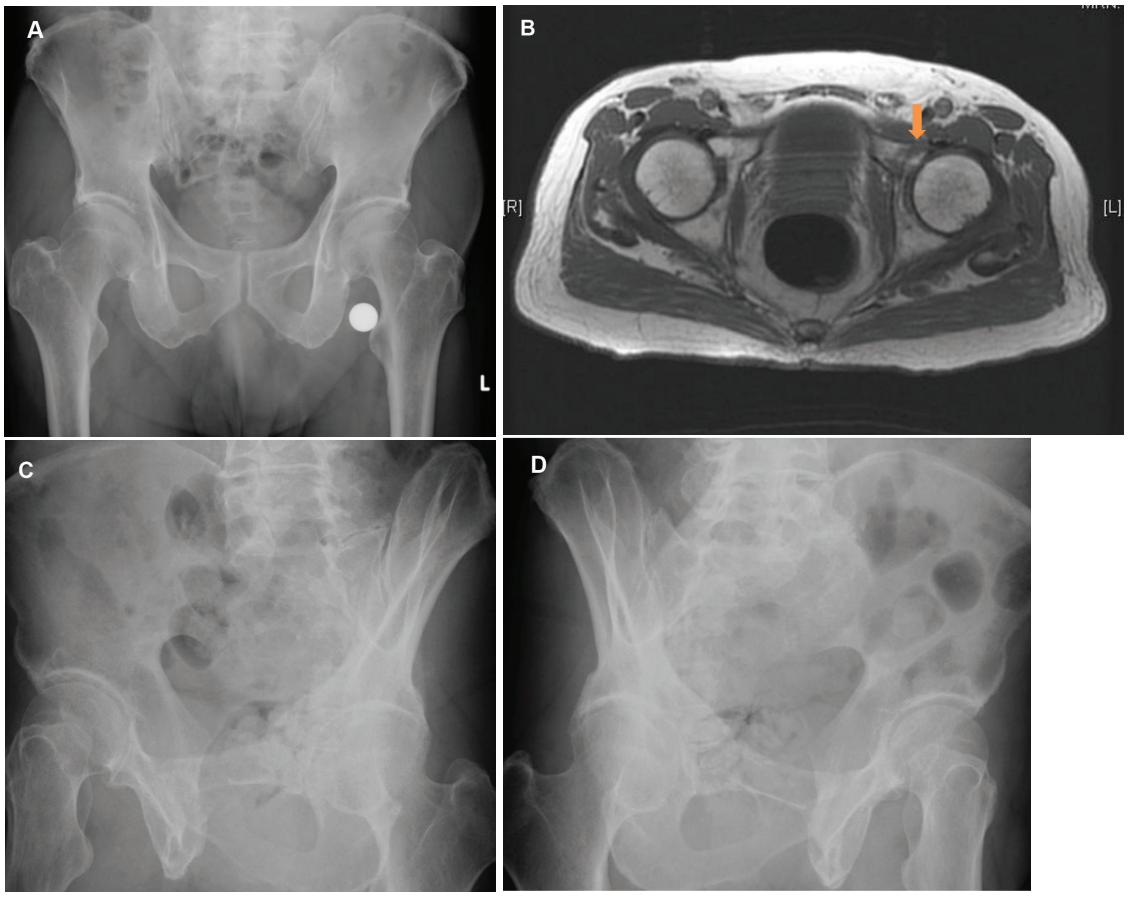

Fig. 1. Imaging of Patient 1. In A, no fracture is revealed in anteroposterior pelvis X-ray of patient performed on the day of admission. In B, MRI scan of the pelvis of patient performed 2 days after admission, showing a non-displaced fracture of the anterior column of the left acetabulum. In C and D, Judet's view of the pelvis of patient performed 1 month after MRI of his pelvis. No definite fracture line was seen.

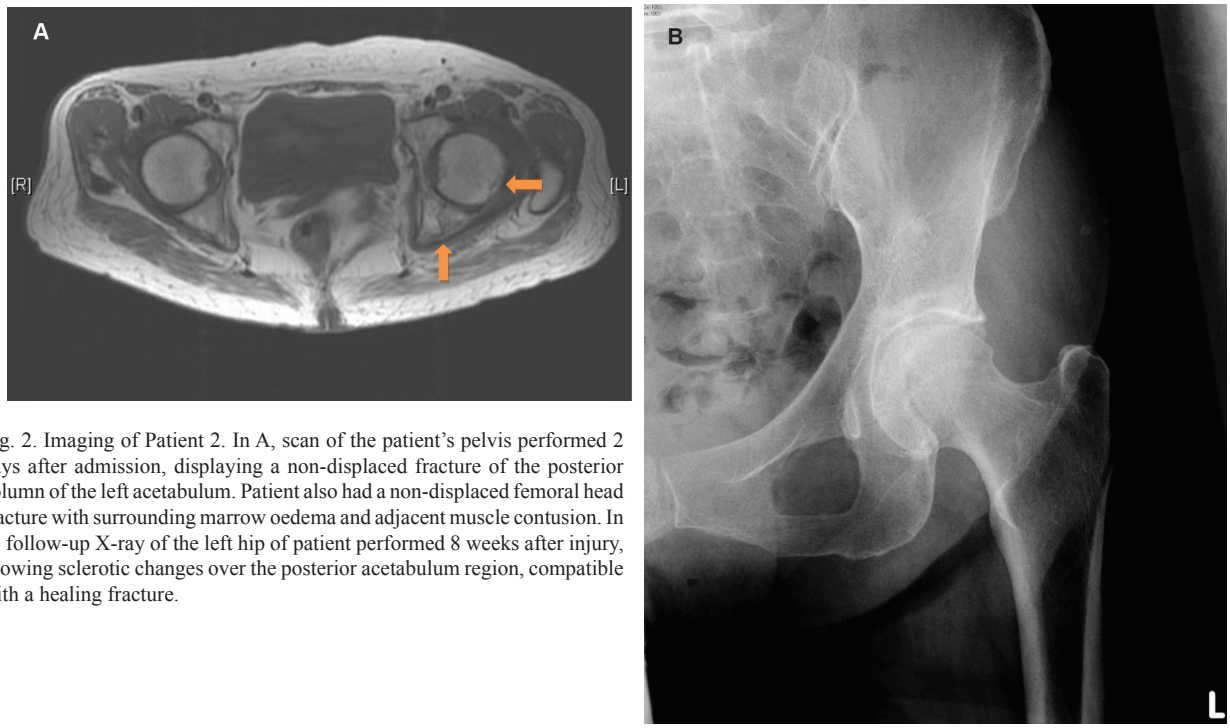

Fig. 2. Imaging of Patient 2. In A, scan of the patient's pelvis performed 2 days after admission, displaying a non-displaced fracture of the posterior column of the left acetabulum. Patient also had a non-displaced femoral head fracture with surrounding marrow oedema and adjacent muscle contusion. In B, follow-up X-ray of the left hip of patient performed 8 weeks after injury, showing sclerotic changes over the posterior acetabulum region, compatible with a healing fracture.

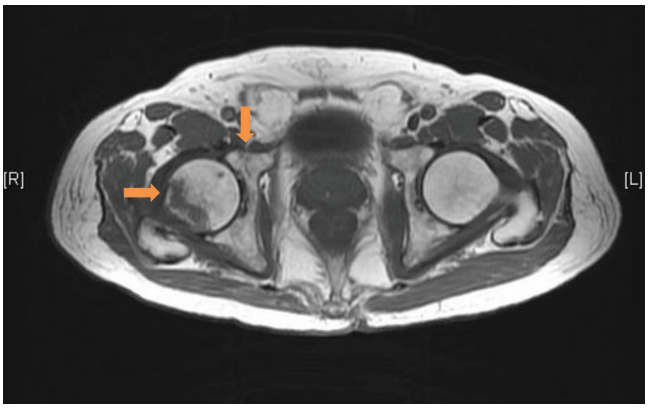

Fig. 3. MRI scan of the pelvis of Patient 3, showing a non-displaced fracture of the anterior column of the right acetabulum. There is also a right non-displaced sub-capital neck of femur fracture with surrounding bone and soft tissue oedema.

to have a high level of suspicion in patients who present with persistent hip pain as an undiagnosed occult acetabular fracture may result in propagation of the fracture on weight-bearing with worsening morbidity.

The clinical presentation of occult acetabular fractures can be non-specific. Patients often complain of persistent hip or groin pain, which may occur after trivial injury. The pain is mechanical in nature and is exacerbated on weight-bearing. Physical examination may be unremarkable. When lying supine with no physiological loading of the hip joint, patients may be pain-free even on ranging of the affected hip. This may be a subtle difference from occult proximal femoral fractures, which can produce pain during rotation of the femur. As such, axial loading of the joint is an important manoeuvre. Even in the absence of other positive findings, this manoeuvre may reproduce pain in the occult acetabular fracture. In addition, these patients may be unable to weight bear and ambulate due to pain. In the elderly, exacerbation of degenerative arthritis of the hip after minor trauma should also be considered. Whilst the history of these patients often reveals long-standing mechanical pain of the affected hip, clinical examination may be inconclusive. Plain radiographs can reveal definitive features of hip arthritis such as joint space narrowing, osteophyte formation, subchondral sclerosis and cyst formation. In contrast, plain radiographs have a limited role in the diagnosis of occult acetabular fractures.[14] Antero-posterior pelvis X-rays may not reveal any findings but can be helpful in ruling out other injuries that may account for the pain. Judet's views are traditionally used to detect acetabular fractures. These specialised views project oblique fracture lines perpendicularly to X-ray beams, thus allowing easier visualisation of acetabular fractures.[14] Judet's views cannot rule out occult acetabular fractures. As such, physicians should have a low threshold for advanced imaging if patients complain of persistent hip pain, even with normal plain radiographs.

CT and MRI have both been shown to be effective in detecting occult fractures but there is no clear superiority of either modality in detecting occult acetabular fractures. CT scans have been found to be more sensitive than plain radiography in detecting fractures of the acetabular roof and of the posterior lip.[15] CT scans not only allow for diagnosis of occult fractures, but have the added benefit of precise delineation of fracture patterns, which may be helpful for preoperative planning. Finally, CT scans have the advantage of a quicker examination time and thus are often more readily available than other forms of advanced imaging. MRI too has been shown to be an effective diagnostic modality in detecting occult fractures.[16] MRI has the advantage of eliminating the need for ionising radiation to the patient and possesses the ability to detect concomitant soft tissue injuries that may be contributing to pain. MRI can also detect bone oedema, which may indicate the presence of non-displaced or insufficiency fracture. There is currently limited evidence comparing the role of both modalities in the diagnosis of occult acetabular fractures. Chatha et al[4] conducted a systematic review and found that MRI was superior to CT scan in accurately diagnosing occult proximal femur fractures. Furthermore, it was noted that for patients whom had their MRI scans done within 48 hours, senior radiologists achieved up to 100% accurate results.[17] Given these findings, the authors suggest that in the clinical setting of a suspected occult fracture of the hip, physicians should obtain MRI scans early and both the proximal femur and acetabulum regions should be inspected carefully to ensure no occult fracture is missed. Other significant soft tissue injuries should also be identified. Should an occult acetabular fracture be diagnosed, the physician can then proceed to obtain a CT scan to assist in fracture delineation and preoperative planning if surgical intervention is being considered. Utilising CT scans as the initial investigation can be performed for patients who have contraindications to MRI scans or in situations where obtaining an MRI scan would result in a significant delay.

Acetabular fracture configurations vary with the mechanism of injury. Letournel et al[18] suggested that fractures involving the anterior acetabulum result from a force applied to the greater trochanter in the axis of the femoral neck. This is consistent with a higher incidence of anterior acetabulum fractures reported in elderly patients, as compared to the younger population, who are more likely to suffer impact to their greater tronchanter following a fall onto their side.[18] This fracture configuration is consistent with the history of a fall in case 3.

It is important to diagnose an occult acetabular fracture early. Low-energy acetabular fractures have a 1-year

mortality of up to 13.9%.[19] Disruption in the congruency of the joint lines can predispose patients to early osteoarthritis. Older patients are also likely to have more comorbidities resulting in a higher risk for surgery. Furthermore, open reduction and internal fixation of displaced acetabular fractures has been considered to be technically more difficult or results in poorer outcomes, especially in elderly patients or those with osteoporotic bones.[20]

The management of acetabular fractures are both patient and fracture dependent, especially in the elderly population. Due consideration to the comorbidities and pre-injury ambulatory status should be given to the elderly patient who suffers an occult acetabular fracture. Elderly patients who are ambulatory prior to presentation should be evaluated fully with advanced imaging so as to diagnose possible occult fractures. This is important as without eliminating a possible occult fracture, these patients would be subject to unnecessary weight-bearing restrictions and its associated risks of prolonged recumbence. Historically, non-operative management of acetabular fractures in the geriatric population have yielded poor results.[8] However, Butterwick et al[9] found that elderly, low-demand patients with acetabular fractures can be managed conservatively and have acceptable functional outcomes if the hip joint exhibits secondary congruence. As such, in elderly patients who are low-demand, conservative treatment of occult acetabular fractures are a viable option.

In terms of fracture configuration, Magu et al[10] performed a retrospective analysis of 69 patients with 71 displaced acetabular fractures who were treated conservatively. Using the Merle d'Aubigne and Postel score to assess functional outcome, Magu concluded that patients who sustain posterior wall, posterior column, anterior column, infratectal transverse and even both column fractures can be treated conservatively and still have good functional outcomes as long as the joint is congruent. Transtectal transverse or T-shaped fractures presenting with the "V" sign should however be managed operatively. Grubor et al[11] recommended surgical fixation in incongruent or unstable acetabular fractures with more than 5 mm displacement of the fracture fragments.

In the literature reviewed, information regarding treatment for 2 patients was not available, whilst 6 out of the 8 (75%) remaining patients were treated non-surgically and all of these patients were eventually able to return to ambulation. Due to the rarity of these injuries, no comparison between surgical and non-surgical treatment has ever been conducted. However, occult acetabular fractures are often not displaced and thus it is likely that these fractures will heal well and patients will still have good functional outcomes even without surgical treatment.

Conclusion

Occult acetabular fractures are rare. These injuries can occur after low-energy trauma in the elderly. Physicians should maintain a high level of suspicion in patients who present with persistent hip pain despite normal radiographs, especially if there is pain on axial loading of the hip. MRI scans should be performed early if occult fractures are suspected. Adequate attention should be placed on the acetabulum when reviewing imaging for occult fractures. There is a role for conservative treatment in low-demand elderly patients whose acetabular fractures display congruence of the joint and less than 5 mm displacement of the fracture fragments.

REFERENCES

1. Rommens PM, Hessmann MH, Gercek E. An unexpected pelvic and acetabular fracture. Osteo Trauma Care 2002;10:50-3.
2. Alonso JE, Volgas DA, Giordano V. A review of the treatment of hip dislocations associated with acetabular fractures. Clin Orthop 2000;377:32-43.
3. Ullom-Minnich P. Prevention of osteoporosis and fractures. Am Fam Physician 1999;60:194-202.
4. Chatha H, Ullah S, Cheema Z. Review Article: Magnetic resonance imaging and computed tomography in the diagnosis of occult proximal femur fractures. J Orthop Surgery (Hong Kong) 2011;19:99-103.
5. Rogers LF. Occult is a matter of definition. AJR Am J Roentgenol 1999;172:283.
6. Vanderschot P. Treatment options of pelvic and acetabular fractures in patients with osteoporotic bone. Injury 2007;38:497-508.
7. Rogers LF, Novy SB, Harris NF. Occult central fractures of the acetabulum. AJR Am J Roentgenol 1975;124:96-101.
8. Matta JM, Anderson LM, Epstein HC, Hendricks P. Fractures of the acetabulum. A retrospective analysis. Clin Orthop Relat Res 1986;205:230-40.
9. Butterwick D, Papp S, Gofton W, Liew A, Beaule PE. Acetabular fractures in the elderly. J Bone Joint Surg Am 2015;97:758-68.
10. Magu NK, Rohilla R, Arora S. Conservatively treated acetabular fractures: a retrospective analysis. Indian J Orthop 2012;46:36-45.
11. Grubor P, Krupic F, Biscevic M, Grubor M. Controversies in treatment of acetabular fracture. Med Arch 2015;69:16-20.
12. Guerado E, Cano JR, Cruz E. Occult acetabular fracture in elderly patients. The Open Orthop J 2012;6:582-6.
13. Mouzopoulos G, Lasanianos N, Mouzopoulos D, Tzurbakis Mathaios, Georgilas I. Occult acetabular fracture. A case report. Emerg Radiol 2008;15:437-9.
14. Beaule PE, Dorey FJ, Matta JM. Letournel classification for acetabular fractures assessment of interobserver and intraobserver reliability. J Bone Joint Surg Am 2003;85:1704-9.
15. Harley JD, Mack LA, Winquist RA. CT of acetabular fractures: comparison with conventional radiography. AJR Am J Roentgenol 1982;138:413-7.

16. Frihagen F, Nordsletten L, Tariq R, Madsen JE. MRI diagnosis of occult hip fractures. Acta Orthop 2005;76:524-30.
17. Verbeeten KM, Hermann KL, Hasselqvist M, Lausten GS, Joergensen P, Jensen CM, et al. The advantages of MRI in the detection of occult hip fractures. Eur Radiol 2005;15:165-9.
18. Letournel E, Judet R, Elson R. Fractures of the acetabulum. 2nd edition. Berlin: Springer-Verlag;1993. p. 733.
19. Gary JL, VanHal M, Gibbons SD, Reinert CM, Starr AJ. Functional outcomes in elderly patients with acetabular fractures treated with minimally invasive reduction and percutaneous fixation. J Orthop Trauma 2012;26:278-83.
20. Papadakos N, Pearce R, Bircher MD. Low energy fractures of the acetabulum. Ann R Coll Surg Engl 2014;96:297-301.

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Recap of the Knee Cap: A "Leave Alone" Lesion

A 13-year-old male with no past medical history presented with anterior left knee pain for 1 year. He had been playing rugby regularly for the past 1 year. There was no history of trauma, although the pain was worse with physical activity. Physical examination revealed mild tenderness at the superior pole of the patella. Frontal radiograph of the left knee (Fig. 1A), skyline radiograph of both knees (Fig. 1B) and magnetic resonance imaging (MRI) of the left knee (Fig. 2) are provided. What is the diagnosis?

A. Chondroblastoma
B. Brodie's abscess
C. Osteochondritis dissecans
D. Dorsal defect of the patella
E. Metastasis

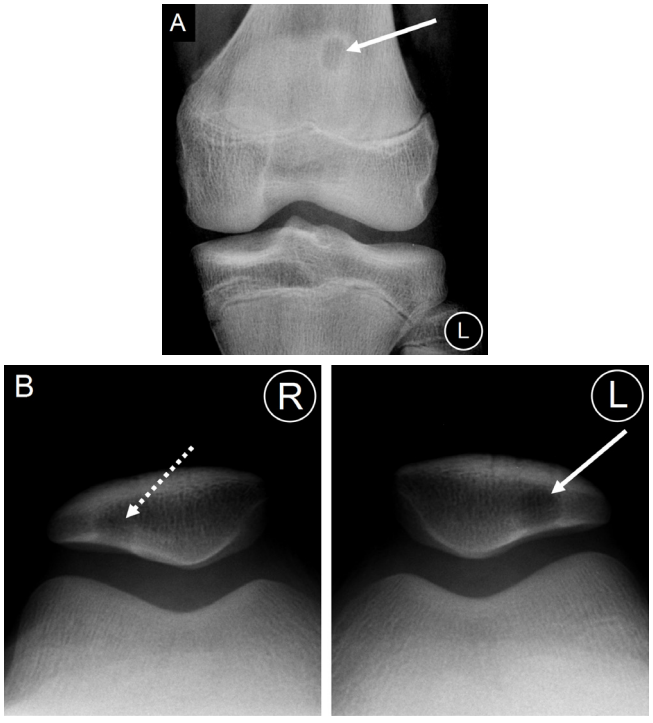

Fig. 1. Frontal radiograph of the left knee (A) and skyline radiographs of both knees (B).

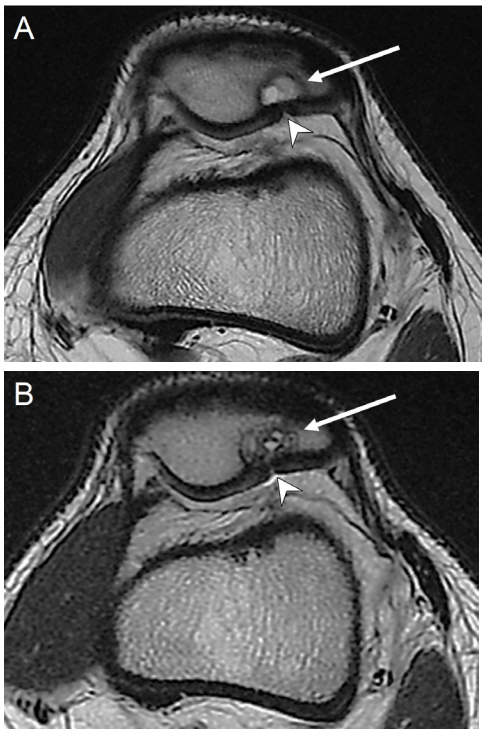

Fig. 2. Axial T2W images of the left knee at the time of presentation (A) and at follow-up MRI 1 year later (B).

Findings and Diagnosis

The frontal (Fig. 1A) and skyline (Fig. 1B) radiographs demonstrate an 8 mm, well defined, ovoid, lucent lesion with a narrow zone of transition (solid arrow) at the dorsal superolateral pole of the left patella. There is a thin sclerotic rim with no matrix calcification. Radiographic features are non-aggressive with no periosteal reaction, cortical break or pathological fracture. A similar lesion (dashed arrow) is seen at the right patella on the skyline radiograph (Fig. 1B). On MRI (Fig. 2A), the lesion corresponds to a well defined, subchondral osseous defect (solid arrow), which is T2W-hyperintense to cartilage with no surrounding marrow oedema. There is an overlying full-thickness chondral fissure (arrowhead). The chondral surfaces are otherwise smooth and no other abnormality is noted. Imaging features (dorsal

Answer: D

superolateral location, non-aggressive imaging features and bilaterality) are consistent with a dorsal defect of the patella (DDP).

The patient defaulted subsequent follow-up. He re-presented a year later with persistent anterior knee pain, now involving both knees, for which MRI was performed. In the left knee (Fig. 2B), the subchondral defect now shows intermediate signal (solid arrow) suggestive of in-filling of reparative tissue but remains stable in size. The overlying chondral fissure (arrowhead) is stable. In the right knee (Fig. 3A), there is a similar lesion (solid arrow) with overlying chondral fissure (arrowhead), although marrow oedema (dashed arrow, Figs. 3B and 3C) is also noted around the subchondral defect. The patient's symptoms improved with conservative treatment, which comprised physiotherapy and activity modification.

Discussion

DDP is an unusual condition (0.3%-1.0% of the population) first described by Caffe and Keats in the early 1970s.[1-4] It is most frequently seen in the second decade of life with no gender predilection, and is bilateral in up to one-third of cases.[1,3-5] It manifests as a well defined lucency with sclerotic rim at the superolateral patella on radiographs, and is often incidentally discovered during the evaluation of knee pain or injury.[1-6] Similar features of dorsal subchondral location, sclerotic border and well defined margins can be demonstrated to greater detail on CT.[2,7,8] Its origin is unclear, but most believe that it relates to anomalous ossification, akin to the formation of a multi-partite patella.[1,3,4] Both DDP and accessory ossification centres, eg. bipartite patella, are found at the superolateral quadrant of the patella.[2,3] At this location, strong traction at the vastus lateralis muscle insertion may also play a contributory role by causing chronic stress-related changes, with deformity in the cartilaginous precursor and subsequent delay in ossification.[3,9] This is supported by the increased tendency to lateral patellar subluxation seen in some patients.[3,5,10] Histopathology shows a non-specific mixture of woven bone, fibrovascular tissue and debris with no evidence of inflammation or neoplasm.[4,5,10,11] It is asymptomatic in most patients and recognised as one of the classic "do not touch" lesions in radiology, typically with no need for further invasive diagnostic or therapeutic procedures.[1,4,5]

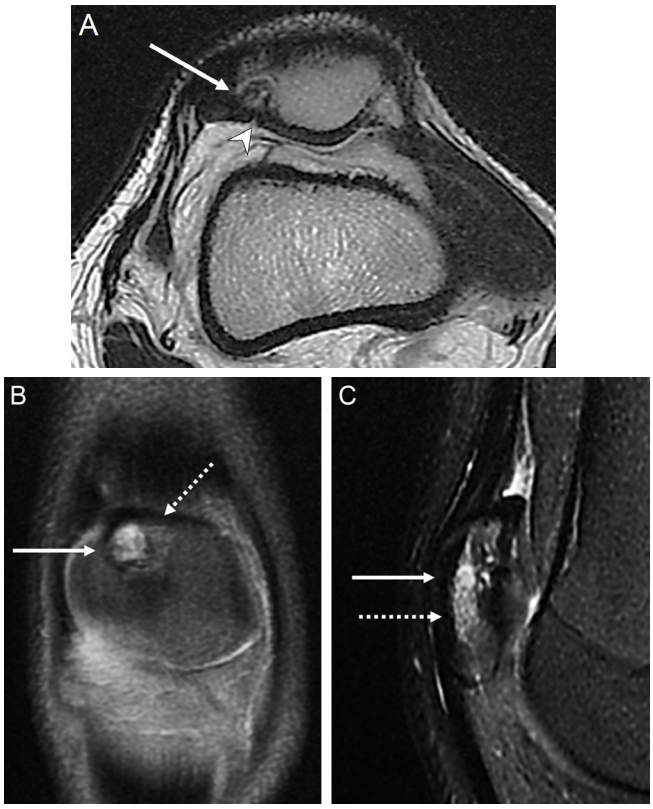

Fig. 3. Axial T2W image of the right knee (A). Coronal fat-suppressed PD-weighted (B) and sagittal fat-suppressed T2W (C) images of the right knee demonstrate marrow oedema (dashed arrows) around the subchondral defect (arrow).

Initial reports of DDP described intact overlying cartilage.[1,4,6,12] However, with the advent of MRI, there have been reports of overlying chondral abnormalities with DDP, ranging from chondral thickening and inhomogeneity with hyperintense streaks, invagination of cartilage into the subchondral defect, to chondral fissures.[5,7,8,10,12] These chondral abnormalities appear to be associated with anterior knee pain, such as in our case, and have been correlated with chondromalacia on arthroscopy.[5,7,8,10,12] In selected patients with persistent symptoms, or when the diagnosis is unclear, arthroscopic curettage of DDP has been reported to show good results.[3,10-12] However, conservative therapy suffices for the vast majority of patients.[4,5,7,8]

Recently, Kwee et al reported a first case of bone marrow oedema on MRI associated with DDP.[13] It was thought that the development (and subsequent resolution) of oedema correlated with the patient's symptoms. In our patient, the presence of oedema appeared to be associated with symptoms in the right knee, although this was not the case on the left.

The natural history of DDP is spontaneous involution with sclerosis over a variable time course.[3-5] In their patient, Kwee et al demonstrated gradual "filling in" of the chondral defect on MRI over 8 months.[13] Similar findings were seen in our patient, in whom intermediate-signal reparative tissue appeared in the left-sided DDP after 1 year. This likely correlates with histological findings of fibrovascular connective tissue filling the defect in curettage specimens.[4,10,11] This may represent an earlier phase of the healing process, usually demonstrated on radiographs as

sclerotic involution.[3-5]

Differentials of DDP include osteochondritis dissecans, chondromalacia patellae, bone tumours such as chondroblastoma or enchondroma, and Brodie's abscess.[5] Distinction from these entities is usually possible due to the characteristic location of DDP, bilaterality (if present) and imaging and clinical features.[2,4,12] Osteochondritis dissecans usually occurs at the medial patellar facet and rarely at the superolateral aspect, and demonstrates an osteochondral fragment, which may be displaced.[4,5] Chondromalacia patellae also typically occurs on weight- or stress-bearing surfaces, although chondral abnormalities have been shown to occur with DDP as mentioned earlier.[5,7,8,12] Accurate characterisation of these findings is important due to implications on therapeutic intervention. Chondroblastomas commonly cause periosteal reaction and marked surrounding marrow and soft tissue oedema.[14] Enchondromas and Brodie's abscesses are rare in this location, with the former demonstrating intact overlying cartilage and the latter typically demonstrating intense uptake on radionuclide bone scans.[4,5]

Conclusion

DDP is one of the skeletal "do not touch" lesions. Recognition of this entity will help avoid unnecessary invasive diagnostic or therapeutic procedures. A minority of these patients may be symptomatic from the DDP, possibly related to associated chondromalacia or marrow oedema, but often respond well to conservative therapy. For these patients, MRI is useful in demonstrating any associated chondral defect or marrow oedema, and to exclude other concomitant pathology.

REFERENCES

1. Johnson JF, Brogdon BG. Dorsal effect of the patella: incidence and distribution. Am J Roentgenol 1982;139:339-40.
2. Ho VB, Kransdorf MJ, Jelinek JS, Kim CK. Dorsal defect of the patella: MR features. J Comput Assist Tomogr 1991;15:474-6.
3. van Holsbeeck M, Vandamme B, Marchal G, Martens M, Victor J, Baert AL. Dorsal defect of the patella: concept of its origin and relationship with bipartite and multipartite patella. Skeletal Radiol 1987;16:304-11.
4. Haswell DM, Berne AS, Graham CB. The dorsal defect of the patella. Pediatr Radiol 1976;4:238-42.
5. Safran MR, McDonough P, Seeger L, Gold R, Oppenheim WL. Dorsal defect of the patella. J Pediatr Orthop 1994;14:603-7.
6. Goergen TG, Resnick D, Greenway G, Saltzstein SL. Dorsal defect of the patella (DDP): a characteristic radiographic lesion. Radiology 1979;130:333-6.
7. Locher S, Anderson S, Ballmer FT. Noninvasive management of a dorsal patellar defect. Arch Orthop Trauma Surg 2002;122:466-8.
8. Mellado JM, Salvado E, Ramos A, Camins A, Sauri A. Dorsal defect on a multi-partite patella: imaging findings. Eur Radiol 2001;11:1136-9.
9. Ogden JA. Radiology of postnatal skeletal development. X. Patella and tibial tuberosity. Skeletal Radiol 1984;11:246-57.
10. Sueyoshi Y, Shimozaki E, Matsumoto T, Tomita K. Two cases of dorsal defect of the patella with arthroscopically visible cartilage surface perforations. Arthroscopy 1993;9:164-9.
11. Hunter LY, Hensinger RN. Dorsal defect of the patella with cartilaginous involvement. A case report. Clin Orthop Relat Res 1979:131-2.
12. Monu JU, De Smet AA. Case report 789: dorsal defect of the left patella. Skeletal Radiol 1993;22:528-31.
13. Kwee TC, Sonneveld H, Nix M. Successful conservative management of symptomatic bilateral dorsal patellar defects presenting with cartilage involvement and bone marrow edema: MRI findings. Skeletal Radiol 2016;45:723-7.
14. Weatherall PT, Maale GE, Mendelsohn DB, Sherry CS, Erdman WE, Pascoe HR. Chondroblastoma: classic and confusing appearance at MR imaging. Radiology 1994;190:467-74.

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