

Malaysian Family Physician

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Official Journal of the Academy of Family Physicians of Malaysia
and Family Medicine Specialist Association of Malaysia

2022 Volume 17 No. 1



- Development, validity and reliability of instrument to evaluate implementation fidelity of the Family Doctor Concept (FDC) programme in public primary care clinics in Malaysia
- Distribution of refractive error among chinese primary school children in a rural area in Pahang, Malaysia
- The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor



PP2089/12/2012 (031677)
ISSN :
1985-207X (Print)
1985-2274 (Electronic)



About MFP

The *Malaysian Family Physician* (MFP) is the official journal of the Academy of Family Physicians of Malaysia (AFPM). It is jointly published by the Family Medicine Specialist Association (FMSA) of Malaysia. The MFP is published three times a year. It also started an Online First section in January 2021, where accepted articles are published online ahead of the issue.

Goal: The MFP is an international journal that disseminates quality knowledge and clinical evidence relevant to primary care. The journal acts as the voice of family physicians, researchers and other members of the primary care team on clinical practice issues.

Scope: The MFP publishes:

- i. Research – Original Articles and Reviews
- ii. Education – Case Reports/Clinical Practice Guidelines/Test Your Knowledge. We only encourage case reports that have the following features:
 1. Novel aspects
 2. Important learning points
 3. Relevant to family practice
- iii. Invited debate, commentary, discussion, letters, online, comment, and editorial on topics relevant to primary care.
- iv. A Moment in the Life of a Family Physician – We encourage submission of a short narrative to share perspectives, voice, views and opinions about a family physician's experience that has affected their practice or life. This moment should be a reflective piece of fewer than 500 words in length.

Strength: MFP is the only primary care research journal in Malaysia and one of very few in the region. It is open access and fully online. The journal is indexed in Scopus and has a relatively fast review time. The journal has a strong editorial team and an established pool of readers with increasing recognition both locally and internationally.

Circulation: The journal is freely available online.

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Ethics

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3. Final approval of the version to be published.
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The **Malaysian Family Physician** welcomes articles on all aspects of family medicine in the form of original research papers, review articles, CPG review, case reports, test your knowledge and letters to the editor. The journal also publishes invited debate, commentary, discussion, letters, comment, and editorials on topics relevant to primary care.

Articles are accepted for publication on condition that they are contributed solely to the Malaysian Family Physician. Neither the Editorial Board nor the Publisher accepts responsibility for the views and statements of authors expressed in their contributions. All papers will be subjected to peer review. The Editorial Board further reserves the right to edit and reject papers. Authors are advised to adhere closely to the instructions given below to avoid delays in publication.

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 - **All figures, tables and illustrations are placed at the appropriate sections in the manuscript file** rather than at the end of the manuscript or submitted separately.
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 - Provide URLs for references where available.
 - Where available, URLs for the references have been provided.
3. The **Title Page** must be uploaded separately from the main manuscript file in Microsoft Word. Please refer to the required sub-headings in the Title Page section below.
4. A **Cover Letter** must be signed by the corresponding author on behalf of all authors. This letter must include this statement “this manuscript is my (our) own work, it is not under consideration by another journal, and this material has not been previously published.”
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7. When preparing your manuscript, please follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals recommended by the International Committee of Medical Journal Editors (<http://www.icmje.org/icmje-recommendations.pdf>).

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For all types of manuscript, please include all the sub-headings below in the Title Page:

- **Article Type:** Original Research / Review / CPG Review / Case Report / Test Your Knowledge / Letter To Editor
- **Title:** Please state the title in detail to include the study design, particularly for original research.
- **Author(s):** The full names, professional qualifications (limited to two only) and institutions of all authors.
- **Shortened name of author(s):** should be written in the style of surname or preferred name followed by initials, e.g. Abdullah KS, Rajakumar MK, Tan WJ, for future indexing.
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- **Funding:** Please state if the study was funded; if so, by which institution and the funding ID.
- **Ethical Approval:** Please state if the study was approved; if so, by which institution and the approval ID.
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MAIN MANUSCRIPT

For every article submitted, please follow the requirements according to the type of article.

Original Research (Including Clinical Audit Article)

The original research (including clinical audit) should be conducted in the primary care setting on a topic of relevance to family practice. Both qualitative and quantitative studies are welcome. The length should **not exceed 3000 words with a maximum of 5 tables or figures and 30 references**. Please include the following sub-headings in the manuscript:

1. **Title:** State the title based on PICO, including study design.
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3. **Keywords:** 3-5 keywords, preferably MeSH terms.
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10. **How does this paper make a difference in general practice?:** This section should be written in bullet points (up to five points) and must not exceed 100 words.
11. **References:** Refer to the References section below for more details.

Review

All types of review articles, including narrative review, scoping reviews and systematic reviews are accepted for publication in MFP. A comprehensive review of the literature with a synthesis of practical information for practising doctors is expected. For a systematic review, the PRISMA checklist (<https://www.equator-network.org/reporting-guidelines/prisma/>) must be followed. For a scoping review, the PRISMA-ScR checklist (<https://www.equator-network.org/reporting-guidelines/prisma-scr/>) should be followed. The length **should not exceed 4000 words with a maximum of 5 tables or figures and 40 references**. Please include the following sub-headings in the manuscript:

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7. **Discussion (*for systematic and scoping reviews):** This section is required for systematic and scoping reviews. Please follow the guideline in the PRISMA and PRISMA-ScR checklists.
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Case reports should preferably be less-commonly seen cases that have an educational value for practising doctors. Only case reports that are novel, have important learning points and relevant to family practice will be accepted for publication in this journal. The case report must be written in a **patient-centred manner instead of a disease-centred focus**. The length **should not exceed 1500 words and cite no more than 20 references**. Before submitting the case report, the authors must ensure that the patient's identity is protected both in the text and pictures. Please include the following sub-headings in the manuscript:

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The CPG should be relevant to primary care. Its length **should not exceed 4000 words and 40 references**. An abstract is required (no more than 300 words) together with the keywords. The CPG review should be written with case vignettes to illustrate its application in primary care practice.

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4. **Introduction:** Describe the condition and aim of the CPG review.
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6. **Key recommendations of the CPG:** Describe the key recommendations primary care doctors should know.
7. **Key changes in the CPG (only applicable for revised CPGs):** Describe the key changes or updates from the previous CPG.
8. **How to apply the CPG into practice in primary care?** Explain how the CPG can be used in primary care practice.
9. **Case vignettes as examples of application:** Use case vignettes to illustrate the application of the CPG.
10. **Conclusion:** Summarise the key learning points.
11. **Acknowledgements:** Acknowledge grants awarded in aid of the study and people who have contributed significantly to the study (but do not qualify for authorship).
12. **Conflicts of interest:** All authors must declare any conflicts of interest.
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14. **References:** Refer to the References section below for more details.

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A Test Your Knowledge article should be relevant to primary care and preferably be about less-commonly seen cases that have an educational value for practising doctors. The length **should not exceed 1000 words and no more than 20 references**. Please include the following sub-headings in the manuscript:

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7. **Acknowledgements:** Acknowledge grants awarded in aid of the study and people who have contributed significantly to the study (but do not qualify for authorship).
8. **Conflicts of interest:** All authors must declare any conflicts of interest.
9. **How does this paper make a difference in general practice?:** This section should be written in bullet points (up to five points) and must not exceed 100 words.
10. **References:** Refer to the References section below for more details.

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A letter to the editor should be of relevance to primary care and **in response to an article or topic published in previous issues** of this journal. The length **should not exceed 1000 words and cite no more than 20 references**. Please include the following sub-headings in the manuscript:

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REFERENCES

Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals (in superscript). Please use the citation style adopted by the National Library of Medicine, Maryland, USA, (<http://www.pubmed.gov>), some examples are given below. For indexed journals, the short forms for the journal names can be accessed at the PubMed website (search within Journal Database). Where possible, avoid citing abstracts, personal communication or unpublished data as references. Include among the references manuscripts accepted but not yet published and designate the journal followed by "in press" (in parenthesis). When referencing a website, please include the full title and accessed date. Notice article titles are capitalised in sentence case; book and journal titles are capitalised in title case. **Some examples of reference list entries:**

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- **Standard journal article:** Corporate Author International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997 Jan 23; 336(4):309–16.
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- **Books and other monographs:** Corporate Author Wonca International Classification Committee. International Classification of Primary Care, ICD-2. 2nd ed. Oxford: Oxford University Press; 1998.

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CONTENTS

i **About MFP**

ii **Editorial board**

iii **Information for authors**

Editorial

1 **The future direction of Malaysian Family Physician**
Ping Yein Lee

Review

2 **Management of gout in the primary care setting**
Qin Jian Low, Tzyy Huei Lim, Shu Ann Hon, Qin Jia Low, Mak Woh Wei, Seng Wee Cheo, Azwarina Hanim Ramlan

10 **A practical approach to chronic kidney disease in primary care**
Seng Wee Cheo, Qin Jian Low, Tzyy Huei Lim, Woh Wei Mak, Chow Alexander Kok Yip, Koh Wei Wong

Original Article

20 **Development, validity and reliability of instrument to evaluate implementation fidelity of the Family Doctor Concept (FDC) programme in public primary care clinics in Malaysia**
Muhammad Alimin Mat Reffien, Aniza Ismail, Saperi Sulong, Tengku Putri Zaharah Tengku Bahanuddin, Noridah Mohd Salleh, Nazrila Hairizan Nasir

29 **Distribution of refractive error among chinese primary school children in a rural area in Pahang, Malaysia**
Rokiah Omar, May Ek Su Wong, Chiranjib Majumder, Victor Feizal Knight

36 **The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor**
Ping Yein Lee, Hani Syahida Salim, Yee Gin Cheng, Zunayrah Zainuddin, Harvind Singh, Kien Woon Loh

44 **Low birth weight infant among teenage pregnancy in Terengganu, Malaysia: A cross-sectional study**
Siti Fatimah Samsury, Tengku Alina Tengku Ismail, Raihan Hassan

52 **Primary care of preputial adhesions in children – a retrospective cohort study**
Varunkumar Maddileti, Suhasini Gazula, Praveena Dantala

57 **Thalassemia screening: Low level of knowledge among unmarried youths in Kota Bharu, Kelantan, Malaysia**
Muhammad Akmal Mohd Nor, Nur Suhaila Idris, Maryam Mohd Zulkifli, Ruzilawati Abu Bakar, Imran Ahmad

66 **Incidence of angiotensin-converting enzyme inhibitor-induced cough in a Malaysian public primary care clinic: A retrospective cohort study**
Hou Chan Loo, Fairuz Osman, Siew Lee Ho, Sing Yee An, Yim Mei Au Yong, Ee Ming Khoo

CPG Update

71 **Case scenario: Management of major depressive disorder in primary care based on the updated Malaysian clinical practice guidelines**
Uma Visvalingam, Umi Adzlin Silim, Muhammad Muhsin Ahmad Zahari, Firdaus Abdul Gani, Noormazita Mislán, Noor Izuana Redzuan, Peter Kuan Hoe Low, Sing Yee Tan, Masseni Abd Aziz, Aida Syarinaz Ahmad Adlan, Suzaily Wahab, Aida Farhana Suhaimi, Nurul Syakilah Embok Raub, Siti Mariam Mohtar, Mohd Aminuddin Mohd Yusof

Case Report	78	White-eyed blowout fracture, child in danger: A case report Abdul-Hadi Rosli, Mohd-Hudzaifah Nordin, Zunaina Embong, Wan-Hazabbah Wan Hitam
	82	Dizziness and syncope after subclavian steal: A case report of a rarely symptomatic, common vascular disorder Nik Mohamed Firdaus Nik Mohamed Kamal, Nasibah Mohamad, Bazli Md Yusoff
	86	Type 2 Diabetes Mellitus with HbJ trait: A management conundrum Wan Natrah Wan Yaacob, Lili Husniati Yaacob, Nani Draman
	90	Where are the vesicles? A case report of Ramsay Hunt syndrome Farhan bin Fader, Hardip Singh Gendeh, Bee See Goh
	94	Insulin oedema in type 2 diabetes mellitus: A case report Mohd Aznan Md Aris, Kui Foun Tan, Abdul Hadi Said
Test Your Knowledge	99	Rash, red eyes, lip erosions and genital ulcer - What is the diagnosis? Evelyn Wen Yee Yap
A Moment in the Life of a Family Physician	103	A family physician's impossible choices & lessons learned through illness Su May Liew
Obituary	105	Liew Su May (1970–2021): A champion of evidence-based primary care medicine Editorial board members of Malaysian Family Physician

EDITORIAL

The future direction of Malaysian Family Physician

Ping Yein Lee

Editor in Chief

Lee PY. The future direction of Malaysian Family Physician. *Malays Fam Physician*. 2022;17(1);1. <https://doi.org/10.51866/ed0003>

We are saddened by the passing of Professor Dr Su May Liew, who led the Board of Editors excellently between 2016 and 2021. Over the past five years, Professor Liew presided over 213 articles and ensured the publication of journal articles of the highest standard. We hope to continue her admirable efforts for the journal in future. At the end of this issue, we have published an article on a moment in the life of a family physician written by Professor Liew,¹ sharing her personal experiences of making decisions about her illness before her passing. This is followed by Professor Liew's obituary, which highlights her remarkable achievements in the field of primary care.²

This first issue of Malaysian Family Physician (MFP) for 2022 observes a change in the chief editorship and an expansion of the Board of Editors. We have appointed new international associate editors from Thailand and Singapore as well as local associate editors. With the expansion of the Board of Editors, we will continue to strive towards providing a platform for primary care researchers to publish their work and keep readers updated on new evidence in primary care locally and internationally. Currently, MFP is indexed in PubMed Central and Scopus, with future aims to achieve indexing in Web of Science (ISI).

Over the past three years, an increasing number of high-quality research articles have been submitted to MFP. The present issue includes two review articles, seven original research articles, one Clinical Practice Guideline (CPG) review, five case reports and one test your knowledge quiz. The two review articles and CPG review highlight the management of chronic conditions (i.e.: gout, chronic kidney disease and major depression) in primary care.³⁻⁵ The original research articles encompass a diverse range of patients and medical conditions of primary care, ranging from screening to complications in chronic diseases and covering all ages from children, adolescence to older age groups.⁶⁻¹¹ I hope that MFP will continue to receive support from all our readers, contributors, reviewers and editors for the continuing progress of the journal.

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REVIEW

Management of gout in the primary care setting

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Low QJ, Lim TH, Hon SA, et al. Management of gout in the primary care setting. *Malays Fam Physician*. 2022;17(1);2–9. <https://doi.org/10.51866/rv1165>

Keywords:

Colchicine, gout, hyperuricemia, urate lowering therapy, tophi

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Abstract

Gout is a commonly treated inflammatory arthritis that is often managed in the primary care setting. This disease is prevalent among the multi-ethnic Malaysian population. Unfortunately, gout is still frequently managed sub-optimally, even in the hospital and primary care settings. Gout should be considered a major disease since it can potentially lead to multiple disabilities from joint destruction, nephropathy and increased cardiovascular morbidity and mortality. The objectives of this review are to summarise the latest updated information and management of gout in the primary care setting.

Introduction

Gout is an ancient disease first described by Hippocrates in fifth-century BC. Gout is also known as the “Disease of Kings”. It remains the commonest type of inflammatory arthritis and is an often disabling but treatable arthritis of adulthood.¹ The commonest cause of gout is a decrease in urate clearance (renal underexcretion), resulting in a raised serum uric acid level.² That said, hyperuricemia alone is not adequate for the development of urate crystal disease. Deposition of monosodium urate crystals in the joint interacts with macrophages and subsequently perpetuates the secretion of various cytokines. This cascade amplifies the inflammatory process, leading to a clinical manifestation of painful swollen joints.² The incidence of gout is on the rise due to the increasing prevalence of metabolic syndrome.³ Moreover, the progression from asymptomatic hyperuricemia to chronic tophaceous gout is escalating.^{3,4} Gout often occurs earlier in males than females. Women of child-bearing age rarely develop gout, as oestrogen has a uricosuric effect.¹ Notably, a variety of dietary and physical factors, comorbidities, medications, and other factors may predispose an individual to a gouty flare.

Internationally, the *British Journal of General Practice* published a guideline on improving gout management in primary care in 2017.⁵ In 2019, the *Australian Journal of General Practice* issued an article on the challenges of managing gout in primary care.⁶ In 2020, the American College of Rheumatology released its latest guideline on the management of gout.¹ Malaysia's clinical practice guideline (CPG) on the management of gout was released in 2008,

and a newer CPG update is in the pipeline.⁷ The authors believed that an updated local gout management guideline for primary care doctors would be timely, considering the many newer drug options, additional data on safety and efficacy of available drugs and new practices to help primary care doctors provide the latest evidence-based medicine.

Disease Burden of Gout Internationally and in Malaysia

In the United States, the prevalence of gout ranges from less than 3 million to 8 million individuals; the latest estimate suggested a prevalence of gout to be around 3% of the adult American population.⁸ In general practice in the United Kingdom, the overall prevalence of gout increased from 1.4% in 1999 to 2.49% in 2012.⁹ To date, there is still a lack of national prevalence study of gout. In an article on epidemiology and the management of gout in a rheumatology tertiary centre in Perak, Malaysia, Wahinuddin Sulaiman et al. (2019) reported 54 cases of gout under their rheumatology clinic follow-up. The predominant ethnic group affected was Malay, followed by Chinese. The mean age of onset of gout in this study was 53.1 (Standard deviation 13.6) years, with a duration of 7 years.⁴

Teh et al. (2014) reported on a total of 126 patients with acute gout who were admitted from 1 July 2011 to 1 July 2012 at Sarawak General Hospital. Among those admitted, 112 (88.9%) were male.¹⁰ A majority of these patients were from the indigenous population of Sarawak. The mean age was 60 (SD 14.2) years. Most of the patients were overweight (68%), with comorbidities including

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hypertension (78.6%), chronic kidney disease or CKD (48.4%), type II diabetes mellitus (30.2%), dyslipidaemia (27.8%) and ischaemic heart disease (11.9%).¹⁰

Reasons for Poor Management of Gout^{1,9-11}

The management of gout is suboptimal, as:

- Primary care doctors are often unclear about the diagnosis.
- Some patients only present to a doctor when they have an acute gouty attack but do not return for follow-up to initiate urate-lowering therapy (ULT).
- Patients may not be compliant with therapy.
- More than 50% of patients do not reach the targeted serum uric acid.
- Guidelines for the management of gout are often not followed, and the availability of ULTs may be limited.
- There is a lack of alternative xanthine oxidase inhibitors or uricosuric agents.

Diagnosis of Gout

The diagnostic criteria for gout include 2 of the following:

- (a) A clear history of at least 2 attacks of painful joint swelling with complete resolution within 2 weeks;
- (b) A clear history or observation of podagra, presence of tophus;
- (c) A rapid response to colchicine within 48 hours of starting treatment.¹

Definitive diagnosis: Presence of monosodium urate crystals in the serum, joint fluid or in the tissues.

The diagnosis of gout concentrates on the fundamental pathophysiologic events defining the clinical state: tissue deposition of urate crystals and accompanying inflammatory and potentially destructive consequences. A gout flare involves the presence of monosodium urate (MSU) crystals in synovial fluid obtained from joints or bursas visualised under polarised light microscopy, a technique that is frequently used to identify these crystals. In contrast, plain radiography may not reveal the presence of early disease that may not demonstrate any abnormality, as the joint spaces are usually preserved, and periarticular osteopenia is absent, unlike in the radiographic changes characteristic of rheumatoid arthritis. Advanced gout typically shows bone erosions characterised by an overhanging edge and sclerotic rim. Ultrasonography can be very

useful in early detection and in the case of a diagnostic dilemma. Critical diagnostic features include hyperechoic linear density (double contour sign) overlying the surface of the hyaline cartilage or tophaceous deposits in joints or tendons, described as hyperechoic, in homogenous material surrounded by a small anechoic rim.

The primary care setting employs a clinical diagnostic rule to estimate the likelihood of gout without joint fluid analysis. The model uses seven variables, including male gender (2 points), previous patient-reported arthritis (2 points), onset within one day (0.5 points), joint redness (1 point), first metatarsal phalangeal joint involvement (2.5 points), hypertension or at least one cardiovascular disease (1.5 points), serum urate level >5.88 mg/dL or 350 micromol/L (3.5 points).¹² Based on the total score, patients can be identified as having low (≤ 4 points), intermediate (>4 or <8 points), or higher (≥ 8 points) probability of gout. Patients in the intermediate category benefit most from a further evaluation via synovial fluid analysis.¹² This clinical diagnostic rule was validated in a group of 390 Dutch primary care patients with acute monoarthritis, where this diagnostic rule outperformed a physician diagnosis and offered a good outcome in the derivation study.¹³

Primary care doctors should beware that gout flares can occasionally coexist with another type of joint disease, such as septic arthritis or acute calcium pyrophosphate crystal arthritis (pseudogout). A referral to an orthopaedic surgeon or rheumatologist for joint aspiration will help with the analysis of the synovial fluid and subsequently establish the diagnosis.

Three classical stages of gout are currently seen in our daily clinical practice:

- (a) Acute gout flare
- (b) Inter-critical gout
- (c) Chronic gouty arthritis and tophaceous gout

Management of Acute Gout

A gout flare, which frequently occurs in the lower extremities, is commonly monoarticular and intensely inflammatory. Patients often report severe pain, redness, warmth, swelling and disability, with the maximum severity within 12 to 24 hours from onset. Twenty per cent of patients experience a polyarticular gouty flare.¹⁴

The principles of managing an acute gouty flare include the following.^{1,16-17}

- (a) In an acute flare, oral colchicine, non-steroidal anti-inflammatory agents (NSAIDs), or glucocorticoids (oral, intra-articular or intramuscular) are appropriate first-line therapy. There is no superiority between NSAIDs versus colchicine in an acute attack, and the decision should be based on the suitability of the patient's profile. For example, in patients with CKD or ischaemic heart disease, NSAIDs should be avoided.¹³ The use of NSAIDs should also be avoided in patients with poorly controlled hypertension or known peptic ulcer disease. In patients exhibiting inadequate response to monotherapy, a combination therapy (colchicine plus NSAIDs or glucocorticoids) can be used.^{1,15}
- (b) **Pill in the pocket:** Treat as early as possible. Oral colchicine 1 mg stat and 0.5 mg 1 hour later during an acute attack, followed with colchicine 0.5 mg bd to tds subsequently. Patients should be taught how to self-monitor and watch for warning signs of an impending gouty attack.^{1,16-17}
- (c) Adjunctive (s)¹⁶⁻¹⁹:
Adequate fluid intake of 2-3 L per day.
Ural sachets, 1 sachet 3 times a day.
Oral vitamin C 500 mg daily.
Elevate leg, ice and rest.
- (d) ULT^{1,18}
During an acute attack, do not stop allopurinol. Conventionally, ULT is not started during an acute gouty flare based on observations that it may worsen or prolong an existing flare.¹⁸ However, two small, randomised control trials and one observatory study on initiating ULT during a flare showed no differences between the 2 arms in mean pain scores, the frequency of additional gout flares, or in levels of acute phase reactants.²¹ Hence, some experts have suggested that ULT can be initiated for a selected group of patients with very difficult to manage or continuous flares, along with anti-inflammatory therapy. In 2020, the American Society of Rheumatology conditionally recommended this new approach of initiating ULT during a flare based on patient factors or preferences using a case-by-case technique.^{1,20}

Colchicine

Table 1: Colchicine dose in acute gout management.²¹⁻²³

Colchicine dose	
eGFR (ml/min/1.73 m ²)	Dosage
>50	0.5 mg tds
10-50	0.5mg od to 0.5 mg bd
<10	Contraindicated

Colchicine can be given both during an acute gout flare or as prophylaxis. The prophylactic dose of colchicine is 0.5 mg once to twice daily for up to 6 months.²² The potential side effects of colchicine include diarrhoea, nausea and vomiting, bone marrow suppression, myopathy and rhabdomyolysis. Colchicine should not be given to patients who are receiving CYP 3A4 inhibitors such as clarithromycin.²³ The dose adjustment for colchicine should be in accordance with the creatinine clearance (**Table 1**).

Steroid

Table 2: Steroid dose in acute gout management.²⁴⁻²⁵

	Steroid dosages
Polyarticular gout	Oral prednisolone 30-35 mg daily for 5 days. Intra-muscular triamcinolone acetate up to 1 mg/kg.
Monoarticular gout or polyarticular involvement with effusion	Ultrasound-guided intra-articular steroid injection. 40 mg into large joints or 10-20 mg into small- to medium-sized joints. In monoarticular joint involvement, intra-articular steroid injection is an option.

Steroids are highly effective as rapid-acting anti-inflammatory agents in an acute flare. The route of administration of steroids will depend on several factors, including the number of affected joints, patient preference, availability of joint injection services, clinician experience and patient preferences.²⁴ Clinicians should exercise caution when using steroids in patients with heart failure, poorly controlled hypertension, uncontrolled diabetes or moderate to severe renal insufficiency. A rebound flare is common when steroids are withdrawn, especially in patients not on anti-inflammatory flare prophylaxis. Thus, clinical follow-up is required to ensure an adequate treatment response is achieved.^{25,26}

NSAIDs

Table 3: Choice of NSAIDs in acute gout management.²⁷⁻²⁸

Choice of NSAIDs			
Non-selective NSAIDs		Selective COX-2 inhibitors	
Indomethacin	25-50 mg tds	Etoricoxib	90 mg od 120 mg od
Meloxicam	15 mg od	Celecoxib	200 mg bd
Naproxen	500 mg bd		
Mefenamic acid	500 mg tds		
Diclofenac sodium	50 mg bd to tds		

NSAIDs are most effective when initiated within 48 hours of symptom onset. NSAIDs can be discontinued 2 to 3 days after clinical signs have completely resolved.²⁹ A typical duration of NSAIDs in gout flare is 5 to 7 days (Table 3). Patients should not be treated concurrently with more than one NSAID, and a detailed review of medication history should be conducted to avoid any potential over-the-counter therapies that may include NSAIDs.³⁰ Caution should be taken in the use of NSAIDs in patients with known cardiovascular disease. Aspirin should not be used to treat gout flare, as it has a paradoxical effect on serum uric acid.²⁸ However, low-dose aspirin, such as the doses taken by many patients as cardiovascular prophylaxis, does not need to be discontinued during a gout flare.^{18,28}

ULT

During the initial initiation phase of ULT, concomitant anti-inflammatory prophylaxis with colchicine for 3-6 months should be given to reduce the risk of a flare.^{20,31} Before initiation of ULT, patients should be educated on the indications of ULT, modes of action, dosing regime, monitoring and uric acid targets, compliance, possible side effects, gout flares and risk hypersensitivity reaction, especially to allopurinol.^{1,20} Shared decision-making with the patient is essential for the best outcome.

Allopurinol

Allopurinol remains the first line ULT for all patients, including those with stage 3 and above CKD. This substance is a purine analogue xanthine oxidase inhibitor (XOI). Often there is an underdosing issue among gout patients, as most of them receive a dose of 300 mg daily instead of the maximum 900 mg daily dose.¹ The serum urate levels are not commonly measured after initiation of allopurinol; consequently, serum urate targets are not achieved. The authors recommend an initial dose of 50 mg daily for allopurinol and subsequent up-titration every 4 weeks until the

target uric acid level is achieved. That said, a lower starting dose of allopurinol could reduce the risk of allopurinol acute hypersensitivity syndrome.^{28,32}

The starting dose of allopurinol should be adjusted according to the eGFR (Table 4). In addition, primary care providers should aim for dose reduction of allopurinol in CKD patients and monitor their serum creatinine trend. It is well known that allopurinol is associated with severe cutaneous adverse drug reactions in patients who carry the genotype HLA-B*58:01 or 73, which is common among African Americans, Koreans, and Han-Chinese.^{28,33} Patients should be counselled to stop allopurinol immediately and seek medical attention if they experience any coryzal symptoms, fever, mucosal ulcers, or rashes.²⁰

Table 4: Allopurinol initiation dose according to eGFR level.^{1,20}

eGFR (ml/min/1.73m ²)	Allopurinol initiation dose
Less than 5	50 mg per week
5-15	50 mg twice a week
16-30	50 mg every 2 days
31-45	50 mg/day
46-60	50 mg alternate 100 mg od
61-90	100 mg per day
91-130	150 mg per day
More than 130	200 mg per day

Historically, allopurinol is commenced 2 weeks after the complete resolution of an acute gout attack.³⁴ However, some studies have shown that starting allopurinol during an acute gout flare does not prolong the flare, provided the acute episode is being treated adequately.^{1,21} Whenever allopurinol regimen is newly initiated, regular oral colchicine prophylaxis should be prescribed to be taken along with allopurinol for at least 2 weeks and can be continued up to 6 months to avoid an acute gout flare.^{1,20-21}

Febuxostat

Another ULT is febuxostat, a non-purine analogue XOI. Febuxostat is a second line ULT when allopurinol is not tolerated or contraindicated and should be used in patients with a history of hypersensitivity reactions to allopurinol. Note that the manufacturer recommends periodic liver function test monitoring.³² The doses of febuxostat are 40, 80 and up to 120 mg daily. There is no dose adjustment required if eGFR is above 30 ml/min/1.73m² (Table 5).³⁵ There is strong evidence in favour of febuxostat in flare reduction, tophi resolution, and safety, especially in the mild to moderate renal impairment group (more than 30 ml/min/1.73m²).^{20,32} Unlike allopurinol, febuxostat is rarely associated with hypersensitivity reactions. However, there is a

cardiovascular safety concern with febuxostat in patients with an increased cardiovascular risk, as seen in a previous trial of around 6200 patients with gout and coexisting cardiovascular conditions.²⁸ The Febuxostat versus Allopurinol Streamlined Trial (FAST) results released in November 2020 showed that among 6100 patients enrolled, there was a non-significantly lower risk of composite cardiovascular safety outcome among the febuxostat group with a median follow-up of 4 years.³³ The European Medicines Agency, which recommended the FAST study, has not yet released a new position regarding its warnings. Until more cardiovascular safety data are available, we continue to prefer allopurinol over febuxostat, particularly in patients at higher cardiovascular risk.²⁰

Table 5: Initiation dose of febuxostat in renal impairment patients.³²⁻³³

Creatinine clearance (CrCl) (ml/min/1.73m ²)	Febuxostat dose
30-89	No dosage adjustment. Initiation dose is 40 mg daily; may increase up to 80 mg, then 120 mg daily if target serum uric acid is not achieved.
<30	Maximum 40 mg daily.
Dialysis	No data.

Uricosurics

Uricosurics, another group of drugs used in urate lowering, work by enhancing uric acid renal excretions.³⁴ These drugs can be used in patients who are resistant or intolerant to xanthine oxidase inhibitors. Uricosurics can also be used in combination with xanthine oxidase inhibitors. Examples of uricosurics are probenecid 500-2000 mg daily, benzbromarone 50-200 mg daily or sulfinpyrazone 200-800 mg daily.^{20,34} Uricosurics are contraindicated in patients with renal impairment with creatinine clearance of less than 30 ml/min, patients with high urine uric acid excretions, urolithiasis or nephrocalcinosis.^{20,36} Benzbromarone can be used in patients with moderate renal impairment, but there is a risk of liver toxicity.³⁴⁻³⁵

(a) Probenecid

Probenecid is a potent uricosuric agent with a starting dose of 500 mg once or twice daily, with dose titration up to 2000 mg daily.³⁴ Allopurinol in combination with probenecid is an option for patients who have failed to achieve their target serum uric acid level and have a high cardiovascular disease risk. Probenecid has a diminished urate-lowering efficacy in patients with

moderate to severe CKD (creatinine clearance less than 45 mL/minute).^{35, 37}

Treat to target

Primary care providers should educate gout patients who have been started on ULT and should provide an individual uric acid target. All gout patients on ULT should aim to achieve a serum uric acid of less than 360 µmol/L (6 mg/dL) for flare prevention, as well as reduction of gout attack and tophi formation. In contrast, in patients who have tophaceous gout, the target for serum uric acid should be below 300 µmol/L or 5 mg/dL. Gout flares have almost been eliminated after one year of treatment by targeting a serum uric acid level below 6 mg/dL. A lower serum uric acid can decrease tophus size faster. However, a serum uric acid level below 180 µmol/L is not recommended, as some studies have suggested that uric acid may be protective against neurodegenerative diseases such as Alzheimer's, Parkinson's, or amyotrophic lateral sclerosis.

Lifestyle modification

Regular exercise, weight loss and a low-purine diet should be advised to all patients with gout. Such a diet includes avoiding organ meat with

a high purine content, such as kidney, liver, or brain. Patients should also abstain from food or drinks containing high-fructose corn syrup and avoid alcohol overuse.³⁶ Additionally, medical professionals should encourage patients with gout to limit their seafood intake, such as sardine and shellfish, which are high in purine. Instead, a balanced diet consisting of high-fibre fruits and vegetables, along with low-fat or non-dairy products, should be encouraged. Avoidance of alcohol, especially beer products, should be emphasised.³⁷

Management of gout in CKD and end-stage kidney failure patients

Gout has been closely associated with kidney disease and is a risk factor for the development of CKD. Uric acid is the final product of xanthine/hypoxanthine, which is catalysed by xanthine oxidase in endogenous urate biosynthesis. Renal excretion of uric acid

follows 4 pathways: filtration, reabsorption, secretion, and post-secretory reabsorption.^{28,37} Acute uric acid nephropathy develops due to oligo-anuric renal failure caused by renal tubular obstruction by urate and uric acid crystals. This is commonly observed in the setting of malignancy such as leukaemia, lymphoma, small cell lung cancer and germ cell tumour, in which a rapid cell turnover or cell lysis occur, especially post chemotherapy. Chronic urate nephropathy features long-standing micro-tophi formation in the renal medullary interstitium. Uric acid nephrolithiasis due to uric acid precipitation in the collecting system represents 5 to 10% of all renal calculi in the United States population.³⁹ Gout is a risk factor for incident CKD stage ≥ 3 CKD, which can then progress to end-stage kidney failure. The associations between hyperuricemia, gout and CKD are bidirectional.^{1,36}

Table 6: Management of gout in renal impairment patients.³⁶⁻³⁷

	CKD	End-stage kidney failure
Acute gout	Colchicine is contraindicated if eGFR <10 mL/min/1.73 m ² (Table 1). Oral or intravenous steroids (Table 2). Monoarticular involvement: Intraarticular steroids. NSAIDs are contraindicated if creatinine clearance is less than 60 mL/minute per 1.73 m ² .	Oral or intravenous steroids (Table 2). Monoarticular involvement: Intraarticular steroids. In patients with no residual kidney function, NSAIDs should be avoided. Avoid colchicine in haemodialysis patients, as it is not removed by dialysis and there is a risk of colchicine toxicity.
Chronic gout	Allopurinol is recommended, with a lower allopurinol starting dose (Table 4). In mild to moderate renal impairment, febuxostat is an option (Table 5).	Allopurinol is recommended with a lower allopurinol starting dose (Table 4). No data are available on febuxostat use in end-stage kidney failure patients.

Referral to a rheumatologist

The following are indications for referral of gout patients to rheumatologists:³⁸⁻³⁹

- Unclear aetiology
- Refractory disease
- Recurrent gouty attacks
- Difficulty in achieving target serum urate level
- Renal impairment
- Adverse effects of ULT or intolerance
- Chronic tophaceous or/and erosive gouty arthritis

Conclusion

Gout is an easily treatable disease and may be curable. The aim of management in an acute flare is the rapid resolution of pain with early introduction of treatment and disability prevention. ULTs are readily available and effective, and allopurinol remains the first-line treatment.³⁹ Primary care providers should be familiar with

the indications for initiating ULT and setting serum uric acid targets with patients, as well as being competent in handling possible side effects of ULTs and educate patients about lifestyle and dietary modifications.³⁸ Because gout is frequently part of the metabolic phenomenon, testing for hypertension, diabetes, and hypercholesterolemia and monitoring weight is pivotal, not only through diet and lifestyle modification but also treatment when necessary.³⁹

Acknowledgements

The authors would like to thank the Director of Health Malaysia for his permission to publish this article.

Conflicts of interest

The authors declare that they have no competing interests in the publication of this article.

How does this paper make a difference to general practice?

- The increasing prevalence and consequences of poorly treated gout mandate a greater focus for practitioners to improve and ensure a better outcome for patients.
- As gout is the most prevalent type of inflammatory arthritis, this is the first local paper written that summarises a wide range of aspects related to better gout management.

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REVIEW

A practical approach to chronic kidney disease in primary care

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Cheo SW, Low QJ, Lim TH, et al. A practical approach to chronic kidney disease in primary care. *Malays Fam Physician*. 2022;17(1);10–19. <https://doi.org/10.51866/rv1186>

Keywords:

Chronic kidney disease, primary care, practical approach

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Abstract

Chronic kidney disease (CKD), a common clinical problem in primary care, can be defined as any abnormality of the kidney structure and/or function that has been present for at least 3 months. Over the past 20 years, the incidence and prevalence of CKD have been increasing in Malaysia in line with the rising number of non-communicable diseases. At present, CKD has no cure. The treatment of CKD is very much dependent on early diagnosis and prevention of CKD progression. In this article, we aim to illustrate a practical approach to CKD in primary care, including diagnosis, evaluation, and management of CKD.

Introduction

Chronic kidney disease (CKD) spans a broad range of disease severity and heterogeneity concerning its risk of clinical progression to end-stage renal disease (ESRD). Long-term complications of CKD include ESRD, complications of ESRD, cardiovascular disease and death.¹ In Malaysia, the incidence and prevalence of CKD and ESRD have risen alarmingly over the past 20 years, which has been partly driven by the rising number of non-communicable diseases, especially diabetes mellitus. Management of CKD is largely dependent on early detection and prevention of disease progression. There is no definite cure for this disease. Because most CKD patients are managed in primary care, we aim to illustrate a practical approach to CKD in a primary care setting in the present article.

Disease Burden of CKD in Malaysia

Globally, CKD prevalence is estimated to be between 10% to 15%.^{2,3} An earlier population-based study in 2011 done in Peninsular Malaysia found that 9.1% of Malaysians had CKD.⁴ A more recent study that included the Sabah and Sarawak population found that CKD prevalence had increased to 15.5%.⁵ Out of this 15.5%, 6.81% had CKD stage 3 to 5. Diabetes mellitus continues to be the leading

cause of ESRD in Malaysia, with 69.2% of new ESRD patients in Malaysia in 2018 resulting from diabetic nephropathy.⁶ The National Health Morbidity Survey 2019 estimated that 3.9 million Malaysian adults had diabetes mellitus, and 6.4 million Malaysians were hypertensive.⁷ It is not surprising, therefore, that the number of patients with CKD is increasing.

Besides mortality and morbidity, CKD also contributes to a significant burden in terms of health care cost. Based on data reported in 2019, the estimated cost of haemodialysis per patient per year was RM39,791, while the cost for peritoneal dialysis reached RM37,576.⁸ In total, RM1.12 billion was spent on ESRD in 2016.⁹ Given these serious public health impacts, diagnosing CKD early in order to prevent progression to ESRD is therefore essential for primary care practitioners.

1.0 Diagnosis of CKD

1.1 Definition of CKD

CKD can be defined as any abnormality of kidney structure and/or function that has been present for at least 3 months.¹⁰ (See Table 1.)

Table 1: Criteria for diagnosis of CKD

Markers of kidney damage (1 or more)	• Albuminuria (AER >30 mg/24 hours; ACR >30 mg/g [>3 mg/mmol]) • Urine sediment abnormalities • Electrolyte and other abnormalities due to tubular disorders • Abnormalities detected by histology • Structural abnormalities detected by imaging • History of kidney transplantation/donation
Decreased GFR	GFR <60 ml/min/1.73 m ² (GFR categories G3a-G5)
<i>CKD may be diagnosed when either criterion is present for 3 months or more</i>	

*AER: albumin excretion rate, ACR: albumin-to-creatinine ratio

Notably, CKD is not defined solely based on glomerular filtration rate (GFR), as other markers of kidney damage must be taken into consideration. These indications include pathological abnormalities, structural abnormalities or increased urinary albumin excretion. Additionally, the persistence of abnormalities for at least 3 months is necessary to distinguish CKD from acute kidney injury (AKI).¹⁰

In comparison, ESRD is defined as an irreversible decline in a person's own kidney function, which can be fatal in the absence of renal replacement therapy (RRT). Patients with ESRD are usually dependent on RRT.

1.2 Staging of CKD

The International Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend classification of CKD based on cause, GFR category and albuminuria category (Tables 2 and 3).¹⁰ Identifying the cause and staging of CKD can help in predicting outcome and guiding disease-specific treatment. The degree of albuminuria has also been shown to portend poorer outcomes in terms of cardiovascular issues, mortality and the kidneys.¹¹ Together, these factors (cause of CKD, staging and degree of albuminuria) facilitate predicting the prognosis of kidney disease.

Table 2: Staging of CKD based on GFR

GFR category	GFR (ml/min/1.73 m ²)	Term
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mild to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

Table 3: Staging of CKD based on albuminuria

Category	AER (mg/24 hours)	ACR		Terms
		mg/mmol	mg/g	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

*relative to young adult level.**including nephrotic syndrome.

1.3 Screening for CKD

As there is no definite cure for this illness, early detection is vital to help delay the progression of CKD. Population-based screening is currently not recommended.¹² A more targeted approach to screening can be more practical and cost-effective. Specifically, screening should be focused on individuals with risk factors for CKD (Table 4).¹³ Screening methods include examining serum creatinine (to estimate the GFR) and urine for albumin secretion.

Table 4: Risk factors for CKD that require CKD screening

	Risk factors
Sociodemographic factor	Age > 65 Family history of kidney disease
Comorbid conditions	Diabetes mellitus Hypertension Obesity Gout Metabolic syndrome Cardiovascular disease Autoimmune disease Recurrent urinary tract infection Previous AKI ¹⁴
Structural abnormalities	Structural renal tract abnormalities Benign prostatic hypertrophy Renal calculi
Drugs	Chronic non-steroidal anti-inflammatory drugs Chronic nephrotoxic agents Chronic use of proton pump inhibitor ¹³

2.0 Evaluation of CKD

2.1 Clinical Evaluation

Most patients with CKD who are seen in the primary care setting are often in the early stages. Hence, these patients are frequently asymptomatic and typically unaware of their CKD and its seriousness.¹⁴ These factors make it imperative for primary care doctors to identify individuals at risk. Clinical evaluation of these patients starts with a full medical history, a detailed drug and dietary history, the person's history of past blood pressure (BP) and sugar control, and a physical examination. Investigations include renal function test and collecting urine for microscopy and albuminuria.

Some patients may present to the primary care setting with a more advanced stage of CKD. They may have non-specific signs and symptoms of uraemia, such as fatigue, loss of appetite, weight loss, sleep disturbances, and poor concentration.¹⁵ Meanwhile, those who present with acute medical emergencies, such as acute pulmonary oedema, seizures, or uncontrolled hypertension, will need to be referred for hospital care immediately.

After the diagnosis of CKD is confirmed and the cause and stage of the disease have been established (**Table 5**), patients should then be treated and managed according to the stage of CKD. However, unless the patient presents early in the course of CKD, the cause of the CKD may not be confidently ascertained.

Table 5: Approach to CKD

Establish the diagnosis of CKD – persistent kidney damage for >3 months
Stage the CKD by GFR
Look for the cause of CKD
Provide treatment according to stage and cause
Monitor for CKD progression and CKD-related complications
Employ risk stratification and management of cardiovascular risk factors

2.2 Blood test

Serum creatinine is affected by many factors, such as age, gender, muscle mass and protein meals. That said, it is an insensitive marker of GFR early in the course of CKD, as an initial rise in serum creatinine indicates about 50% loss of GFR.¹⁶ Hence, detection of CKD based on estimated GFR is a more accurate assessment of renal function than serum creatinine.¹ A normal GFR is approximately 120 to 130 ml per minute per 1.73 m² in young adults, decreasing by an average of 1 ml per minute per 1.73 m² per year beginning at the age 30–40 years.¹⁷

Estimated GFR (eGFR) can be derived from serum creatinine based on several equations (**Table 6**). The more commonly used formulas for GFR estimation in daily practice are the modification of diet in renal disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The highly recommended CKD-EPI represents the current standard of care, as it provides a more accurate eGFR in a normal individual or in GFR >60 ml/min/1.73 m².¹⁸

The Cockcroft-Gault formula is now used only for adjusting medication dosage.¹² Serum cystatin C based GFR is most beneficial when false positive decreased GFR is suspected.¹² However, this latter test is more expensive than other options and is not widely available.

Table 6: Equation to derive eGFR

Equation for GFR estimation	Variables	Notes	Online calculator
4 variable MDRD	Age, sex, race, and creatinine level	Reasonably accurate in non-hospitalised patients with CKD. Less accurate in normal or obese individuals.	https://qxmd.com/calculate/calculator_140/mdrd-egfr
CKD-EPI	Age, sex, race, and serum creatinine level	More accurate assessment for normal individuals or individuals with mildly reduced GFR.	https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi
Cockcroft-Gault formula	Age, weight, sex, serum creatinine	Medication dosage adjustment.	https://qxmd.com/calculate/calculator_51/crcl-cockcroft-gault
Cystatin C	Age, sex, race, serum cystatin C level	Beneficial when false positive decreased GFR is suspected.	https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr

A few caveats should be noted when applying these equations for eGFR. The eGFR is not accurate in the setting of AKI, as kidney function is not in a steady state.¹ It is also less accurate in patients with extreme muscle mass, malnutrition, or liver disease.

2.3 Urine examination

Urine examination is performed to detect proteinuria or microscopic haematuria. Proteinuria, which refers to increased excretion of any urinary protein, has both diagnostic and prognostic value in CKD.¹⁷ Persistent proteinuria is often a defining marker of renal injury and a sign of glomerular or tubular disease. Notably, patients with proteinuria may still have normal eGFR. Prognostically, the presence of proteinuria also signifies a higher risk of cardiovascular disease and death.¹² Several methods that are available to evaluate for proteinuria include urine dipstick, automated urinalysis, albumin-to-creatinine ratio (ACR), urine protein-to-creatinine ratio (PCR) and 24-hour urine protein (Table 7).

A urine dipstick analysis is an inexpensive and widely available test. This simple semiquantitative test can be employed in the

primary care setting. However, it is important to keep in mind the possibility of false positivity in the event of concentrated urine, gross haematuria or the presence of antibiotics.¹⁹ Apart from false positivity, the urine dipstick test is relatively insensitive to non-albumin protein. Automated urinalysis in this setting will help improve predictive value for significant proteinuria.

Moderately increased albuminuria is defined as a urinary albumin excretion rate of 30-300 mg/day and is often the earliest sign of diabetic kidney disease. Moreover, a urine albumin measurement provides a more sensitive and specific measure of changes in glomerular permeability than total urine protein.⁸ A single early morning urine sample for ACR is a sufficiently sensitive test to detect moderately increased albuminuria.²⁰ In contrast, urine spot PCR also includes tubular secreted proteins, as well as plasma protein from disease processes and infection, making it a less sensitive test.¹² Routine 24-hour urine quantification for protein is both cumbersome and often poorly performed. Hence, the KDIGO guidelines recommend urine ACR as an initial screening test for proteinuria.

Table 7: Different tests that can be used to detect proteinuria or albuminuria

Test	Significant proteinuria
Urine dipstick	Positive when proteinuria >500-1000 mg per day
Automated urinalysis	Positive when proteinuria ≥300 mg per day
Urine albumin-to-creatinine ratio	≥30-300 mg/g – moderately increased albuminuria >300 mg/g – severely increased albuminuria
Urine protein-to-creatinine ratio	>200 mg/g signify presence of proteinuria
24-hour urine protein	≥150 mg/day signify presence of proteinuria >3 g/day signify nephrotic range proteinuria

In addition to tests aimed at identifying proteinuria, urine examination is also used to evaluate microscopic haematuria, which can be caused by structural renal tract disease or glomerular disease. Common causes of microscopic haematuria include urinary tract infection, benign prostatic hyperplasia and urinary calculi.²¹ A patient with isolated microscopic haematuria should be evaluated for urological causes of haematuria. The presence of hypertension, elevated creatinine, cellular cast, and proteinuria should prompt a nephrology referral, as these may indicate glomerular disease.²¹

2.4 Ultrasound

All patients with CKD should undergo an ultrasound. This procedure can provide the following information:

- Renal size, shape and location – small kidney size may suggest chronicity of kidney disease. Renal size assessment is an important consideration prior to renal biopsy. It may detect abnormal anatomy, such as horseshoe kidney.²²
- Renal cortex and echogenicity – a thin renal cortex and increased renal echogenicity are signs of CKD.²²
- Obstruction – the presence of hydronephrosis and hydroureter is suggestive of renal tract obstruction.
- Structural pathology – renal calculi and polycystic kidney disease can be diagnosed from an ultrasound.

2.5 Causes of CKD

Once the diagnosis of CKD has been established, the next step is to look for the cause. Causes of CKD can be broadly classified according to their pathophysiological mechanism (**Table 8**). Such mechanisms include pre-renal, renal vascular, glomerular, tubulointerstitial, hereditary and obstructive causes. In the case of pre-renal causes, clinical evaluation may elucidate the patient's history and detect the presence of signs and symptoms of chronic heart failure or chronic liver disease.

The presence of dysmorphic red blood cell cast, proteinuria and haematuria points towards a possible glomerular cause of CKD. If a glomerular disease is suspected, a serologic workup is indicated.¹ A renal biopsy may be needed to establish the underlying glomerular

disease since specific treatment may be given depending on the histopathological diagnosis. Those with CKD of uncertain cause may need a nephrologist consult. Meanwhile, obstructive causes of CKD should be referred to urology for intervention.

Table 8: Common causes of CKD

a) Pre-renal causes
1. Cardiorenal syndrome – chronic heart failure may lead to CKD
2. Liver cirrhosis
b) Renal vascular causes
1. Hypertensive nephrosclerosis
2. Renal artery stenosis
3. Vasculitis
4. Renal vein thrombosis
c) Glomerular disease – characterised by proteinuria and haematuria from urine examination
1. Primary glomerular disease
• Membranous nephropathy
• Ig A nephropathy
• Focal segmental glomerulosclerosis
• Minimal change disease
2. Secondary glomerular disease
• Lupus nephritis
• Diabetic nephropathy
• Rheumatoid arthritis
• Amyloidosis
• Light chain deposition disease
• Neoplasia
d) Tubulointerstitial disease
1. Drug induced
2. Infection
3. Multiple myeloma cast nephropathy
e) Cystic/hereditary disease
1. Alport syndrome
2. Autosomal dominant polycystic kidney disease
3. Fabry disease
f) Urinary tract obstruction of any causes, such as renal stone disease, benign prostatic hyperplasia, etc.

2.6 Referral to nephrologist

Primary care physicians play a central role in referring patients to nephrologists in a timely manner,¹ especially since a timely referral can facilitate intervention to delay CKD progression and allow time to prepare the patient for RRT. Timely referral has been shown to improve the preparation for RRT, lower the use of a dialysis catheter, reduce emergency dialysis and improve survival (**Table 9**).

Table 9: Indication for nephrology referral

CKD with rapid decline in eGFR >5 ml/min/1.73 m ² in 1 year or >10 ml/min/1.73 m ² within 5 years
CKD with heavy proteinuria (urine protein >1 g/day) despite optimal treatment
Persistent unexplained microscopic haematuria and proteinuria (proteinuria >0.5 g/day)
CKD of unknown cause
CKD stage 4 (eGFR <30 ml/min) for preparation of RRT
CKD in pregnancy or when planning for pregnancy
CKD with refractory hypertension
Isolated microscopic haematuria after excluding urological causes
Suspected hereditary cause of CKD (eg, polycystic kidney disease)
Metabolic workup for recurrent renal stones
Persistent abnormalities of serum potassium

3.0 Management of CKD

3.1 General management

The aim of management of CKD are as follows²³:

- To delay progression of CKD
- To reduce cardiovascular risk
- To reduce further kidney injury, avoidance of nephrotoxic drugs
- To identify patients who need renal replacement therapy
- To manage complications of CKD
- To adjust medications based on GFR

In general, the management of CKD depends on the stages of CKD. Most stage 1-3 CKD patients can be managed in the primary care settings, whereas CKD 4-5 should be managed in the hospital setting. In CKD 1-3, the treatment mainly aims to halt the progression of CKD (**Table 10**).

Table 10: Management of CKD according to stage

Stage	Management plan
Stage 1	Treat comorbid condition, manage cardiovascular risk factors and delay progression of CKD
Stage 2	Delay progression of CKD
Stage 3	Delay progression of CKD and treat CKD complications
Stage 4	Refer to hospital for RRT preparation and treatment of CKD complications
Stage 5	Initiate RRT

3.2 CKD progression

Patients with CKD will inevitably progress. Progression of CKD is defined as a decline in GFR category or a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline.¹⁰ Patients with CKD 1-3 should have their eGFR regularly monitored 1-2 times/year. A more practical way of assessing CKD progression is to monitor eGFR trajectory, that is, annual change in eGFR or eGFR slope. This practice can encourage primary care physicians to track eGFR changes over time. Patients with risk factors for rapid decline should be identified early, and if the rapid decline is confirmed, they should be referred to a nephrologist's care.

Risk factors for progression of CKD include²⁴:

- Proteinuria
- Suboptimal BP control
- Suboptimal glycaemic control
- Smoking

- Cardiovascular disease
- Acute kidney injury
- Anaemia

3.3 Lifestyle modification

General advice on lifestyle modifications is applicable to all stages of CKD. Lifestyle modifications include smoking cessation, weight reduction, a low-salt diet (<2 g/day) and avoidance of nephrotoxic agents.¹³ Patients with CKD should be encouraged to engage in physical activities compatible with cardiovascular health and tolerance (at least 30 minutes, 5 times per week).¹⁰ Smoking is associated with a higher rate of CKD progression.²⁵ Smoking cessation will reduce the risk of CKD progression as well as cardiovascular risk. Dietary input from a dietitian may help in providing advice regarding a low-salt and low-potassium diet (**Table 11**).

Table 11: Strategies to delay CKD progression

Lifestyle	Physical activity compatible with cardiovascular tolerance (aim for at least 30 minutes, 5 times/week) Smoking cessation Weight reduction
Dietary	Low-salt diets (<2 g/day) Low-protein diet (0.6 g-0.8 g/kg/day)
BP and proteinuria	Target BP for diabetic patient is $\leq 130/80$ mmHg For non-diabetic patient with CKD, the target is - $\leq 140/90$ mmHg if the proteinuria is <1 g/day - $\leq 130/80$ mmHg if the proteinuria is >1 g/day ACEI/ARB is first choice antihypertensive
Glycemic control	Aim for HbA1C of 6.5% to 7.0%
Drug	Avoid nephrotoxic drugs Use of sodium-glucose co-transporter-2 (SGLT2) inhibitors can help delay CKD progression

3.4 Hypertension and proteinuria

BP control and proteinuria reduction are the 2 most important interventions in delaying CKD progression and reducing cardiovascular risk in CKD patients.²⁰ Specifically, the control of hypertension, which is present in more than 80% of CKD patients, is often suboptimal in these patients.¹⁴

Many studies and guidelines have advocated for tight BP control for patients with CKD. Additionally, the BP targets are different for those with diabetes mellitus and those without. The target BP for diabetic patients is $\leq 130/80$ mmHg, which has been shown to reduce the risk of CKD progression. This finding is supported by the RENAAL study revealing that patients who achieved a systolic BP <130 mmHg had a significantly lower risk of ESRD or mortality²⁶ and further supported by the ADVANCE-ON trial where mortality benefits were observed in diabetic patients treated with BP-lowering therapy.²⁷ For non-diabetic patients with CKD, the target is $\leq 140/90$ mmHg if the patient's proteinuria is less than 1 g per day and $\leq 130/80$ mmHg when proteinuria is more than 1 g per day.¹³

Any antihypertensive can be used to control BP in patients with CKD. The most critical issue in prescribing antihypertensive medications is probably medication adherence.²⁸ A renin-angiotensin system (RAS) blockade by way of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) is the preferred first-line option for those with diabetic kidney disease or those with heavy proteinuria (proteinuria >1 g per day).¹³ RAS blockade has been demonstrated to reduce proteinuria and has the effect of slowing the progression of CKD independent

of BP control.²³ This outcome is supported by the RENAAL study and IDNT study. Note that monitoring the renal profile and serum potassium within 2-4 weeks after initiation of ACEI or ARB or within 2 weeks of an increase in dosage is vital. Moreover, combining ACEi and ARB is not recommended, as complications are more common without clear benefits.¹

3.5 Glycaemic control

The current glycaemic control target is an HbA1C of 6.5% to 7.0%.^{1,10,13} Maintaining an optimal HbA1c reduces cardiovascular risk as well as the development of albuminuria and loss of renal function over time.¹ The benefits of strict diabetic control must be weighed against the risk of hypoglycaemia, especially in the older adults and in patients with more advanced CKD. Medications should be reviewed regularly, and dosage may need to be adjusted according to the eGFR, especially in the use of sulphonylurea (hypoglycaemia) and metformin (lactic acidosis).

Recently, SGLT2 inhibitors have been found to have a renal protective effect. The 2019 CREDENCE trial demonstrated that treatment with canagliflozin for patients with type 2 diabetes and albuminuric CKD stage 1-3 (median eGFR 56 ml/min) was associated with a reduced risk of ESRD, reduced progression of CKD and a lower risk of cardiovascular events.²⁵ The DAPA-CKD trial also confirmed the benefits of SGLT2 inhibitors in CKD patients (median eGFR 43 ml/min) regardless of the presence or absence of diabetes. In this trial, the use of dapagliflozin was shown to delay the progression of CKD and reduce the risk of ESRD as well as the risk of death from renal or cardiovascular causes.²⁹ Similarly, in the

EMPA-REG study, the use of empagliflozin also improved the cardiovascular outcome of diabetic patients with CKD (median eGFR 70-80 ml/min).³⁰ Regardless of eGFR, SGLT2 inhibitors have consistently shown benefits in patients with CKD across all trials.

3.6 Dyslipidaemia

Dyslipidaemia is a major risk factor for a cardiovascular event. All patients with newly diagnosed CKD should have a lipid profile evaluation. In adults aged >50 years with CKD not on RRT, treatment with lipid-lowering therapy is recommended. This suggestion is supported by the SHARP trial, in which statin plus ezetimibe therapy led to a significant 17% reduction in the relative hazard of the primary outcome involving a major atherosclerotic event. In adults aged 18-49 years with CKD not on RRT, lipid-lowering therapy is recommended if the patient has 1 of the following conditions: known coronary artery disease, diabetes mellitus, prior ischaemic stroke or 10-year risk of cardiovascular event >10%.³¹

3.7 Risk for AKI and infection

Patients with CKD are at higher risk of developing AKI and infection. Any episode of AKI will further reduce the number of viable nephrons and accelerate the progression of CKD. Infection and nephrotoxic medications are the risk factors for AKI.²⁵ A key consideration includes the identification of a patient at risk of AKI (hypovolemia, sepsis), good management of medication, immunisation and monitoring of GFR.²⁰ Withholding metformin, SGLT2 inhibitors, or ACEi/ARB is recommended in the event that the patient is at risk of dehydration or hypovolaemic, for example, experiencing diarrhoea or vomiting, especially if the patient requires hospital admission.²³ Unless contraindicated, patients with CKD should be offered an annual influenza vaccination.

4.0 Management of complications of CKD

4.1 Anaemia

Anaemia is defined as a haemoglobin level of <13 g/dl in men and <12 g/dl in women.¹⁰ As CKD progresses, patients are at increased risk of developing anaemia, as erythropoietin production decreases with a low GFR. It is recommended that patients with stage 3 CKD should have their haemoglobin level measured at least annually or even more

frequently as renal function declines. Anaemia usually starts to develop when GFR <60 ml/min/1.73 m². The treatment of anaemia in CKD includes iron supplementation, use of an erythropoietin-stimulating agent (ESA) and blood transfusion. All CKD patients with iron deficiency should be treated with iron supplementation. Once iron deficiency has been corrected, the use of an ESA can be considered after discussion with a nephrologist. The optimal Hb target in CKD is 10-12 g/dl.

4.2 Mineral bone disease

CKD-mineral and bone disorder (CKD-MBD) is a common complication of CKD. Patients with CKD stage 3 and above should at least have serum calcium, phosphate, alkaline phosphatase, and parathyroid hormone (PTH) measured annually – or more frequently if any abnormalities. The principle of treatment for CKD-MBD is phosphate level reduction towards a normal level.¹⁰ Initial treatment starts with dietary phosphate restriction when phosphate and PTH levels begin to rise. Dietary phosphate restriction also involves a low-protein diet. Patients who can comply with a low-protein diet will usually exhibit a lower phosphate level.³² Drug therapy with phosphate binders should be considered if a patient demonstrates persistent hyperphosphatemia despite dietary restriction. Excess calcium supplementation and a vitamin D analogue should be avoided, as this combination may increase the risk of vascular calcification.

4.3 Fluid overload

The progression of CKD puts patients at risk of developing fluid overload, mainly due to reduced urine production. Accordingly, assessing the fluid status in the clinic setting is essential, looking for symptoms and signs of fluid overload such as uncontrolled BP, raised jugular venous pressure, crepitations in the lungs and pedal oedema. Patients exhibiting fluid overload may be treated with fluid and salt restriction and loop diuretics.¹

4.4 Cardiovascular risk

Low GFR, proteinuria, and CKD-MBD with vascular calcifications have all been associated with cardiovascular morbidity and mortality.³³ Management of cardiovascular risk in patients with CKD is similar to that for those without CKD, involving BP control, glycaemic control and lipid-lowering therapy. Antiplatelet therapy should be offered only as

secondary prevention due to an increased risk of bleeding in this group of patients.²⁰

4.5 Metabolic acidosis

Metabolic acidosis is a complication of CKD that can be present from stages 3 to 5 and needs attention from primary care physicians. Treatment of CKD-related metabolic acidosis with oral alkali has been shown to delay CKD progression. For example, sodium bicarbonate can be initiated when the patient's serum bicarbonate level is less than 22 mmol/L.^{1,3,4}

Conclusion

In conclusion, CKD is a common clinical problem in primary care practice whose prevalence is likely to increase in line with the ageing population and the growing number of risk factors associated with CKD. This disease is often asymptomatic in its early stage. Primary care practitioners play an essential role in identifying and screening those patients at risk, establishing the cause(s)

of CKD, and managing those patients in the early stages of CKD accordingly. Referral to a nephrologist may be necessary to identify the primary cause of the CKD for specific treatment. Those with more advanced CKD should be referred for tertiary care in a timely manner to slow the progression towards ESRD and prepare the patient for long-term RRT.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

The authors received no financial support for this publication.

Acknowledgements

We would like to thank the Director General of Health of Malaysia for his permission to publish this article.

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ORIGINAL ARTICLE

Development, validity and reliability of instrument to evaluate implementation fidelity of the Family Doctor Concept (FDC) programme in public primary care clinics in Malaysia

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Reffien MAM, Aniza I, Sulong S, et al. Development, validity and reliability of instrument to evaluate implementation fidelity of the Family Doctor Concept (FDC) programme in public primary care clinics in Malaysia. *Malays Fam Physician*. 2022;17(1);20–28. <https://doi.org/10.51866/oa1197>

Keywords:

Fidelity, family doctor, validity, reliability, primary care

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Abstract

Introduction: The Family Doctor Concept (FDC) programme was introduced to public primary care clinics in late 2013 as part of the reform agenda in the primary healthcare delivery system. The study aimed to develop a validated and reliable instrument to evaluate the FDC implementation fidelity in primary care clinics.

Methods: The instrument, which adapted the concept of patient-centred care (PCC), resulted from a series of expert discussions, a literature search, an FDC guideline, and a review of meeting minutes. A 2-step process was conducted with experts to achieve content and face validity. Consequently, the instrument was piloted in 5 public primary care clinics in Selangor involving 8 trained raters. Inter-rater reliability was estimated using intraclass correlation (ICC), while internal consistency was measured using Kuder–Richardson Formula 20 (KR-20).

Results: The final instrument comprises 3 sections (instructions, clinic's characteristics and assessment items), with Section 3 containing 15 items divided into four components – population registration, formation of a primary care team, integrated treatment, and monitoring and evaluation. The ICC for total score was excellent, 0.981, while the ICCs of the individual component scores were good to excellent (population registration: 0.937, formation of primary care team: 0.742, integrated treatment: 0.996, and monitoring and evaluation: 0.996). The value of KR-20 was 0.615, which was considered adequate.

Conclusion: The instrument developed was found to be valid in terms of face and content validity and reliable in measuring the fidelity of FDC implementation with excellent inter-rater reliability.

Introduction

An estimated 4.1 million people aged 18 years and above in Malaysia currently live with 2 or 3 major cardiovascular diseases risk factors, and the number is increasing.¹ Adding to the multimorbidity is an ageing population who typically need long-term care from a team of professionals from multiple disciplines. However, overall, the healthcare delivery system in Malaysia is currently disease-oriented, and decisions concerning treatment options are aimed solely at improving clinical outcomes. This approach to care is less responsive to the comprehensive needs and preferences of people with multimorbidity and may even be harmful to them.² For example, people with multimorbidity are typically seen by healthcare providers from multiple fields who may prescribe various medications without realising the potential danger of drug interaction. Thus,

reform towards more responsive health systems is urgently needed, especially in the primary healthcare delivery system, to cater to the comprehensive needs and preferences of people with multimorbidity.³

The definition of primary health care (PHC) stems from the declaration of Alma-Ata and encompasses the broader spectrum of services beyond the traditional healthcare delivery system. Accordingly, this concept is defined as “a whole society approach to health that aims at ensuring the highest possible level of health and well-being and their equitable distribution”.⁴ It incorporates 3 inter-related and synergistic components – primary care and essential public health functions, empowered people and communities, and multisectoral policy and actions. Thus, primary care is a subset of PHC that is more focused on healthcare delivery. It is

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defined as the provision of integrated healthcare services by clinicians who are accountable for addressing a vast majority of personal healthcare needs, developing a sustained partnership with patients, and practising in the context of family and community.⁵ Since the 1970s, the delivery of public primary care services in Malaysia has comprised a 2-tier system consisting of networks of health centres and community clinics.⁶

As part of the reform of primary care service delivery, the Ministry of Health (MOH) Malaysia embarked on the Family Doctor Concept (FDC) programme in late 2013.⁷ It began with a pilot project involving 14 public primary care clinics across the country in 2015 and was expanded each year to another 48 clinics. Currently, 322 out of 1091 public primary care clinics have implemented the programme. It ensures that the population, whether as individuals or as family units, will be able to enjoy patient-centred care that is continuous, holistic and comprehensive. This objective can be achieved by assigning one primary care physician or a team of healthcare workers to a family.⁸ By following this approach, individuals in a family will be treated by the same team of providers, resulting in more patient-centred or personalised care. Subsequently, the patient–doctor relationship will improve, enhancing the quality of care and increasing patient compliance towards the treatment given.^{9,10}

In general, patient-centred care is made up of 7 dimensions, including respect for patients; coordination of care; information, communication and education; physical comfort; emotional comfort/alleviation of fear and anxiety; involvement of family and friends; and transition and continuity.¹¹ Recently, the integrative model of patient-centredness was introduced to include more elements, such as the essential characteristics of a clinician,

clinician–patient relationship, clinician–patient communication, the patient as a unique person, biopsychosocial perspective, patient information, patient involvement in care, involvement of family and friends, patient empowerment, physical support, emotional support, integration of medical and non-medical care, teamwork and team building, access to care, coordination and continuity of care.¹² However, in developing an evaluation instrument in this study, we chose to adopt Greene et al.'s 3 components of patient-centred care: structural, clinical and interpersonal, as shown in [Table 1](#).¹³ This framework is thought to be actionable and relatable to FDC.

Due to the heterogeneity of the public primary care clinics in Malaysia¹⁴ (for example, some clinics having more resources than others or differences between urban and rural locations), the implementation of the FDC programme may differ across settings. Thus, assessing implementation in comparison with the standard set by the programme developers is crucial to facilitate comparison between clinics. Subsequently, policymakers can use the findings to implement appropriate improvements to the programme. Implementation fidelity, also called “integrity”, is defined as the degree to which a programme is implemented as intended.¹⁵ It provides a picture of the degree to which a programme is successfully implemented into an organisation and mediates the relationships between the programme and the intended outcomes. The probability of having a more successful programme is often associated with higher implementation fidelity.¹⁶

The purpose of this study was to develop a validated and reliable instrument to measure the fidelity of FDC implementation in primary care clinics. The practice instrument developed can be used for future monitoring and evaluation activities.

Table 1. Dimension and attributes of patient-centred primary care clinics, as described by Greene et al.

Structural dimension (System features)	Clinical dimension (Provision of care)	Interpersonal dimension (Relationship)
1. Built environment Calm and welcoming space Cleanliness Signage, easy to find way Electrical appliances and furniture	1. Clinical decision support Ensuring shared decision Best-available evidence Supporting self-management Health education and promotion	1. Communication Training on communication skills, retraining Sharing of information with patients Patients' feedback on communication Communication with family & friends

2. Access to care Population registry Easy appointment system Minimised waiting time	2. Coordination and continuity Care coordination between providers Seamless flow of information Coordinates with community and hospital	2. Knowing the patient Training on patient-centredness for complex, chronic illness Surveying patients about the care experience Multidisciplinary meetings
3. Zoning of clinic Formation of team Family database Tracking patients' preferences, values and needs	3. Types of encounters Home visits and domiciliary care Accommodating virtual visits (Phone and email) Palliative care services	3. Importance of teams Ensuring responsiveness of care team to patient's and family needs Engagement of employees for improvements Involvement of community/ panel of advisers

Methods

The study was conducted from August to November 2019. Figure 1 illustrates the steps followed in developing and validating the instrument. In addition to measuring implementation fidelity by creating a scale, the instrument also collected general data on the characteristics of the clinics, including the size of population covered, location, facility type, availability of a Family Medicine Specialist (FMS), and the use of an electronic medical record (EMR) system called TelePrimary Care (TPC).

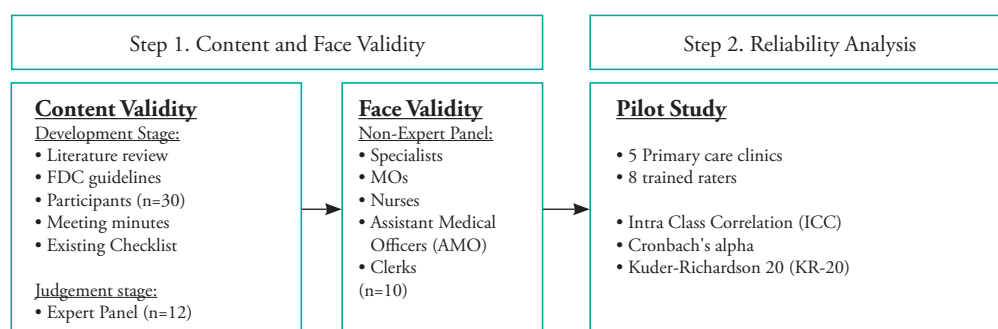


Figure 1: Flow diagram of checklist development, validation and reliability

Step 1

Content and face validity of the checklist

The establishment of content validity is a fundamental step in the development of a new measuring instrument because it represents a precursor for linking abstract concepts with observable and measurable indicators. According to the guideline, the evaluation of content validity consists of a 2-step process, starting with the development stage, which is followed by the judgement stage.¹⁷

Development stage

At this stage, the content for the instrument constituting several domains was obtained primarily from an extensive review of the literature on FDC, person-centred care (PCC), personalised care and other quality improvements interventions, such as the lean healthcare model. In this study, 26 articles were identified as relevant to these topics. In addition, we went through the FDC guidelines provided by the MOH,⁷ reviewed meeting minutes, went through PowerPoint presentations and held discussions with a panel

of experts. All possible components of FDC were extracted to develop the first version of the 4-page instrument, which consisted of three sections, nine components and subcomponents, and 37 items.

A group of experts with experience in FDC implementation provided input and feedback in 2 rounds of consultation and one approval round. The expert group consisted of public health physicians (PHP, n=10), family medicine specialists (FMS, n=6), medical officers (MO, n=4), nurses (n=5), and assistant medical officers (AMO, n=5) from all over the country to achieve a balanced group in terms of multidisciplinary representation and state representation. The first version of the instrument was presented to the experts in a workshop for the development of the instrument, and they provided either written or verbal feedback.

Many of the experts argued that measuring fidelity with a 1 to 5 or 1 to 3 Likert scale would be tedious and might not be practical

in the field. Hence, the panel of experts was in agreement that a “Yes” or “No” response was adequate to capture the implementation of components of FDC. The authors discussed the feedback from every consultation round and agreed on the revisions that were made.

Judgement stage

At this stage, a smaller group of experts, consisting of 12 individuals, 2 from each professional role (PHP, FMS, MO, nurses, AMO and support staff), was required to work independently to evaluate the final version of the instrument. These individuals were selected based on their expertise in healthcare programme implementation, academic credentials and seniority in the MOH. They were also asked to judge the relevance of each component and item in the instrument. At this stage, the instrument contained 3 sections with 22 items.

Face validity

The instrument's face validity was obtained from a non-expert panel involving 10 individuals, 2 from each professional role, including FMS, MO, nurses, AMO, and support staff. They were selected to resemble the target respondents as closely as possible. All of them worked in a primary care clinic located in Selangor that had implemented the FDC programme since 2017. The assessment of comprehensiveness, accuracy, completeness and meaning of all items was conducted in cognitive interview sessions.¹⁸ In these sessions, the participants were asked about their thinking process as they went through the instrument, such as how they interpreted the meaning of questions and possible responses, what they thought about when considering their answers, how they decided on their answers and what each answer meant. Simultaneously, an assessment of the grammar, syntax, organisation, and appropriateness and logical sequence of the items was obtained from the participants. At the end of this stage, the expert panel decided that the 4 components and 15 items with binary “yes” or “no” responses were adequate to assess the implementation fidelity.

Step 2

Reliability analysis

A pilot study was conducted in 5 primary care clinics in Selangor in November 2019 to assess the feasibility and reliability of the instrument. Reliability was measured using internal consistency and inter-rater reliability. Internal consistency measures the degree of

interrelationship or homogeneity among the items, while inter-rater reliability refers to a measurement of the consistency of the absolute value of evaluators' ratings.¹⁹ Additionally, this smaller-scale study was supposed to guide in planning and allow modification of the protocol before researchers would proceed with the real study.²⁰ Thus, this pilot study was also conducted to assess the procedures for approaching the study site and the data collection process.

Eight medical officers with research backgrounds were invited as raters to pilot the instrument by rating 5 purposively selected primary care clinics. They were chosen based on their competency in programme evaluation and vast experience in primary care. The clinics were selected based on their readiness to participate in the project with at least 2 years of experience in the implementation of FDC. The sample size was determined based on a minimum sample of 5 clinics to be assessed by raters that would be required to achieve the statistical significance for an alpha-value set at 0.05 and with the minimum power of at least 80.0%.²¹ Eight raters were required to produce 40 observations, representing the minimum number needed to measure inter-rater reliability.²² The raters were given one hour of training on how to use the instrument and the source of where they could retrieve the information. A glossary containing a description of each item was also given as a guide. The instruments were recorded independently, and raters were not allowed to discuss the findings among themselves. This strategy was employed since the reliability determination depends on the raters, their training and competency.²³

Statistical analysis

The characteristics of the participants and primary care clinics were calculated through descriptive analysis. The internal consistency was measured using Kuder–Richardson Formula 20 (KR-20). The intraclass correlation coefficients (ICC) with a 2-way random effects model and absolute agreement definition and their 95% confidence intervals were used to assess the inter-rater reliability of the items in the checklist. The following classification was used to interpret the ICC values: weak reliability, ICC<0.5; moderate reliability, ICC 0.5–0.75; good reliability, ICC 0.75–0.90; and excellent reliability, ICC≥0.90.²⁴ The level of significance was set at 5% (P<0.05), with a 2-tailed distribution. The data were analysed using IBM SPSS 22.0 for Windows.

Ethical considerations

The study was previously approved by the National University of Malaysia ethical review board (Code: UKM/PPI/111/8/JEP-2019-584) and the Medical Research and Ethics Committee, Ministry of Health Malaysia (Code: NMRR-18-3871-44034).

Results

The final instrument was in the form of a checklist used to measure the implementation fidelity of the clinics based on a scoring system. This 2-page list was easy to complete and took raters an average time of approximately 30 to 40 minutes. The checklist consisted of 22 items, divided into the following 3 sections:

Section 1: The instructions for raters to complete the instrument.

Section 2: Seven items on the characteristics of primary care clinics evaluated, including the size of the population covered, location, facility type, availability of Family Medicine Specialist (FMS), and the use of the TelePrimary Care (TPC) electronic medical record (EMR) system.

Section 3: Fifteen items divided into 4 components (population registration, formation of primary care team, integrated treatment, and monitoring and evaluation)

All items in Section 3 required a binary response of either “yes” or “no”. One point was granted if the answer was “yes” and no points if the answer was “no”. The researchers counted and totalled up the score.

Step 1

Content and face validity of the checklist

At the content-validity developmental stage, several changes were made in terms of the structure of the checklist. The initial draft was longer, consisting of 4 pages divided into 3

sections. Section 3 contained 30 items divided into the three components of patient-centred care proposed by Greene et al.¹³ However, out of 30 items, only 15 were retained; these were rearranged into 4 components. For example, from the structural component, only population registry and formation of teams were considered relevant and retained in the instrument. The majority of items in component 2 involving the clinical component were dropped because they were already measured in the clinical audit; these were replaced with client treatment in an integrated manner component. For component 3, involving interpersonal dimensions, 3 items were considered important: 1. client satisfaction survey, 2. staff personnel survey, and 3. regular meetings. Thus, these items were grouped together and renamed as the monitoring and evaluation component. The measurement of items was also converted from a 3-point Likert scale to a nominal yes or no scale to make the tool more user-friendly for the raters. The changes made were confirmed in the content-validity judgement stage.

The face-validity assessment consisted of the face-to-face interview sessions and professional appraisal of the checklist. The instrument was assessed by physicians, paramedics and support staff, who made 4 changes to the wordings of the items. For example, “integrated care” in component 3 was changed to “treatment in an integrated manner”. The face-validity assessment also resulted in 2 changes to linguistic and interpretative terms in the questionnaire. For instance, “health staff” was changed to “health personnel”.

The final version of Section 3 of the checklist translated from the Malay language is shown in **Table 2**.

Table 2. Final version of Section 3 of the checklist, containing 15 items in 4 components

Items	Yes (1)	No (0)	Notes
Component 1: Population registration			
1. Has a system for registering population. <i>1. Mempunyai sistem untuk mendaftar populasi.</i>			
2. Clinic updates client information in the population register from time to time. <i>2. Mengemaskini maklumat klien dalam daftar populasi dari semasa ke semasa.</i>			
3. The population register has complete personal information details. <i>3. Daftar populasi mempunyai butiran peribadi yang lengkap.</i>			
4. The population register has complete health information details. <i>4. Daftar populasi mempunyai butiran kesihatan yang lengkap.</i>			
5. Population register is used in planning health programmes at clinic level. <i>5. Daftar populasi digunakan dalam merancang program – program kesihatan.</i>			

Component 2: Formation of primary care team			
6. Division of health personnel from various disciplines into several groups. <i>6. Pembahagian anggota kesihatan pelbagai bidang kepada beberapa kumpulan.</i>			
7. Formal discussions among team members are held from time to time. <i>7. Perbincangan dalam satu PHT diadakan dari semasa ke semasa.</i>			
8. Notification to clients in the form of signboards or guides on team division. <i>8. Pemakluman PHT kepada klien dalam bentuk papan tanda atau pemandu arah.</i>			
9. Clinic achievements are distributed according to their respective teams. <i>9. Pencapaian klinik diagihkan mengikut PHT masing - masing.</i>			
Component 3: Client treatment is provided in an integrated manner			
10. Clients from one team are given treatment in the same place. (No OPD and MCH division). <i>10. Klien dari satu pasukan diberikan rawatan ditempat yang sama. (Tiada pembahagian OPD dan MCH)</i>			
11. Medical officers treat patients based on team division. (No OPD and MCH medical officers). <i>11. Pegawai Perubatan merawat pesakit berdasarkan kepada PHT. (Tiada pegawai perubatan OPD dan MCH)</i>			
12. Training to treat patients in an integrated and holistic manner is given to health personnel. <i>12. Latihan merawat pesakit secara integrasi dan holistic diberikan kepada anggota kesihatan.</i>			
Component 4: Monitoring and evaluation			
13. Client survey on FDC. <i>13. Kaji selidik klien tentang FDC.</i>			
14. Health personnel survey on FDC. <i>14. Kaji selidik anggota kesihatan tentang FDC.</i>			
15. Regular clinic-level FDC meetings. <i>15. Mesyuarat FDC peringkat klinik secara berkala.</i>			
Total Score			

Step 2

Reliability test

Table 3 shows the characteristics of the 5 primary care clinics chosen. In the pilot study, a list of liaison officers (LO) for each primary care clinic was obtained from the person in charge of the primary care clinic (either FMS or MO). The job of the LO was to assist the raters' evaluation process. There were no obvious signs of hesitancy or changing opinions based on the markings made by the raters on the instrument.

Table 4 displays the characteristics of the 8 raters.

Table 3: Characteristics of primary care clinics for the pilot study

Characteristics	Clinic A	Clinic B	Clinic C	Clinic D	Clinic E
1. Number of individuals covered	7,595	308,906	No data	182,526	79,906
2. Clinic type	4	3	3	3	3
3. FMS or No FMS	-	FMS	FMS	FMS	FMS
4. TPC or No TPC	-	-	-	-	TPC
5. Location	RURAL	URBAN	URBAN	URBAN	URBAN

Table 4: Characteristics of the 8 raters

Characteristics	Age	Gender	Profession	Level of education	Years of service
Rater 1	38	Male	MO	Master	10
Rater 2	34	Male	MO	Master	8
Rater 3	35	Male	MO	Master	9
Rater 4	35	Male	MO	Master	9
Rater 5	42	Female	MO	Master	15
Rater 6	33	Female	MO	Degree	8
Rater 7	31	Female	MO	Degree	7
Rater 8	32	Male	MO	Degree	8

The minimum total score that raters gave was 5, while the maximum total score was 11. The ICC for total score was excellent, 0.981, while the ICCs of the individual component scores were good to excellent (population registration: 0.937, formation of primary care team: 0.742, integrated treatment: 0.996, and monitoring and evaluation: 0.996), as shown in [Table 5](#). The KR-20 for total items was 0.615, which was considered adequate.

Table 5: ICC and KR-20 values

Component score	ICC	CI (95%)	P value	KR-20
Component 1: Population registration	0.937	0.802-0.993	$P<0.001$	0.615
Component 2: Formation of primary care team	0.742	0.076-0.971	$P<0.001$	
Component 3: Client treatment provided in an integrated manner	0.996	0.988-1.000	$P<0.001$	
Component 4: Monitoring and evaluation	0.996	0.988-1.000	$P<0.001$	
Total score	0.981	0.939-0.998	$P<0.001$	

Discussion

In this study, we were able to develop a checklist based on the components of FDC that all stakeholders found satisfactory. The scaling up of the FDC programme in public primary care clinics over the years has posed challenges to project managers in terms of evaluating its components. FDC is a relatively new concept, introduced in the rather complex environment in healthcare settings; hence, some clinics may find implementing all of its components understandably difficult. Moreover, the concept of patient-centred care is multi-faceted, and the published literature offers well-established instruments to measure each component.^{25,26}

Although a patient-centred care experience may seem aspirational and ideal, Greene et al.'s framework highlights its importance. In the context of FDC, adjustments were made because public primary care clinics had the capacity to implement only a portion of patient-centred care elements, mainly due to limited resources,²⁷ limited consultation time, patient overload and increased clerical and administrative tasks.^{28,29} For example, the interpersonal dimension, such as effective communication that involves active listening to both the patients' medical and non-medical needs (e.g. their values, expectations and life experiences), was not included in the checklist even though it was considered key to delivering patient-centred care.

The findings showed that the ICC values for the individual component scores can be considered excellent, except for component 2, which was good, while the ICC for the total score was excellent (ICC 0.981, $P<0.001$). The results also revealed that the confidence interval (CI) for ICC for component 2 scores was exceptionally wide, 0.076–0.971. This broad

CI could be attributed to the limited number of levels of the component (4 items); moreover, the data were markedly non-normal.³⁰ Additionally, only 7 (17.5%) out of 40 evaluations (made at 5 clinics by 8 raters) gave scores of 3 for domain 2, while the rest yielded scores of 2. None of the raters indicated scores of 1 or 4, resulting in the lower ICC with wide CI. Thus, although this outcome displayed a lack of variability in component 2 scores, it was retained to ensure the content validity of the checklist. Nonetheless, the ICC values for individual score and total score were still in the range of good to excellent.

The study has several limitations. For example, we were not able to select more public primary care clinics in Selangor because not many such clinics fulfilled the criteria for implementing FDC for at least 2 years, which was the MOH's established timeframe for the clinics to adapt to the new approach. The checklist allows the identification of components that require improvement and the identification of potential barriers to the successful delivery of FDC but, it can be further improved by testing the construct validity for each component using a larger sample size. Other limitations involved the lack of variation in the raters. All 8 raters who participated in the study were medical officers with some experience in research. Moreover, all of them had at least a medical degree, along with more than 5 years of service in the MOH.

Conclusion

This study successfully developed an instrument for evaluating FDC implementation fidelity in public primary care clinics. The resulting instrument is valid in terms of content and face validity and has a good to excellent inter-rater reliability with adequate internal consistency.

The inter-rater reliability of individual domain scores was excellent, except for component 2, while the inter-rater reliability of the total score was excellent.

Acknowledgements

We want to thank the Director-General of Health Malaysia for his permission to publish this paper. We must also extend our gratitude to staff from the Ministry of Health Malaysia

who were involved in the study and assisted in data collection. Thanks are also due to the management team from the Family Health Development Division, Ministry of Health Malaysia, for their support and cooperation.

Conflicts of interest

All authors declare that they have no conflict of interest.

How does this paper make a difference to general practice?

- This paper presents an instrument to evaluate implementation fidelity of the Family Doctor Concept (FDC) program established in public primary care clinics.
- The standardised instrument to evaluate implementation fidelity developed can be used in all public primary care clinics so that comparison can be made between them.
- This paper highlights the importance of fidelity to ensure effective implementation of various programs in public primary care clinics

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ORIGINAL ARTICLE

Distribution of refractive error among chinese primary school children in a rural area in Pahang, Malaysia

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Omar R, Wong MES, Majumder C, et al. Distribution of refractive error among chinese primary school children in a rural area in Pahang, Malaysia. *Malays Fam Physician*. 2022;17(1);29–35. <https://doi.org/10.51866/oa1251>

Keywords:

Rural area, refractive errors, Chinese school children, vision screening

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Abstract

Purpose: This study aimed to determine the prevalence and status of refractive error among Chinese primary school children in a rural area in Pahang.

Methods: This investigation entailed a cross-sectional retrospective study design involving case file analyses. The study site was a Chinese medium primary school in a rural locality within Bentong district. A total of 82 school children met the B40 classification and selection criteria; therefore, universal sampling was done. Analyses were done according to age group: Level 1 included ages 7 to 9 years, while Level 2 comprised 10- to 12-year-olds.

Results: The mean age of the 82 Chinese school children was 9.72 ± 1.5 years; the percentage of refractive errors found was 80.48%. A total of 53 (64.63%) children had myopia. Two-way ANOVA showed a significant difference ($P=0.038$) in the refractive error between age groups Level 1 and 2, but no significant difference ($P=0.947$) was observed in refractive error between genders. The chi-square test and Fisher's exact test showed no significant association between the type of refractive error with gender ($P>0.05$) and age group ($P=0.319$).

Conclusion: Myopia was the most common type of refractive error among Chinese school children in a rural area in Pahang. Refractive error severity was influenced by age group but not by gender. Types of refractive error were not associated with age group and gender. Hence, it is recommended that Chinese school children in rural areas seek an annual vision screening or eye test.

Introduction

Refractive errors are among the most common problems that individuals in developing nations in Asia currently face, representing a continuing public health problem across the world. If left untreated, visual impairments resulting from refractive errors can cause disruption of the daily activities of those afflicted,¹ especially among school-age children. Worldwide, 153 million people aged 5 years and above have been identified as visually impaired, and of these, 8 million will become blind as a result of refractive errors.² Previous studies set in Malaysia have shown that 80% of children with reduced vision have uncorrected refractive errors.³⁻⁴ In their findings, these studies also suggested that treatment of visual problems such as refractive errors must be done without delay to ensure a better prognosis.⁵⁻⁶ The types of refractive error discussed in these studies were categorised into myopia, hyperopia and astigmatism.⁷

The environment and genetics have been reported as contributing to the occurrence of

myopia and its progression.⁸ While genetic causes of myopia are more challenging to address, environmental causes can typically be effectively managed. Thus, taking a serious look at the differences in the nature and extent of refractive errors is critical, especially those that are typically closely related to places of habitation and work in both rural and urban (metropolitan) areas. Research has revealed that the prevalence of myopia and refractive error among Chinese primary school children aged between 7 and 12 years in Kuala Lumpur was 37%.⁹ The results of a similar study repeated in an urban area of the Gombak District, Kuala Lumpur, showed that Chinese school children had the highest prevalence of myopia. In contrast, hyperopia was reported to be more common among children of other races.³ Hashim et al. (2008) found that 7.7% of Malay school children aged 6 to 12 years in rural areas of Kota Bharu, Kelantan, had refractive errors.⁴ According to this study, the prevalence of myopia in rural areas was 5.4%, followed by astigmatism (1.0%) and hyperopia (0.6%). These results suggest, that a lower

prevalence of myopia was observed among Malay children who lived in rural areas in Kelantan compared to those who lived in urban areas such as Kuala Lumpur and Singapore.⁴ The findings of these studies also seem to indicate that the prevalence of myopia among Chinese primary school children is higher in urban areas when compared to Malay children; however, the prevalence rate of refractive error in these studies was only an estimated value for rural Malay school children. To the best of our knowledge, little published data are available on the prevalence of uncorrected refractive errors among primary Chinese school children in rural areas in Malaysia. Hence, evaluating the prevalence of refractive error among rural Chinese primary school children is also vital since myopia is known to be more common among the Chinese population compared to the Malays or Indians. While an ethnic difference has been noted in terms of myopia and refractive errors, the presence of a direct genetic component to this matter is unlikely, as studies involving similar ethnic populations reported in neighbouring area (Singapore) have similar findings but with varying magnitudes, leading some researchers to conclude that environmental factors probably play a larger role in this variation in magnitude.¹⁰

Thus, postulating that different lifestyles and surroundings in rural areas may have a significant impact on refractive error among children, especially those attending primary school, identifying the magnitude of this impact is essential. Since children in rural schools frequently face greater learning resource challenges compared to those in urban localities, identifying the prevalence of myopia and refractive error in both rural and urban children is vital. Furthermore, under the current Covid-19 situation, most of the teaching and learning is being conducted online, involving long hours of near work, using small display screens and engaging in longer screen viewing time. These circumstances lend even more urgency to promoting good vision in children.^{4,8,11,12} Learning resource challenges include the availability of printed learning aids, such as workbooks and study guides, and access to online resources. In the case of children in primary school, the Ministry of Education (MOE) measures their ability to complete summative and formative assessments based on their age groups. Two levels are currently employed: Level 1, which encompasses Standard 1 to 3 and involves children from age

7 to 9 years, and Level 2, which covers Standard 4 to 6 and includes children from 10 to 12 years of age. These levels reflect differences in the syllabus and learning comprehension level for the 2 age groups. In addition, the difficulty level of words that children should know and understand differs between levels.¹³ It should also be noted that primary school learning resources, especially printed books and worksheets, exhibit certain differences in the presentation of text font size and level of difficulty in terms of reading comprehension. Hence, any visual disturbances, such as blurred vision caused by refractive error, can make it difficult for affected children to cope and concentrate in class on the learning material during teaching and learning activities. Chinese school children in rural areas may share a significant prevalence of myopia with their urban peers. However, information concerning the prevalence of myopia among these rural Chinese school children is currently limited. Therefore, this study aimed to determine the prevalence and status of refractive error among Chinese primary school children in a rural area. The study was conducted at a Chinese language primary school located in Pahang. One hope for this study was to gain an indication of the prevalence of myopia and uncorrected refractive error among rural Chinese school children in order to confirm the validity of the assumption that refractive errors have a higher prevalence among urban children. Managing refractive errors in children, especially those of school-going age, is important to ensure that their learning experience is not disrupted because of blurred vision caused by uncorrected refractive error, which is an eminently avoidable reason behind visual impairment that is, for the most part, easily treated if detected early.

Methodology

This investigation entailed a cross-sectional retrospective study design involved case file analyses. The case files were obtained from the database of an Universiti Kebangsaan Malaysia, Faculty of Health Sciences, Optometry Clinic filed under the Vision Screening Community Health Programme, specifically, a programme that was carried out in a rural area in the district of Bentong, Pahang. The study site was a Chinese language primary school in a rural locality within the district of Bentong that was attended by the children living in the general vicinity of the school. The student population comprised a mixed ethnic group, with a majority of children having Chinese parents. The study was conducted among the less

privileged students as determined by the school authorities (in the B40 socioeconomic group, that is, families earning less than RM2500 per month). The study's inclusion criteria were as follows: the school child had to be of Chinese ethnicity (both parents being Chinese), had to fall within the range of 7-12 years of age, and required the permission of parents or guardians to participate. According to the study's exclusion criteria, schoolchildren of non-Chinese ethnicity or with 1 non-Chinese parent were ineligible to participate. The sample size for this study was calculated using the formula of estimating a population proportion with specified absolute precision, as described by Lwanga and Lemeshow,¹⁴ yielding a necessary sample size of 100. However, during the period of sample selection, only 82 schoolchildren in total presented and met the B40 classification and selection criteria; thus, universal sampling was done. The Universiti Kebangsaan Malaysia Ethical Committee (NN2172011) approved this study, and its conduct followed the conditions required under the Declaration of Helsinki.

Information regarding demographic data, visual

acuity, an objective and subjective refraction results were extracted from the examination records. The Snellen chart used was a series of the BS 4274-1:2003 type. Monocular visual acuity with and without correction was obtained for the right eye and left eye. The subjective refraction data was considered as the final prescription and used in the analysis. All data analyses for this study employed the Statistical Package for Social Sciences (SPSS) software version 25.0. Normality of the data was determined using the Shapiro–Wilk test. A *P* value of less than 0.05 was used to set the statistical level of significance in the analysis. Descriptive analysis was used to determine the mean, standard deviation, range, and population percentages of interest. The types of refractive errors found were reported. **Table 1** displays a summary of the myopia and hyperopia categories⁸ used. A two-way ANOVA was performed to determine the changes in refractive errors between the age groups and gender. Analyses to determine the relationship between the types of refractive error with gender and age groups included the chi-square test and Fisher's exact test.

Table 1. Category of refractive errors and the severity classification summary

Refractive errors category	Severity		
	Low	Moderate	High
Myopia	-0.25 to -3.00 Ds	-3.25 to -6.00 Ds	>-6.25 Ds
Hyperopia	+0.25 to +3.00 Ds	-3.25 to +5.00 Ds	>+5.25 Ds

Resource: AOA 1997⁸

Results

A total of 82 Chinese primary school children were enrolled in this study. The children's age range was between 7 and 12 years, and the mean age was found to be 9.72±1.5 years. The children's records were separated into 2 categories according to age, namely Level 1 (7 to 9 years) and Level 2 (10 to 12 years), as previously explained. Thirty children fell into Level 1, and the remaining 52 were in the Level 2 age group category. Out of the 82 children, 35 (42.69%) were boys, and 47 (57.31%) were girls.

Refractive Errors

The subjective refraction being prescribed to the children was used to determine refractive errors. Analysis revealed that only 62 (75.61%) of the Chinese primary school children were found to need to wear spectacles. The remaining children did not have any significant refractive errors; thus, no spectacles were prescribed for

them. Therefore, the percentage of refractive errors in the Chinese primary school children in the rural area where this study took place was calculated as 80.48%. Among the children identified as having refractive errors, 53 (64.63%) had myopia, 13 (15.86%) hyperopia, and 16 (19.51%) emmetropia. The refractive error severity level estimation was determined based on the criteria described in **Table 1**. The percentages of low, moderate, and high myopia were 79.70%, 20.75%, and 7.55%, respectively. Meanwhile, the low and high hyperopia percentages were 84.61% and 15.39%, respectively. The mean refractive error for the right eyes was -1.68±1.25 Ds, ranging from -10.00 Ds to +3.50 Ds; for the left eyes, the mean was -1.63±1.25 Ds, ranging from -9.00 Ds to +4.00 Ds. There was no significant difference (*P*=0.542) between the right and left eye refractive error. Therefore, for the subsequent analyses, only the right eye spherical equivalent data were considered and used.

Comparison of Refractive Errors between Age Groups and Genders

The mean refractive error among these Chinese primary school children for Level 1 was -0.67 ± 2.82 Ds (range -10.00 Ds to $+6.00$ Ds). For Level 2, the mean refractive error was -1.83 ± 0.18 Ds (range -9.00 Ds to $+1.50$ Ds). The mean refractive error for boys and girls was -1.69 ± 2.72 Ds and -1.20 ± 2.29 Ds, respectively. A two-way ANOVA revealed a significant difference in the refractive error between Levels 1 and 2 ($F=4.467$, $df=1$, $P=0.038$). Nevertheless, no significant difference was observed in refractive error between genders ($F=0.963$, $df=1$, $P=0.947$), as shown in [Table 2](#).

Table 2. Comparison of refractive error between age group and gender

Descriptive statistics				Test of between-subject effect			
Age group	Gender	N	Mean $\pm$ SD	Variable	Df	F	P value
Level 1	Boys	14	-0.95 ± 2.93 DS	Age group	1	4.467	.038
	Girls	16	-0.43 ± 2.79 DS	Gender	1	.963	.330
Level 2	Boys	21	-2.19 ± 2.53 DS	Age group * Gender	1	.004	.947
	Girls	31	-1.59 ± 1.92 DS				

Association of Types of Refractive Errors with Age Group and Gender

A chi-square test showed no significant association between the type of refractive error and gender [χ^2 (1, $N=66$) = 0.645 , $P>0.05$], as can be seen in [Table 3](#). However, for the age groups, the chi-square test was not considered because more than 20% of the cells in the data table had an expected count of less than 5. Hence, Fisher's exact test was used instead for the analysis. As [Table 4](#) illustrates, the analysis showed no significant association between the type of refractive error and age group ($P=0.319$).

Table 3. Association between gender with type of refractive error

		Type of refractive error		Total	Chi-square tests for age group					
		Hyperopia	Myopia			Value	df	Asymptotic significance (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
Gender	Boys	7 (5.7)	22 (23.3)	29	Pearson's chi-square	.645	1	.422	-	-
	Girls	6 (7.3)	31 (29.7)	37	Continuity correction ^a	.241	1	.623	-	-
Total		13	53	66	Likelihood ratio	.641	1	.423	-	-
a. 0 cells (0.0%) have expected count < 5. The minimum expected count is 5.71.					Fisher's exact test	-	-	-	.537	.310
b. Computed only for a 2x2 table.					N of valid cases	66	-	-	-	-

Table 4. Association of age group with type refractive error

		Type of refractive error		Total	Chi-square tests for age group					
		Hyperopia	Myopia			Value	df	Asymptotic significance (2-sided)	Exact sig. (2-sided)	Exact sig. (1-sided)
Age group	Level 1	6 (4.1)	15 (16.9)	21	Pearson's chi-square	1.534 ^a	1	.216	-	-
	Level 2	7 (8.9)	38 (36.1)	45	Continuity correction ^b	.821	1	.365	-	-
Total		13	53	66	Likelihood ratio	1.467	1	.226	-	-
a. 1 cell (25.0%) had expected count < 5. The minimum expected count is 4.14.					Fisher's exact test	-	-	-	.319	.181
b. Computed only for a 2x2 table.					Linear-by-linear association	1.510	1	.219	-	-
					N of valid cases	66	-	-	-	-

Discussion

In this study, refractive errors were determined based on the final prescription of the subjective refraction prescribed to rural Chinese primary school children from the case files. A total of 75.61% of these school children were prescribed spectacles. In comparison, previous studies have identified the number of primary school children who need to wear spectacles as ranging from 17.1% to 37%.^{3,9} Thus, the present study's findings regarding the percentage of Chinese primary school children

needing spectacles was higher. A possible explanation could be attributed to differences in the study population, as the current study focused on Chinese primary school children, while previous studies investigated all ethnicities among primary school children. Moreover, we postulated that the parents or these children themselves may not have been aware that their vision was blurred and that it could be improved by wearing spectacles. It is also possible that the Chinese primary school children in this study had not attended any vision screening programme before, despite the School Health Team Vision Screening Programme by the Ministry of Health (MOH) that conducts vision screening regularly at schools.¹⁵ Notably, the MOH-sponsored School Health Team Vision Screening Programme's coverage is limited to about 10% of school populations due to certain constraints, such as scheduling issues, available teams and accessibility to the schools. The lack of awareness of the impact of uncorrected refractive errors might be considered as a major factor for the raised percentage refractive error found in this study. This lack of awareness, in combination with other factors, such as being in a rural area or of a lower socioeconomic level, as well as the availability of vision care resources, are probably complicit in the high prevalence observed regarding refractive errors needing correction. Accordingly, a comprehensive awareness programme and better visual screening coverage should be designed and implemented. Engagement with parents and the community concerning the importance of vision screening and visual error correction is an ongoing need in order to empower parents and the community to be more attentive to visual issues that can afflict their children and, furthermore, can impact their scholastic performance and achievements.

This study demonstrated the prevalence of refractive error among Chinese primary school children in a rural area to be 80.48%, which suggests that refractive error problems are not exclusive to school children in urban areas. Hence, all primary school children should undergo vision screening regardless of their locality, whether urban or rural. The refractive errors noted in this study's rural Chinese primary school children were found to be predominantly in the lower categories of either myopia or hyperopia. Similar findings have been reported among urban primary school children in Petaling Jaya.¹⁶ In the study, the children were found to have low myopia, ranging from -0.25 to -1.75 Ds in a total of 58% of the right

eye and 61.8 % of the left eye. These findings suggest that Chinese primary school children in both rural and urban areas suffer mainly low to moderate types of refractive errors, which vision screening can identify, making correction possible. Furthermore, the refractive error found, when compared between the right and left eye, did not differ significantly. This finding also suggests that less anisometropia might occur among rural Chinese primary school children.

Visual efficiency, which describes the quality of performance of the information gathering process, depends on focusing, vergence and eye movement abilities in an individual. Poor focus has a significant impact on learning and reading. The occurrence of a persistent visual problem can impact a child's visualisation skills and can affect learning ability in terms of spelling and the child's recall of spelling.¹⁷ Moreover, 80% of learning comes from visual interaction through the visual pathway.¹⁸ An earlier study showed how visual impairment could affect children's development and eventual academic performances.¹¹ As refractive error will lead to poor focusing, it is therefore necessary to highlight this issue. The percentage of myopia in this study was found to be 64.63%, a figure much higher than that found in a previous study.⁹ This finding suggests that rural Chinese primary school children experience the same problem as their peers from urban areas. Nevertheless, primary school children from rural areas face the same academic pressure as those in urban areas; moreover, competition for further education is very much contingent on the children's scholastic achievements at the end of their secondary schooling. Furthermore, under the current Covid-19 pandemic conditions, teaching and learning have mostly been conducted online, causing the learning environment to be dependent on a visual display unit such as desktop and laptop computers or even through portable devices, including mobile telephones. The different screen sizes of these devices make near tasks a challenge, typically resulting in longer viewing times.¹² This situation can cause fatigue to the visual system; moreover, previous studies have shown that excessive near tasks can accelerate the progression of myopia.^{4,8,19} Therefore, vision screening should be emphasised and conducted among all Chinese primary school children in both urban and rural areas to address and treat refractive errors as early as possible. That said, refractive errors are the only vision problem easily detected using a visual acuity test and able to be corrected easily by wearing spectacles. The

percentage of myopia is known to be higher among Chinese primary school children, and it is found in both rural and urban areas. For example, Goh et al. found that 45.3% of Chinese school-age children in Gombak had myopia compared to 13.9% Malays and 15.5% Indians from the same district.³ Thus, parents must be made aware and must be encouraged to take the initiative to bring their children for vision screening, as children may be ignorant of the fact that they have blurred vision and rarely complain of it. However there is a study reported the percentage of myopia as 5.4% among 12-year-olds, which is considerably lower than that found in this study.⁴ The difference may be due to the location of the school and the ethnic mix of the schoolchildren in the school. Regardless of the studies done, all of these investigations have reported at least or more than 10% of school children to have refractive errors; many, if not all, would benefit from treatment. Thus, eye examinations for children are essential to rule out the presence of refractive errors, many of which would require treatment, while others would need on going follow-up to manage any deterioration as the children age. Impaired vision can interfere with a child's learning process, as blurry vision can result in poor performance in school. In turn, poor performance can lead to a loss of confidence among the children, which could contribute to further deterioration in scholastic performance. In this study, the percentage of hyperopia among rural Chinese primary school children was 15.86%. This finding suggests that only a small number of Chinese primary school children had hyperopia. A previous study by Reddy et al. reported a similar finding where only a small number of hyperopia cases were identified.¹⁶ Therefore, even though the numbers are small compared to myopia, hyperopia is still a problem that can occur in Chinese primary school children. Hence, healthcare professionals should be aware of the possibility of hyperopia and should be corrected. The associated symptoms of uncorrected hyperopia are usually headache and asthenopia, and this affliction can also affect children's ability to learn.

This study showed no significant association between the types of refractive error related to age group or gender. Although there was no significant association between the types of refractive error and age group, it was noted that Level 2 (10 to 12 years) had a higher percentage of myopia (71.70 %) compared to Level 1 (7 to 9 years) children (28.30%). These findings

resemble those from a study among school-age children in Gombak. In that study, myopia was present in 9.8% of 7-year-old children, increasing to 34.4% among those 15 years old. The study concluded that myopia was associated with older age.³ Other studies that reported on the distribution pattern of refractive errors with increment in age among rural Chinese primary school children also showed a shift towards myopia with increasing age.⁹ This phenomenon was attributed to the natural physiological development of children's eyes as they grow older. The rapid growth in childhood tends to lead to myopia increments, involving changes in refractive power, corneal curvature, and axial length of the eye.²⁰ This effect can accelerate with the performance of excessive near tasks (learning activities) and through machine dependence that increases as school children grow older and progress to a higher degree of learning.^{4,21}

It was noted that gender did not seem to have any association with the types of refractive error in this study. However, myopia was found to occur in higher proportions in girls, at 58.50%, compared to boys, at 41.50%. This finding was in agreement with Goh et al.'s findings that associated myopia with the female gender.³ School children who are identified as having any refractive error should be referred to an optometry clinic for further evaluation and then received prescription according to the most appropriate management. Furthermore, refractive error needs to be treated as early as possible to minimise any adverse implications. Hence, annual vision screening programmes should be implemented for all school children to ensure that existing vision errors are detected early and any latent errors can be monitored and treated when appropriate throughout a child's school life. Parents and teachers should also be empowered via health education about the eye diseases and visual disorders that commonly occur among school children. This approach will help them detect the possible occurrence of vision problems, allowing them to seek help for investigation and treatment. For future research, it is suggested to re-evaluate and compare the prevalence of refractive error between rural and urban school children after their exposure to greater use of digital devices, as has occurred because of the ongoing Covid-19 pandemic.

Conclusion

The percentage of refractive error among rural Chinese school children was found to be 80.48%. Myopia was the most common type

of refractive error seen. The refractive error was significantly different between the Level 1 and Level 2 age groups, but no significant difference was observed between genders. There was no significant association of age group and gender with the types of refractive error, but the older age group and girls displayed a higher occurrence of myopia. As the prevalence of refractive error was found to be high among these school children, it is therefore a matter

of importance to conduct adequate vision screening in rural schools and provide a suitable annual vision screening programme for these school children.

Acknowledgements

We would like to acknowledge and thank the school children, their parents and their school for participating in this study.

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ORIGINAL ARTICLE

The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor

Ping Yein Lee, Hani Syahida Salim, Yee Gin Cheng, Zunayrah Zainuddin, Harvind Singh, Kien Woon Loh

Lee PY, Hani SS, Cheng YG, et al. The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor. *Malays Fam Physician*. 2022;17(1):36–43. <https://doi.org/10.51866/oa1297>

Keywords:

Diabetes, Diabetic Polyneuropathy, Neuropathic Symptoms Score, Malaysia

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Abstract

Introduction: Diabetic Peripheral Neuropathy (DPN), the most common complication of Diabetes Mellitus (DM), is often under-diagnosed and inadequately treated. This study identified the proportion of undiagnosed DPN and its associated risk factors among patients with established type 2 DM (T2DM) in community health clinics in the Gombak district.

Methods: A cross-sectional study was conducted in 2 community health clinics within the Gombak district between September and December 2017. Adults with T2DM were selected via systematic random sampling and screened using the Neuropathy Symptoms Score (NSS). Clinical records of participants' foot examinations were reviewed to identify positive findings of DPN and compared with the NSS.

Results: The study's sample comprised 425 patients. Most had co-morbidities, including hypertension, dyslipidaemia and pre-existing DM-related complications. About two-thirds of them performed no daily foot inspection and had no proper footwear. The proportion of patients with positive NSS was 49.4%. However, only 0.2% were diagnosed with positive DPN in their clinical foot examination record.

Conclusion: Although a positive NSS was identified in 1 out of 2 patients with established DM, only 0.2% of patients had DPN on their examination records. Most patients had never done daily foot inspections and lacked proper footwear. A positive NSS was associated with uncontrolled diabetes and lower BMI. Proper screening and examination for patients, especially those with uncontrolled diabetes and low BMI, is crucial in identifying DPN to ensure that these diabetic patients receive better preventative care, especially proper foot care and strict diabetic control, to prevent DPN-related complications.

Introduction

The World Health Organization has reported that about 422 million people worldwide have diabetes as of date. Moreover, the prevalence of this disease has been increasing over the past 3 decades.¹

The National Health and Morbidity Survey 2019 revealed that the prevalence of diabetes in Malaysia has increased in recent years from 11.2% in 2011 to 18.3% in 2019.¹ According to the International Diabetes Federation, the prevalence of diabetes among Malaysian adults reached 16.8% in 2020.² Treatment for diabetes and its complications are costly, calculated to be at 5.6% of health GDP in 2013 in Malaysia.³

Diabetic peripheral neuropathy (DPN) is the

commonest long-term complication, affecting an estimated 78.5% of diabetic patients⁴; moreover, its prevalence increases with the duration of diabetes. DPN is symmetric and predominantly sensory, starting distally and gradually spreading proximally in a glove-and-stockings distribution pattern. It causes substantial morbidity and increased mortality. DPN often leads to many hospitalisations and 50-75% of non-traumatic amputations, resulting in low quality of life^{5,6} and an enormous economic burden.

DPN is often misdiagnosed and inadequately treated despite the implementation of foot screening programmes among diabetic patients, possibly due to the failure of physicians to diagnose DPN when using perception alone

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(instead of using a diagnostic tool).⁷ Failure to diagnose DPN early leads to challenging complications, for example, neuropathic pain and diabetic foot ulcers.

This study aimed to identify the proportion of patients with DPN symptoms and associated factors among T2DM patients using the Neuropathy Symptom Score (NSS) questionnaire. Thus, this study provides the potential missed diagnosis of DPN and its associated factors, in turn helping clinicians to identify patients at risk of DPN. The recognition of a potential missed diagnosis is crucial since appropriate management following a diagnosis of DPN can prevent further complications.

Methods

This cross-sectional study was conducted on type-2 diabetes mellitus (T2DM) patients who attended diabetic follow-up appointments in 2 urban health clinics (KK Taman Ehsan and KK Hulu Kelang) in the Gombak district from September to December 2017. These clinics had a high prevalence of diabetic patients undergoing regular follow-up checks. A pilot study that was conducted yielded good outcomes. Participants were recruited via a systematic random sampling method. The first participant was selected randomly using the dice method; subsequently, every second patient from the registry who fulfilled the inclusion criteria were selected to participate in the study until the target number of samples was reached. Those who met the inclusion criteria were Malaysian citizens more than 18 years old with >5 years' history of T2DM.

Patients with T2DM duration <5 years and/or who had pre-existing DPN were excluded from the study. The sample size of 425 participants was calculated using StatCalc Epi Info 7 while considering a 20% dropout rate. The study's response rate was 100%. Informed consent was collected before each interview.

A questionnaire guided the participants' interviews. Part 1 of the questionnaire collected details regarding their social demographic data, smoking status, alcohol intake, physical activity, footwear choices and performance of daily foot inspections. Participants were interviewed in person by researchers who were trained before starting data collection in both clinics.

Part 2 of the questionnaire, with results obtained from the patients' medical records, explored the clinical characteristics of the participants, including weight, height, blood pressure, latest fasting/random blood sugar, HbA1c, clinical history and list of medications.

Part 3 involved the use of the NSS questionnaire, a validated instrument used to aid in the diagnosis of DPN. The NSS has 82% sensitivity (indicating positive predictive value) and 67% specificity (referring to negative predictive value).⁸ This tool was verified in a multicentre study in 118 UK hospitals in 1993,⁸ where the NSS was combined with the neuropathy disability score (NDS) to establish the prevalence of DPN. The same tool was also used in a study conducted in 1998-1999 in a primary care clinic at UM hospital and Hospital Kuala Lumpur.⁹

Table 1. Neuropathy Symptom Score

Neuropathic Symptoms	Scores
1. Burning/ Numbness/ Tingling	2
Fatigue/Cramping/Aching	1
None of the above symptoms	0
2. Symptoms present in feet	2
Symptoms present in calves	1
Symptoms present elsewhere	0
3. Nocturnal exacerbation of symptoms	2
Symptoms present day and night	1
Symptoms present during daytime only	0
4. Symptoms wake patient up from sleep	1
5. Manoeuvres to reduce symptoms	
Walking	2
Standing	1
Sitting/lying	0
Total Score	

Note: Mild symptoms 3-4, Moderate symptoms 5-6, Severe symptoms 7-9

The presence of any symptoms was considered as a positive NSS indicating the probable presence of DPN.⁹

Part 4 of the questionnaire involved reviewing the clinical records of participants who had undergone foot examinations to identify positive findings of DPN.

The data were analysed using SPSS 25.0. Descriptive analysis was performed, and continuous variables were presented in terms of mean and standard deviation, while categorical data were presented in the form of numbers and percentages. The association of factors with a positive NSS was done using a chi-square test. P value<0.05 was considered statistically significant. Lastly, this study was approved by

the Medical Research and Ethics Committee, NMRR-17-1065-35860 (IIR).

Results

In total, 425 diabetic patients were recruited for this study. The overall proportion of patients with a positive NSS was found to be 49.4%. As can be seen in **Table 2**, the sample population consisted largely of females >60 years old (66.8%). They mainly represented Malay (40%) and Chinese (44.9%) ethnicities and came from a low socioeconomic group (56.9%).

Most of the participants were non-smokers (87.3%), non-alcohol consumers (89.9%) and physically active (53.6%). More than half of them did not use proper footwear (60.5%) and did not perform a daily foot inspection (57.9%).

Table 2. Social Demographic Data of Patients

Demographic Data	N	%
Age		
<60 years old	141	33.2
>60 years old	284	66.8
Gender		
Male	141	33.2
Female	284	66.8
Ethnicity		
Malay	170	40
Chinese	191	44.9
Indian	64	15.1
Occupation		
Employed	114	26.8
Unemployed	311	73.2
Education level		
None	26	6.1
Primary	152	35.8
Secondary	216	50.8
Tertiary	31	7.3
Household income		
< RM1000/month	242	56.9
RM1001-3000/month	127	29.9
RM3001-6000/month	44	10.4
> RM6000/month	12	2.8
Marital status		
Single	15	3.5
Married	395	92.9
Others	15	3.5
Smoking status		
Smoker	54	12.7
Non-smoker	371	87.3
Alcohol status		
Alcohol drinker	43	10.1
Non-alcohol drinker	382	89.9
Physical activity		
Physically active	228	53.6
Physically inactive	197	46.4
Footwear		
Proper shoes	168	39.5
Improper shoes	257	60.5
Daily foot inspection		
Done	179	42.1
Not done	246	57.9

Table 3 reveals that the sample population consisted of patients with multiple co-morbidities, including hypertension (90.4%), dyslipidaemia (81.6%), overweight (83.3%) and pre-existing complications of diabetes (81.6%).

Table 2. Clinical Characteristics of Participants

Clinical characteristics	N	%
<i>Family history of DM</i>		
Yes	201	47.3
No	224	52.7
<i>Hypertension (on antihypertensive medication)</i>		
Yes	384	90.4
No	41	9.6
<i>Dyslipidaemia (on lipid-lowering medication)</i>		
Yes	347	81.6
No	78	18.4
<i>Pre-existing DM complications (diagnosed retinopathy/polyneuropathy/nephropathy)</i>		
Yes	82	81.6
No	343	18.4
<i>Blood pressure (<140/80)</i>		
Controlled	185	43.5
Uncontrolled	240	56.5
<i>Annual foot examination</i>		
Done	411	96.7
Not done	14	3.3
<i>Antidiabetic agent</i>		
Monotherapy	85	20.0
Combination	158	37.2
Insulin	182	42.8
<i>HbA1c</i>		
<6.49 %	99	23.3
>6.5%	326	76.7
<i>BMI</i>		
<23kg/m ²	71	16.7
>23kg/m ²	354	83.3
<i>Diabetic duration</i>		
5-10 years	260	61.2
>10 years	165	38.8

Table 4 displays the sample population's NSS-related factors. A positive NSS was found to be associated with a higher HbA1c level ($P=0.041$) and lower BMI ($P=0.039$). However, a positive NSS was not found to be associated with other social demographic factors, as shown in the table

Table 4. Factors associated with Positive NSS

Variable	NSS negative N(%)	NSS positive N(%)	P value
<i>Age</i>			0.45
<60 years old	75 (34.9)	66 (31.4)	
>60 years old	140 (65.15)	144 (68.6)	
<i>Gender</i>			0.09
Male	97 (45.1)	78 (37.1)	
Female	118 (54.9)	132 (62.9)	
<i>Ethnicity</i>			0.62
Malay	86 (40)	84 (40)	
Chinese	100 (46.5)	91 (43.3)	
Indian	29 (13.5)	35 (16.7)	
<i>Education level</i>			0.73
None	15 (7.0)	11 (5.2)	
Primary	72 (33.5)	80 (38.1)	
Secondary	112 (52.1)	104 (49.5)	
Tertiary	16 (7.4)	15 (7.1)	
<i>Occupation</i>			0.16
Employed	64 (29.8)	50 (23.8)	
Unemployed	151 (70.2)	160 (76.2)	

Variable	NSS negative N(%)	NSS positive N(%)	P value
Household income			0.94
< RM1000/month	122 (56.7)	120 (57.1)	
RM1001-3000/month	63 (29.3)	64 (30.5)	
RM3001-6000/month	23 (10.7)	21 (10.0)	
> RM6000/month	7 (3.3)	5 (2.4)	
Marital status			0.48
Single	6 (2.8)	9 (4.3)	
Married	203 (94.4)	192 (91.4)	
Others	6 (2.8)	9 (4.3)	
Smoking status			0.17
Smoker	32 (14.9)	22 (10.5)	
Non-smoker	183 (85.1)	188 (89.5)	
Alcohol status			0.94
Alcohol drinker	22 (10.2)	21 (10.0)	
Non-alcohol drinker	193 (89.8)	189 (90.0)	
Physical activity			0.79
Physically active	114 (53)	114 (54.3)	
Physically inactive	101 (47)	96 (45.7)	
Footwear			0.43
Proper shoes	81 (37.7)	87 (41.4)	
Improper shoes	134 (62.3)	123 (58.6)	
Daily foot inspection			0.61
Done	88 (40.9)	91 (43.3)	
Not done	127 (59.1)	119 (56.7)	
Family history of DM			0.895
Yes	101 (47)	100 (47.6)	
No	112 (53)	110 (52.4)	
Hypertension			0.567
Yes	196 (91.2)	188 (89.5)	
No	19 (8.8)	22 (10.5)	
Dyslipidaemia			0.059
Yes	168 (78.15)	179 (85.2)	
No	47 (21.9)	31 (14.8)	
Pre-existing DM complications			0.111
Yes	35 (16.3)	47 (22.4)	
No	180 (83.7)	163 (77.6)	
Blood pressure			0.197
Controlled	87 (40.5)	98 (46.7)	
Uncontrolled	128 (59.5)	112 (53.3)	
Annual foot examination			0.964
Done	208 (96.7)	203 (96.7)	
Not done	7 (3.3)	7 (3.3)	
Antidiabetic agent			0.092
Monotherapy	46 (21.4)	39 (18.6)	
Combination	88 (40.9)	70 (33.3)	
Insulin	81 (37.7)	101 (48.1)	
HbA1c			0.041*
<6.49%	59 (27.4)	40 (19)	
>6.5%	156 (72.6)	170 (81)	
BMI			0.039*
<23kg/m ²	28 (13)	43 (20.5)	
>23kg/m ²	187 (87)	167 (79.5)	
DM duration			0.059
<10 years	141 (65.6)	119 (56.7)	
>10 years	74 (34.4)	91 (43.3)	

*A chi-square test was used to test the association of factors with a positive NSS.

The significant associated factors were identified from $P < 0.05$.

We found that 210 patients had symptoms of DPN; hence, we considered these individuals NSS positive in varying degrees of severity. Table 5 depicts severity scores reported by patients with a positive NSS.

Table 5. NSS Severity Reported by Patients

NSS severity (Score ranges)	Number of patients
None (0)	215
Symptom present (1-2)	7
Mild (3-4)	59
Moderate (5-6)	86
Severe (7-9)	58

A comparison was made between a positive NSS and positive clinical foot examination findings. Out of all participants, 14 patients (3.3%) were missing data on the clinical foot examination record. Nevertheless, the remaining results revealed that only 0.2% (n=8) of the patients were diagnosed with a positive clinical foot examination, compared to a positive NSS of 49.4%. The discrepancy between these 2 values was 49.2%.

Discussion

This study's findings demonstrated that 49.4% of the patients examined had a positive NSS. Moreover, a significant association of a positive NSS with higher HbA1c level and lower BMI emerged in the results.

Out of all our studied patients, 61.2% had been diagnosed with DM within 5-10 years and 96.7% had annual foot examinations done. However, their HbA1c was largely not optimised, with 76.7% of them having HbA1c>6.5%. Insulin usage was 42.8%. The latest Malaysian CPG T2DM has recommended an individualised HbA1c target; hence, a less stringent HbA1c target for many of our study participants who are in the age range > 60 years old should be considered.

A positive NSS result was seen in almost half of the patients. A previous local study reported similar findings, showing a 50.7% prevalence of DPN using the same NSS and NDS scores.⁹ The reports of other studies regarding variations in the prevalence of DPN from 29.1%¹⁰ to 56.2%^{9,11,12} are probably due to using different criteria and scoring systems to diagnose DPN (for example, a translated version of the Michigan Neuropathy Screening Instrument). The gold standard of diagnosis for DPN is a nerve conduction study, which is scarce and costly.

In this study, a positive NSS was associated with a higher HbA1c. The high prevalence of DPN could be due to a higher percentage of patients (81%) who had poorly controlled diabetes

with HbA1c>6.5% ($P<0.041$). This finding correlates with UK diabetes studies that have suggested improved glycaemic control is likely to prevent or delay DPN.¹³ The development of diabetic neuropathy is also associated with a number of modifiable and non-modifiable risk factors, such as hypertension, dyslipidaemia, obesity, cigarette smoking and alcohol consumption. However, these factors were not significant in our study.

We found a significant association between a lower BMI and a positive NSS ($P<0.039$). Similar findings were reported in an African study that found a higher proportion of DPN among underweight and morbidly obese participants¹⁴. Although the finding was not significant, the researchers observed a trend where patients on insulin therapy had a higher percentage of DPN. Exogenous insulin use in T2DM might reflect an advanced stage in the natural progression of diabetes and could be associated with DPN.

Our study found that 56.7% of respondents with a positive NSS was found in individuals diagnosed with diabetes within the previous 5-10 years. This late diagnosis of diabetes could be explained by a late presentation, poor awareness of diabetes symptoms or not performing regular health screenings. Hence, more health screening campaigns should be implemented in adults above age 30, along with close follow-up on high-risk patients. Frequent audits and taking relevant remedial actions in medical practices would contribute to improving the standard of care for all diabetic patients.

Our study did not show a significant association between patients' demographic factors with the presence of DPN. Factors (such as age and DM duration) were not found to have significant associations with DPN in comparison to a Malaysian study done at a university.⁸ This contrasting result could be due to differences in variables' cut-off point. As another possibility, some older adults may

attribute DPN symptoms to normal ageing. Regardless, raising diabetic patients' awareness of DPN symptoms is vital to enable the early detection of DPN.

Gender and ethnicity were not found to be strongly associated with the presence of DPN in our study. In contrast, another study done in California did show a statistically significant difference in DPN onset between genders, where males were shown to have a higher risk of foot ulcerations.¹⁵ This difference in study results could be related to a higher proportion of female than male participants in our study. Nevertheless, all diabetic patients with DPN should be managed aggressively to prevent foot ulcerations and possible amputations.

For diabetic patients experiencing the complication of DPN, lifestyle modifications are essential. Although our study did not find any association between DPN and factors such as smoking, physical inactivity and alcohol intake, other studies have reported contrasting results. For example, a study set in Scotland¹⁶ showed a higher prevalence of DPN in excessive alcohol (>3 alcoholic beverages) consumers. In the same vein, a Jordanian study found that patients who exercised moderately were at less risk for DPN.¹⁰ The poor association linking DPN with smoking and alcohol intake in our study could reflect the lower percentage of smokers and alcohol consumers among our studied populations.

Another vital lifestyle modification demanding attention is the usage of proper footwear among diabetic patients. Our study showed that only 39.5% of patients wore suitable shoes, and only 42.1% performed a daily foot inspection. Improper footwear predisposes these patients to foot ulcerations, especially among those with DPN.¹⁷ These figures underline the urgent need on wearing appropriate footwear and regular checking of their feet.

This study has several strengths. Using the NSS questionnaire to diagnose DPN was effective as well as less costly than conducting a nerve conduction study, which is not widely available. According to the data we collected, a positive NSS is almost equivalent in diagnosing probable DPN. The prevalence reported using the NSS was similar to that found in a Malaysia UM study that used NSS and NDS scoring.⁸ We were also able to find a discrepancy between a positive NSS and clinical foot examination records among our patients (49.2%). Routine

foot examinations did not detect most DPN, likely due to under-diagnosis of DPN during a routine clinical foot exam. The NDS information was taken from the clinical records. Even though 93% of the respondents had an annual foot exam, half of them were not detected as having DPN. Due to highly subjective nature of neurological examinations, foot examinations done by different healthcare providers might have been inconsistent.

This study also has various limitations. For example, as a cross-sectional study, this investigation did not assess the dynamic of the relationship between the variables evaluated. The studied population were limited to only 2 community clinics and may not represent diabetic patients from other settings, such as private clinics. Variations in a patient's response to the NSS questionnaire might have introduced potential bias. Furthermore, the NSS symptoms were non-specific and could have been caused by some other non-DM polyneuropathy. The scoring system also did not take into account the frequency of symptoms. Lastly, we did not examine differences in findings according to different HbA1c targets.

Conclusion

This study identified a high proportion of diabetic patients with a positive NSS. It revealed weaknesses in the early detection of DPN, especially in those with lower BMI, indicating advanced diabetes. The mismatch of positive DPN between using NSS questionnaires in this study and the medical records highlights the need to raise awareness and provide training for healthcare providers. The possibility of poor documentation in the patient's medical record also exists. According to the results of this study, implementing NSS in busy primary care clinics can be recommended, owing to its simplicity and low cost.

Recommendations

A focused, structured diabetes management programme should be implemented in all community health clinics. Currently, many obstacles stand in the way of optimising diabetes management in clinics, including treatment inertia, low patient acceptance, non-adherence to medications and inexperienced clinicians who are managing these patients. For example, compulsory annual foot examinations were incomplete.

The NSS offers a quick screening method for DPN among patients with diabetes as well as a cost-effective approach when used in the primary care setting. A team-based system is needed, where all healthcare workers involved should receive adequate training in using this tool. Additionally, a regular audit should be carried out to ensure that foot examinations are done properly and timely. Campaigns concerning DPN can also be carried out regularly to raise awareness among diabetic patients. Lifestyle and behavioural changes should be emphasised, especially in terms of healthy eating, regular exercise and proper foot care to prevent development and delay progression of DPN. Posters on diabetic foot complications and examples of suitable footwear can be displayed in waiting areas during diabetic

follow-up. All of these efforts can contribute to detecting and managing DPN more effectively, benefiting a broad population of present and future diabetic patients.

Acknowledgements

We thank the diabetic nurses and occupational therapists who were involved in recruiting and interviewing participants during the study.

Funding

This research was funded by a grant from the Academy of Family Physicians of Malaysia.

Conflicts of interest

The authors declare that they have no competing interests in the publication of this article.

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ORIGINAL ARTICLE

Low birth weight infant among teenage pregnancy in Terengganu, Malaysia: A cross-sectional study

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Samsury SF, Tengku Ismail TA, Hassan R. Low birth weight infant among teenage pregnancy in Terengganu, Malaysia: A cross-sectional study. *Malays Fam Physician*. 2022;17(1);44–51. <https://doi.org/10.51866/oa.59>

Keywords:

Teenage pregnancy, obstetric outcomes, perinatal outcomes, low birth weight

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Abstract

Introduction: The purpose of this research is to determine the factors associated with low-birth-weight (LBW) infants in teenage pregnancy.

Methods: A cross-sectional study was conducted in Terengganu, Malaysia, from January 1, 2020, to May 31, 2020. Records of teenage pregnancies in 2018 were retrieved from the Maternal Health Record Book and Pregnant Woman and Postnatal Book Registry. Simple logistic and multiple logistic regression analysis was used to analyse the factors associated with LBW infants in teenage pregnancy.

Results: All 357 cases that fulfilled the study criteria were included. LBW infants were the most common perinatal outcome among teenage pregnancies (19.3%), followed by preterm birth (9.0%), and both low Apgar score and stillbirth (1.4% each). Factors associated with low-birth-weight infants in teenage pregnancy in Terengganu were a teenage husband (AOR 2.0; 95% CI: 1.01, 3.96; $p=0.047$) and a mother with a low level of education (AOR 3.07; 95% CI: 1.20, 7.85; $p=0.019$).

Conclusion: Teenage husband and low level of maternal education are significant factors that need to be addressed to improve teenage pregnancy outcomes. Interventions to improve these factors should continue to be encouraged.

Introduction

A low-birth-weight (LBW) infant is defined as an infant who is born with a birth weight less than 2,500 grams.¹ The World Health Organization documented a global prevalence of LBW infants of 15%.¹ About 20 million LBW infants are born each year, mostly in developing countries.¹ The prevalence of low birth weight in Malaysia was 10% in 2000 and increased to 11.3% in 2012 and 2015.² In Malaysia, the number of LBW infants admitted to neonatal intensive care units increased from 32.8% to 38.6% between 2012 and 2016, respectively.^{3,4} LBW presents a burden to the hospitals and the Ministry of Health to provide optimal treatment with limited resources.

Common causes of LBW are restricted intrauterine foetal growth or intrauterine growth retardation (IUGR), small for gestational age (SGA), foetal malnutrition, and preterm birth.⁵ Birth weight is one of the predictors for foetal growth, and it is a significant determinant of mortality and morbidity in infancy and childhood. LBW

can predict short-term survival and influence the long-term health of the newborn.⁶

LBW has become the leading cause of neonatal death; it is responsible for nearly 80% of all neonatal deaths.¹ LBW has also been associated with complications such as hypothermia, respiratory problems, gastrointestinal problems like necrotising enterocolitis, anaemia, impaired nutrition with low weight gain, neurological problems, and sudden infant death syndrome.⁷ A systematic analysis found evidence that lower birth weight was associated with increased adult morbidity and mortality. The results also showed strong evidence that LBW had a significant association with metabolic syndrome, including type 2 diabetes mellitus, hypertension, and coronary heart disease.⁶

The World Health Assembly Resolution 65.6 endorsed a policy that aimed to reduce the prevalence of LBW by 30% between 2012 and 2025.⁸ Malaysia is still struggling to achieve this target, as our progress in reducing the prevalence of LBW has stagnated since 2000; therefore, increased understanding of

the factors leading to LBW is needed. Studies in Malaysia and other countries reported teenage pregnancy as a factor that increased the risk of delivering a LBW infant.⁹⁻¹² One of the studies was conducted using data from the National Longitudinal Study of Adolescent Health in the United States. Prevalence of LBW was 8.5% among female participants younger than 20 years of age in this study.¹¹ A WHO multi-country study conducted in 2013 reported that LBW had significant perinatal outcomes in teenage pregnancy cases.¹²

Worldwide, it is reported that 16 million teenage pregnancies occur each year,¹³ and the global population of teenagers continues to rise. In Malaysia, the prevalence of teenage pregnancy was 10.0% in 2001,¹⁴ which decreased to 5.0 % in 2010 and increased to 2.8% in 2016.^{10,15}

In view of the limited studies on teenage pregnancy in Malaysia, especially on factors associated with LBW infants in teenage pregnancy, this study provides valuable information on the existing problems in our local setting. Furthermore, reducing the prevalence of LBW in teenage pregnancies would help to reduce the number of admissions to the neonatal intensive unit. Subsequently, it would decrease the burden on the workload and resources of the Ministry of Health for managing infants with LBW and the subsequent complications. In addition, we suggest several strategies to reaching the target 30% reduction in low-birth-weight prevalence between 2012 and 2025. This can be achieved by performing interventions focused on the factors associated with LBW in teenage pregnancy. Finally, by reducing the prevalence of LBW, perinatal, neonatal, and child mortality and morbidity may also be reduced in Malaysia. Therefore, this study aimed to determine the factors associated with LBW infants in teenage pregnancy in Terengganu, Malaysia, in 2018.

Methods

Study design and participants

A cross-sectional study was conducted from January 1, 2020, to May 31, 2020, in Terengganu, Malaysia. We reviewed the records of pregnant teenagers younger than 20 years of age who were registered in government health clinics with available information on infant birth weight. Records from January 2018 to December 2018 were

retrieved. Non-Malaysian citizens were excluded.

Sample size calculation was performed by using SPSS software version 24 to calculate sample size comparing two independent proportions. The power of the study was set at 80%, with $\alpha=0.05$. The largest sample size was underweight mothers, which was 359. P0 was the probability of having an underweight mother in a teenage pregnancy with a normal birth weight infant, and was 8%.¹⁶ P1 was the estimated probability of having an underweight mother in a teenage pregnancy with a LBW infant, and was set at 20%. Only 357 cases fulfilled the study criteria. The pooled data were smaller than the calculated sample size needed; therefore, universal sampling was applied.

Research tools and data collection

Secondary data was collected using a proforma from January 2018 until December 2018. The information was obtained from the Teenage Pregnancy List of 2018, Maternal Health Record Book KIK 1/(b)/96, and Pregnant Woman and Postnatal Book Registry KIB 101 (pind2/2007) and was reviewed at the respective district office. A single researcher documented the relevant information based on the proforma checklist. The proforma checklist consisted of three main components of the data: a) women's socio-demographic data, b) obstetric data, and c) obstetric and perinatal outcomes. The socio-demographic data consisted of the age of the pregnant teenager, age of the husband, ethnicity, marital and employment status, and educational level. The obstetric data consisted of parity, history of miscarriages, gestational age at booking, body mass index (BMI) at booking, number of antenatal care visits, and status of the conception (whether premarital or not). Eleven obstetric and perinatal outcomes were measured in this component. The first outcome was infant birth weight, which refers to the weight of the infant, measured at birth (in grams). The infant was then classified as 'LBW' if the weight was less than 2,500 grams, as stated in the antenatal card record book (KIK 1/(b)/96).¹⁷ The other outcomes were maternal mortality, anaemia, pregnancy-induced hypertension, pre-eclampsia or eclampsia, gestational diabetes mellitus, caesarean section, postpartum haemorrhage, preterm birth, low Apgar score, and stillbirth.

Statistical analysis

Data were entered and analysed using SPSS version 24. Descriptive statistics were used for the analysis of socio-demographic characteristics, obstetric characteristics, nutritional status, and the perinatal and obstetric outcomes of the teenage pregnancy. Univariable analysis using simple logistic regression was used to identify preliminary factors associated with LBW infants in teenage pregnancy. The dependent variable was a LBW infant, and the independent numerical variable was age. The independent categorical variables were marital status, age of the husband, employment status, education level, parity, history of miscarriages, gestational age at booking, uncertain date of last menstruation, number of antenatal care visits, premarital conception, and BMI at booking. Multivariable analysis using multiple logistic regression was used to identify factors associated with low-birth-weight infants in teenage pregnancy; only variables with a p-value less than 0.25 were selected for multiple logistic regression. Age, marital status, age of husband, education level, uncertain date of last menstruation, number of antenatal care visits, premarital conception, and BMI at booking were variables with a p-value less than 0.25. The forward (Likelihood ratio) LR and backward

LR methods were used to compare the models, and a preliminary main effect model was obtained. The preliminary main effect consisted of two variables, which were the age of husband and level of education. The level of significance was set at a p-value less than 0.05 with a two-tailed test.

Statement about ethics

Ethical approval to conduct this study was obtained from the Human Research Ethics Committee Universiti Sains Malaysia (USM/JEPeM/19100594) and the Medical Research and Ethics Committee Malaysia (MREC) Ministry of Health Malaysia (NMRR-19-3112-512730).

Results

Socio-demographic characteristics of teenage pregnancies

After excluding cases involving non-Malaysian citizens and incomplete data, a total of 357 cases were included in the study. **Table 1** presents the socio-demographic characteristics of the study sample. Maternal ages were between 12 and 19 years, with a mean (SD) of 17.47 (1.33) years. All 357 (100%) cases were Malay. Most of the mothers were married (299 [83.8%]) and unemployed (317 [88.8%]).

Table 1. Socio-demographic characteristics of teenage pregnancies in Terengganu in 2018 (n=357).

Variables	Mean (SD)	n (%)
<i>Age (years)</i>	17.47 (1.33)	
<i>Marital status</i>		
Married		299 (83.8)
Single		58 (16.2)
<i>Age of husband (years)^a</i>	22.92 (4.67)	
Adult		230 (78.2)
Teenage		64 (21.8)
<i>Employment status</i>		
Employed		40 (11.2)
Unemployed		317 (88.8)
<i>Education level</i>		
Secondary or higher		328 (91.9)
Primary or lower		29 (8.1)

^a Among married cases only (n=294, 1.7% missing data)

Obstetric characteristics and nutritional status of teenage pregnancies

Table 2 shows the obstetric characteristics and nutritional status of the teenage pregnancies. Among the pregnancy cases in this study, 61 (17.1%) were multiparous, and half of them (51.8%) attended their first antenatal booking after 12 weeks gestation.

Table 2. Obstetric characteristics and nutritional status of teenage pregnancies in Terengganu in 2018 (n=357).

Variables	Mean (SD)	n (%)
<i>Parity</i>	1.20 (0.46)	
Multiparous		61 (17.1)
Primiparous		296 (82.9)
<i>History of miscarriage</i>		
No		348 (97.5)
Yes		9 (2.5)
<i>Gestational age at booking (weeks)</i>	15.82 (8.71)	
≤12		172 (48.2)
>12		185 (51.8)
<i>Uncertain date of last menstrual period</i>		
No		124 (34.7)
Yes		233 (65.3)
<i>Number of antenatal care visits</i>	15.43 (8.42)	
≥8		289 (81.0)
<8		68 (19.0)
<i>Premarital conception^a</i>		
No		215 (61.1)
Yes		137 (38.9)
<i>Body mass index (BMI) (kg/m²)^b</i>	22.64 (4.77)	
Underweight		59 (17.4)
Normal weight		189 (55.8)
Overweight or obese		91 (26.8)

^a n=352 (1.4% missing data)^b n=339 (5% missing data)*Obstetric and perinatal outcomes of teenage pregnancies*

The obstetric and perinatal outcomes of the teenage pregnancies are presented in **Table 3**. The most common obstetric outcome was anaemia in 148 cases (41.5%), followed by caesarean section in 39 cases (10.9%) and gestational diabetes mellitus in 10 cases (2.8). There was no maternal mortality reported among the teenage pregnancies in Terengganu in 2018. LBW infants were the most common perinatal outcome among teenage pregnancies, with 69 cases (19.3%), followed by preterm birth in 32 cases (9.0 %) and both low Apgar score and stillbirth, with 5 cases (1.4%) each.

Table 3. Obstetric and perinatal outcomes of teenage pregnancies in Terengganu in 2018 (n=357).

Variables	n (%)
Anaemia	148 (41.5)
Pregnancy-induced hypertension	5 (1.4)
Pre-eclampsia	2 (0.6)
Gestational diabetes mellitus	10 (2.8)
Caesarean section	39 (10.9)
Postpartum haemorrhage	2 (0.6)
Low-birth-weight infant	69 (19.3)
Preterm birth	32 (9.0)
Low Apgar score	5 (1.4)
Stillbirth	5 (1.4)

Factors associated with low-birth-weight infants in teenage pregnancy

Simple logistic regression analysis determined that the age at pregnancy, the number of antenatal care visits, and the BMI at booking were significantly associated with LBW infants in teenage pregnancies (**Table 4**).

Table 4. Simple logistic regression analysis of factors associated with LBW infants in teenage pregnancies in Terengganu in 2018.

Variable	Low birth weight		Normal birth weight		Crude OR (95% CI)	Wald statistic (df)	p-value
	Mean (SD)	n (%)	Mean (SD)	n (%)			
<i>Age (years)</i>	17.10 (1.72)		17.56 (1.20)		0.78 (0.65, 0.95)	6.53 (1)	0.011
<i>Marital status</i>							
Married		53 (76.8)		246 (85.4)	1		
Single		16 (23.2)		42 (14.6)	1.77 (0.93, 3.38)	2.97 (1)	0.085
<i>Age of husband</i>							
Adult		37 (69.8)		193 (80.1)	1		
Teenage		16 (30.2)		48 (19.9)	1.74 (0.89, 3.39)	2.65 (1)	0.104
<i>Employment status</i>							
Employed		6 (8.7)		34 (11.8)	1		
Unemployed		63 (91.3)		254 (88.2)	1.41 (0.57, 3.49)	0.54 (1)	0.464
<i>Education level</i>							
Secondary or higher		60 (87.0)		268 (93.1)	1		
Primary or lower		9 (13.0)		20 (6.9)	2.01 (0.87, 4.63)	2.69 (1)	0.101
<i>Parity</i>							
Multiparous		11 (15.9)		50 (17.4)	1		
Primiparous		58 (84.1)		238 (82.6)	1.11 (0.54, 2.26)	0.08 (1)	0.779
<i>History of miscarriage</i>							
No		66 (95.7)		282 (97.9)	1		
Yes		3 (4.3)		6 (2.1)	2.14 (0.52, 8.76)	1.11 (1)	0.292
<i>Gestational age at booking (weeks)</i>							
≤12		31 (44.9)		141 (49.0)	1		
>12		38 (55.1)		147 (51.0)	1.18 (0.69, 1.99)	0.36 (1)	0.548
<i>Uncertain date of last menstrual period</i>							
No		19 (27.5)		105 (36.5)	1		
Yes		50 (72.5)		183 (63.5)	1.51 (0.85, 2.70)	1.94 (1)	0.164
<i>Number of antenatal care visits</i>							
≤8		49 (71.0)		240 (83.3)	1		
>8		20 (29.0)		48 (16.7)	2.04 (1.11, 3.74)	5.33 (1)	0.021
<i>Premarital conception</i>							
No		35 (50.7)		180 (63.6)	1		
Yes		34 (49.3)		103 (36.4)	1.70 (1.00, 2.89)	3.82 (1)	0.051
<i>Booking BMI (kg/m²)</i>							
Normal weight		31 (48.4)		158 (57.5)	1		
Underweight		18 (28.1)		41 (14.9)	2.24 (1.14, 4.40)	5.47 (1)	0.019
Overweight or obese		15 (23.4)		76 (27.6)	1.01 (0.51, 1.98)	0.00 (1)	0.986

Table 5. Multiple logistic regression analysis of factors associated with LBW infants of teenage pregnancies in Terengganu in 2018.

Variable	B	Adjusted OR (95% CI)	Wald statistic (df)	p-value
<i>Age of husband</i>				
Adult		1		
Teenage	0.692	2.0 (1.01, 3.96)	3.94 (1)	0.047
<i>Education level</i>				
Secondary or higher		1		
Primary or lower	1.122	3.07 (1.20, 7.85)	5.49 (1)	0.019

Forward LR method was applied

No multicollinearity and no interaction

Hosmer-Lemeshow test, p-value 0.713

Classification table 82.2% correctly classified

The area under the curve, Receiver Operating Characteristic (ROC) was 57.9%

Table 5 shows factors associated with LBW infants of teenage pregnancies using multiple logistic regression analysis. The significant variables were the age of the husband and maternal education level. Pregnant teenagers with teenage husbands were twice as likely to have LBW infants as compared with those with adult husbands, when other variables were controlled. Pregnant teenagers with primary education or lower had 3.07 times the odds of having a LBW infant as compared with those with secondary education or higher, when other variables were controlled.

Discussion

This study revealed that 16% of the teenage mothers were single. Compared with other teenage pregnancy studies in Malaysia, the prevalence of single teenage mothers in our study was considered low. Other studies reported a higher prevalence of single teenage mothers; for example, 35% in¹⁰ study and 52.0% in Omar, et al.⁹ study. We observed a lower prevalence of teenage pregnancies because our study was conducted in the outpatient setting, which had a diverse population of outpatient maternal and paediatric cases, unlike the studies conducted in obstetric departments in hospitals that had specific antenatal clinics.^{9,10} In addition, we observed a premarital conception rate of 38%, and only 16% were single teenage mothers. It is possible that some of the teenage pregnancies were registered after conception and others after marriage registration.

The majority of teenage mothers in this study were unemployed. There are varying opinions regarding the association of maternal occupational status and LBW. Some studies suggested that working mothers had a higher risk of having poor perinatal outcomes, such as LBW and preterm birth.¹⁶ Another study reported that unemployed mothers had a higher likelihood of having LBW infants.¹⁸ Unemployed mothers had poor perinatal outcomes due to their lower socio-economic status, which affected their health due to decreased access to nutritious food and healthcare.¹⁸ We postulate that the teenage mothers in our study likely had low socio-economic status, which contributed to the observed LBWs.

There were limited studies regarding paternal age in teenage pregnancies. One study conducted in 2018 by Goisis, et al.¹⁹ found an association between paternal age and the risk of LBW and preterm birth; however, the prevalence of teenage husbands in this study was only 10.1%. In our study, the proportion of teenage husbands was higher, at 21%. This difference may be due to different study populations; our study population involved teenagers, while the study by Goisis, et al.¹⁹ involved the general population. Problems may arise when there is an increased prevalence of teenage husbands. Studies have shown a strong association between teenage fathers and poor perinatal outcomes, such as LBW, preterm birth, small for gestational age, low Apgar score, and infant mortality.²⁰

In this study, two factors were significantly associated with having a LBW infant in a teenage

pregnancy. Pregnant teenagers with teenage husbands had two times the odds of having a LBW infant compared with mothers with adult husbands. Several studies support these results. A study in 2018 on infants in Finland also revealed that having a father younger than 25 years old was associated with a 1% higher risk of having a LBW infant (95% CI: 0.6, 1.3).¹⁹ A large population-based study in the United States reported that teenage fathers had an increased risk of having a LBW infant, preterm birth, small for gestational age infant, low Apgar score, and higher infant mortality, independent of other risk factors.²⁰

The role of teenagers as husbands and parents may explain why teenage husbands represent a significant factor for having a LBW infant. Issues that may arise when teenagers become parents include their incompetence in performing the caregiving task of parent and husband, their lack of interest in the infant, and their lack of knowledge of normal infant development.²¹ The teenage period represents the gradual shifting of independence away from the family. The early onset of fatherhood in a teenage husband can be challenging, especially if the husband is still financially and emotionally dependent on his family. Once the teenage husband has committed to their new family, it is difficult for them to simultaneously continue their schooling and work; usually, they tend to terminate their formal education. Unfortunately, with a low level of education, there are limited choices of occupations with sufficient incomes.²²

Having a stable and adequate income is essential for a husband, as his main expenses will be food, clothing, housing, transport, maternal care, childcare, and health. Therefore, a teenage father with a low income who is married to a teenage wife might be unable to provide proper nutrition and adequate health care, leading to late and inadequate antenatal care and subsequently giving rise to poor perinatal outcomes, such as LBW.²⁰ Further studies must be conducted to assess the knowledge of teenage husbands regarding parenthood, as this could be one of the determining factors in the high prevalence of LBW infants.

The second significant finding in our study was that pregnant teenagers with only primary education or lower had 3.07 times the odds of having a LBW infant as compared with teenagers with a secondary education or higher. This result is not surprising considering that education is an indicator that, in part, measures

early life socio-economic position, and is an important determinant of health. This finding was supported by a study that reported that having some high school education was associated with lower odds of having a LBW infant than women with no primary education.²³ In addition, when the level of education of mother increases, the prevalence of LBW decreases. For example, the prevalence of LBW infants decreased when their mothers were educated from middle school to matriculation and bachelor level.⁷ In evaluating education levels, the likelihood of having a LBW infant for illiterate mothers was three times higher than educated mothers; therefore, illiterate mothers were more vulnerable.¹⁶ The aforementioned association could be because teenage mothers with low education levels lack the knowledge and awareness regarding pre-pregnancy care, the importance of early antenatal booking, adequate antenatal care, nutritional requirements during pregnancy, essential diet, and the effects of maternal behaviour on the foetus.⁷ Knowledge and skills learned through education could develop the cognitive functioning of a teenager and make them more receptive to health education, or make it easier for them to communicate and access appropriate health services.²⁴

Pregnant women who are highly educated have a better understanding of the health education provided by health care providers or by other media, such as social media or television. The health knowledge obtained will influence their behaviour to choose a diet that benefits their health. Moreover, a low level of education in women may be correlated with less decision-making power in the household regarding food acquisition, distribution, and financial issues, which may also contribute to their low nutritional status.²⁵ Maternal education is thus considered a significant predictor when evaluating inequalities in health care, socio-economic status, and in determining birth outcomes.

The main limitation of this study was the use of secondary data. Some vital information was unavailable in these tools, such as household income, social support, and mental health assessment of the teenage mothers. This study only included two measurements of socio-economic status, which were maternal education and occupation. Other measurements or social determinants of health, such as household income and paternal occupation, were not included in this study. Similarly, the potential link between psychosocial factors and LBW was not addressed. Therefore, we could not determine the impacts of high levels of environmental stress, lack of social support, and poor economic support, which could be risk factors for LBW.

Having a teenage husband and a low maternal education level were the factors associated with LBW infants in teenage pregnancies. Identifying these factors may help to improve the prevention and management of these pregnancies, and to subsequently improve pregnancy outcomes. Modifiable factors, such as maternal education, access to antenatal advice, and nutritional education during antenatal visits can be addressed and may subsequently lead to a reduction in the prevalence of LBW infants in teenage pregnancies.

Acknowledgements

We would like to thank the Director General of Health of Malaysia for his permission to publish this article. We want to express our gratitude to the Terengganu State Health Department and to all the maternal and paediatric health staff in all health districts in the state of Terengganu for their contribution to this research.

Conflicts of interest

The authors declare no conflicts of interest.

How does this paper make a difference in general practice?

- In view of limited studies on teenage pregnancy in Malaysia, and especially on factors associated with LBW infants among teenage pregnancy, this study may provide valuable information on the existing problems in our local setting.
- By reducing LBW prevalence among teenage pregnancy, it will help reduce the number of admissions to the neonatal intensive unit. It will decrease the burden of workload and resources in managing infants with LBW and its complications.
- By reducing the prevalence of LBW, it may help to reduce perinatal, neonatal and child mortality and morbidity in Malaysia.

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ORIGINAL ARTICLE

Primary care of preputial adhesions in children – a retrospective cohort study

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Varunkumar M, Suhasini G, Praveena DL. Primary care of preputial adhesions in children – a retrospective cohort study. *Malays Fam Physician*. 2022;17(1):52–56. <https://doi.org/10.51866/oa.27>

Keywords:

Preputial adhesions, phimosis, circumcision, preputial adhesiolysis, balanitis xerotica obliterans

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Abstract

Introduction: Aside from religious circumcisions, the indications for circumcision are few. However, in the cultural context, many patients are unnecessarily referred for circumcision for physiological phimosis (adhesions). Due to parental concerns and misperceptions by general practitioners, non-retractile prepuce is one of the most common indications for referral to a paediatric surgeon in many countries. This study aimed to determine whether preputial adhesiolysis successfully managed symptomatic non-retractile foreskin and therefore prevented the need for circumcision.

Methods: A retrospective review was performed of the health records of children who presented with preputial adhesion. We included 65 symptomatic patients (ballooning of the prepuce in all cases and additional dysuria in three cases) who underwent preputial adhesiolysis. All cases were followed up for 2 years. Circumcision was subsequently carried out for patients who developed fibrous scarring resulting in difficult retraction due to the development of thick adhesions or skin fissuring with persistence of symptoms.

Results: Of the 65 boys, 58 (89.2%) achieved complete retraction of the prepuce. The remaining 7 boys (10.8%) presented with recurring symptoms and thick fibrosed prepuce, and they underwent circumcision due to the dense adhesions. Histopathological examination of the circumcised prepuces revealed balanitis xerotica obliterans in two cases.

Conclusion: Preputial adhesiolysis is a safe and effective treatment for symptomatic preputial adhesions in boys younger than 5 years old. The procedure avoids circumcision and its associated risks. Preputial adhesiolysis should be offered as a primary treatment instead of circumcision.

Introduction

Circumcision is one of the most performed procedures throughout history, with the most common indication being a non-retractile prepuce.¹ Apart from religious circumcisions, the indications for circumcision are few. One of the indications is dense fibrotic adhesions of the prepuce in vesicoureteral reflux and posterior urethral valve, and circumcision prevents urinary tract infection in these cases.² However, many circumcisions are performed for physiological phimosis without need in the cultural setting. Non-retractile prepuce is one of the most prevalent reasons for referring a child to a paediatric surgeon in many countries, owing to parental anxieties and general practitioner misperceptions.³ Data from the American Association of Paediatrics regarding circumcision is not sufficient to conclude the true advantages of male circumcision.⁴ Most infants have a physiological non-retractile prepuce that resolves spontaneously by 4 or 5 years of age⁵; however, a subset of children develop symptoms, such as ballooning of prepuce with

dribbling and dysuria. The release of preputial adhesions successfully relieves these symptoms, thereby avoiding a circumcision that would be unnecessary as this natural preputial separation can be achieved by 5 years of age in most children.⁶ This study reviewed the practice of preputial adhesiolysis at a tertiary paediatric surgical centre. The study aimed to determine whether preputial adhesiolysis was successful in treating non-retractile foreskin, thereby preventing the need for circumcision.

Methods

A retrospective review was performed of the health records of children who presented with preputial adhesion. We included 65 symptomatic patients (ballooning of the prepuce in all cases and additional dysuria in three cases) who underwent preputial adhesiolysis. Asymptomatic cases, religious circumcision cases, and those with absolute indications for circumcision were excluded from this study. Asymptomatic cases with preputial adhesions were advised routine cleaning without any further intervention.

Absolute indications for circumcision included a thick fibrosed prepuce and religious indications.

Histopathological correlation was done for circumcisions involving thick fibrosed skin to assess for balanitis xerotica obliterans (BXO). After written informed consent was obtained from the parent or guardian, all symptomatic cases underwent gentle adhesiolysis to visualise the meatus. The patients were advised local hygiene and followed up weekly until resolution of the condition, which was determined when the parent could easily retract the prepuce to visualise the meatus and perform local cleaning. Circumcision was

carried out for patients who developed fibrous scarring resulting in difficult retraction due to the development of thick adhesions or skin fissuring with persistence of symptoms.

Results

The 65 boys included in the study were aged between 2 months and 144 months old (mean 40 months); 17 boys were ≥ 5 years of age at presentation. Ballooning at voiding was observed in 65 patients, and 3 patients had dysuria with ballooning (**Figure 1**). Of the 65 patients, 53 (81.5%) had white smegma in the coronal sulcus (**Table 1**), and 58 (89.2%) required a single session of adhesiolysis (**Figure 2**).

Figure 1. Indications for the release of preputial adhesions

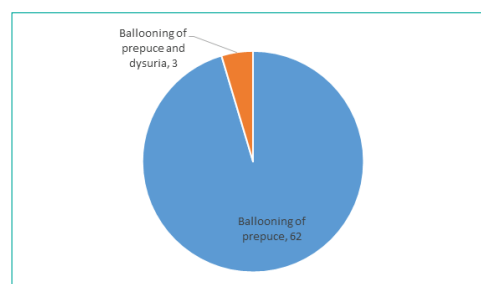
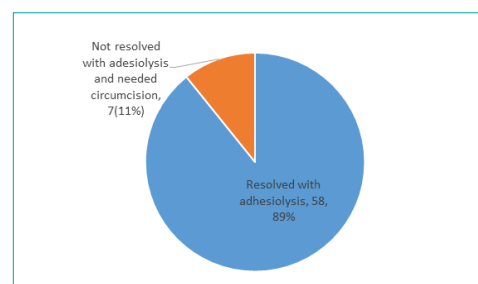


Figure 2. Treatment received for symptomatic preputial adhesions



The follow-up period was 1 year in person and 1 year by telephone consultation due to social restrictions caused by the COVID-19 pandemic. Of the 65 cases, 7 were non-respondents; these patients developed thick adhesions, and skin abrasion occurred on attempted adhesiolysis. These children underwent circumcisions at various times from initial adhesiolysis, as shown in **Table 1**. All children who underwent circumcision after an adhesiolysis attempt were older than 5 years of age (5–12 years). Circumcision was performed at a mean time of 7.4 months (6–10 months) post-preputial adhesiolysis. Among the seven circumcised cases included in the study, two had histopathological changes consistent with BXO and were 82 and 126 months old, respectively.

Table 1. Findings of adhesiolysis and circumcision

Adhesiolysis	Preputial pearls (white smegma) in 53 cases
	Mucosal tears due to dense adhesions in 7 cases
Circumcision	White scaly glans in 2 cases (BXO)
	Normal glans in 5 cases

Table 2. Data of children who underwent circumcision

Sl. No.	Age at circumcision (months)	Length of time between last adhesiolysis and circumcision (months)	Histopathology
1	70	6	Non-specific inflammation
2	71	7	Non-specific inflammation
3	82	6	Balanitis xerotica obliterans
4	80	8	Non-specific inflammation
5	110	10	Non-specific inflammation
6	120	9	Non-specific inflammation
7	126	6	Balanitis xerotica obliterans

The remaining five children who underwent circumcision had chronic non-specific inflammatory changes on histopathology. No development of meatal stenosis was observed in the BXO cases. There were no recurrences in children who successfully underwent adhesiolysis and maintained strict local hygiene. However, long-term follow-up is needed given the recurrent nature of adhesions and to evaluate the long-term effects of BXO. No complications of the circumcision procedure occurred during the study.

Discussion

Most of the children in the present study were younger than 5 years of age. The majority (89.2%), after gentle adhesiolysis, did not require a further treatment because their symptoms resolved. Only symptomatic children (ballooning of prepuce in the majority) underwent gentle preputial adhesiolysis to visualise the meatus. Asymptomatic cases do not require any treatment, as preputial adhesions in children are physiological and only local hygiene is encouraged because the foreskin will eventually retract as the child ages, in a majority by 5 years of age. However, preputial retraction can occur at different ages, with the mean age being approximately 10.4 years.⁶ The adhesiolysis procedure is used less often with the increased awareness of normal physiology by parents and general practitioners.⁷

Symptoms recurred in 7 children who underwent circumcision due to a thick fibrosed prepuce, where adhesiolysis was not possible. Adhesiolysis is difficult with a tight prepuce and may lead to skin abrasions, tears, and can result in scarring. It is also difficult to practice local hygiene in such cases, which results in recurrence of adhesions and symptoms.

The prepuce initially forms on the dorsal aspect of the glans at approximately 12 weeks of gestation. After sequential proximal-to-distal remodelling of the ventral urethral plate along with the ventral aspect of glans, the prepuce, which is of epidermal origin, fuses in the ventral midline. Separation of the prepuce from the glans occurs around 24 weeks of gestation.^{7,8} There are numerous preputial adhesions between the glans and the foreskin in the neonatal period, so it is non-retractable at this time (physiological phimosis).⁸ These

adhesions break down as the child ages, and there may be ballooning of the foreskin. Preputial pearls are foci of smegma build-up that consist of sebaceous secretions and shed skin that collects underneath the prepuce due to preputial adhesions; these are benign and do not need to be treated by circumcision. As shown in the present study, the majority of cases (89.2%, 58/65) required only a gentle retraction, and only 10.2% (7/65) required circumcision due to persistence of symptoms. Adhesions became denser and skin excoriations occurred after unsuccessful attempts of re-adhesiolysis. The foreskin eventually becomes fully retractile, a process that occurs by 5 years of age, though it may rarely take longer.⁹

Histopathologically, BXO is characterised by moderate lymphocytic infiltration of the superficial dermis and basal epidermis and is associated with epidermal basal vacuolar changes.¹⁰ BXO is rare in children, with a prevalence of 0.01% to 0.07% in the pre-pubertal age group.¹¹ Circumcision is the treatment of choice in cases of BXO, with or without adjuvant topical steroids. The most concerning complications of BXO are meatal stenosis and urethral stricture. In the present study, the two children with BXO did not have such complications. There is no evidence of penile carcinoma within the paediatric population with BXO.¹¹ In the present study, the two children with BXO were 82 and 126 months old, respectively. Those with chronic inflammation on histology, which may be an early finding of BXO, were also over 5 years old at the time of circumcision.

Aworanti et al. published a similar study in which 534 preputial adhesiolysis procedures were performed, and circumcision was subsequently required in 45 (8.4%) children. The children who underwent circumcision were older than 5 years of age, which was also the case in the present study. In Aworanti et al.'s study, two children had BXO-associated changes on histology, although many specimens were not sent for histopathological evaluation. Histopathological analysis of the 44 excised prepuces revealed BXO in two patients (4.5%), chronic inflammation in 11 (25%), normal histology in 26 (59%), and no histopathology report in 6 patients (13%) respectively. The median age at the time of circumcision for children with BXO and chronic inflammation was 65 months old (28–135 months). In these children,

circumcision was performed at a mean age of 15.7 months (1.8–40.4 months) after adhesiolysis. The two children with BXO were 83 and 125 months old at the time of circumcision.¹² The results were comparable with the present study. Kumar et al. published a study on the outcomes of circumcision for presumed phimosis. Only 4 (4.5%) out of 92 children required circumcision due to failed adhesiolysis. The remaining children responded to preputial adhesiolysis, with few requiring multiple sessions; two children did not respond to the adhesiolysis and were circumcised after two sessions of adhesiolysis within 3 weeks of follow-up. Two other children, who were lost to follow-up after initial adhesiolysis, reported fibrotic foreskins after 2 years and were circumcised without further trials of adhesiolysis.¹³ Due to these findings, long-term follow-up is needed.

Many studies support a trial of topical steroid-based cream before considering circumcision. A Cochrane systematic review in 2014 reported that topical steroids significantly increased partial or complete clinical resolution of phimosis.¹⁴ Topical steroids were not considered in the present study because most children were younger than 5 years of age and symptoms were relieved by the first follow-up visit, and fibrotic changes occurred in a few children who eventually underwent circumcision. Topical steroids should have been considered in children over 5 years of age, and may have prevented the need for circumcision. Studies by Shankar et al.¹⁵ and Osters et al.¹⁶ reported the onset of pathological phimosis by 15 years of age, with an incidence of 0.5%. Balanitis occurs in children in whom toilet training starts at around 3 years of age; patients with balanitis in this age group would probably benefit from topical steroids, especially when parents are concerned about the condition.

Preputioplasty could not be considered in the present study in place of circumcision because the patients who underwent circumcision had thick fibrotic skin, which was associated with suspicion of BXO. Several studies recommended preputioplasty followed by topical steroids in BXO, but only mild cases respond to steroids, and mild cases cannot be diagnosed without histopathology, thus favouring circumcision as a definitive treatment.¹⁷

The natural history of the prepuce and its adhesions should be understood by the parents of the patients as well as by fellow physicians and colleagues to avoid the unnecessary surgical intervention of circumcision and its associated complications.¹⁸ Circumcision should be restricted to religious and other absolute medical indications. Preputial adhesiolysis for symptomatic physiological phimosis and encouragement of local hygiene is key to facilitating its natural course.

Preputial adhesiolysis is a safe and effective treatment for symptomatic physiological phimosis in children younger than 5 years old as it avoids circumcision and its associated risks. Preputial adhesiolysis should be offered as primary treatment instead of circumcision. The normal physiology of preputial adhesions in children should be understood. Circumcision is the treatment of choice for BXO.

Acknowledgements

The authors would like to acknowledge all the staff of the Paediatric Surgery department involved in this study.

Conflicts of interest

The authors declare that there were no conflicts of interest.

How does this paper make a difference in general practice?

- Due to parental concerns and misperceptions by general practitioners, the non-retractile prepuce is one of the most common indications for referral to a paediatric surgeon in many countries.
- Asymptomatic cases do not require treatment as preputial adhesions in children are physiological. Only local hygiene is encouraged because foreskins will eventually retract as the child ages and, in a majority, by 5 years of age.
- Preputial adhesiolysis is a safe and effective treatment for symptomatic preputial adhesion in boys and avoids circumcision and its associated risks. Preputial adhesiolysis should be offered as primary treatment instead of circumcision.

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ORIGINAL ARTICLE

Thalassemia screening: Low level of knowledge among unmarried youths in Kota Bharu, Kelantan, Malaysia

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Mohd-Nor MA, Idris NS, Zulkifli MM et al. Thalassemia screening: Low level of knowledge among unmarried youths in Kota Bharu, Kelantan, Malaysia. *Malays Fam Physician*. 2022;17(1):57–65. <https://doi.org/10.51866/oa.31>

Keywords:

thalassaemia, unmarried youths, knowledge, attitude, intention

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Abstract

Introduction: Thalassemia is a common genetic blood disorder. Knowledge, awareness, attitude towards, and intention to screen for thalassemia among Malaysians is poor. Screening for thalassemia in unmarried individuals plays a key role in preventing thalassemia major births.

Methods: A cross-sectional study was conducted on unmarried individuals aged 18 years and older in Kota Bharu, Kelantan, Malaysia. A questionnaire was used to collect the general data of the participants, their knowledge of thalassemia, attitude towards thalassemia, and intention to screen for thalassemia.

Results: A total of 278 respondents were included in this study. The mean (SD) knowledge score was 8.8 (4.99) out of a possible score of 21, with higher scores indicating better knowledge. The factor associated with good knowledge of thalassemia was being a professional. Most respondents agreed that unmarried individuals should be screened for thalassemia before marriage.

Conclusion: In conclusion, knowledge of thalassemia among unmarried individuals who were not professionals was low.

Introduction

Thalassemia is a common genetic blood disorder. It is a heterogeneous group of genetic disorders characterised by defective synthesis of one or more globin chains (alpha or beta). Reduced globin chain synthesis causes a reduction in haemoglobin synthesis and eventually results in hypochromic microcytic anaemia.¹ Thalassemia causes significant morbidity and mortality.^{2,3} Thalassemia also has significant psychosocial and emotional impacts on patients and their families. Being a thalassemia carrier can lead to social isolation, marital tension, and stigmatisation.⁴

Many countries, including Iran, Bahrain, and Cyprus, employ premarital screening programmes for haemoglobinopathies, which have decreased the incidence of thalassemia. Screening, particularly of people in the premarital phase of life, is important because it can provide early detection of thalassemia carriers and help to prevent new cases. Premarital screening is superior to neonatal screening because the former is a primary prevention mechanism, while the latter is a secondary prevention mechanism.⁵

In Malaysia, thalassemia continues to be a significant burden for many patients of different ethnic groups. There are also many factors that influence public perception, knowledge, and attitude towards thalassemia and its screening.⁴ The Malaysian Ministry of Health established the National Thalassemia Prevention and Control Program in late 2004.⁶

This study aimed to determine the level of knowledge of thalassemia, its screening programme, individual attitudes towards the programme, and intention to screen among unmarried individuals in Kota Bharu, Kelantan, Malaysia.

Methods

Study design and participants

A cross-sectional study was conducted from May 1, 2017, to May 30, 2017, with 278 unmarried participants who attended a premarital course in Kota Bharu, Kelantan, Malaysia. Respondents were aged 18 years and older. Female respondents were all premenopausal and none had undergone hysterectomy. Ethical approval for this study was obtained from the Human Research

Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/16090312) and followed the principles of the Helsinki Declaration.

Research tools

The questionnaire used to collect information about the variables of interest was adapted and modified from Wong et al.,⁴ with permission from Professor Wong Li Ping of the Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia. The questionnaire comprised 44 questions and was divided into 4 parts; it was administered via a computer-assisted telephone interview (CATI) system. The questionnaire was altered in view of the method of administration being changed from telephone interview to a self-administered questionnaire; a face validation study was conducted for this purpose.

The first part of the questionnaire was designed to obtain information on the sociodemographic data of the respondents, including age, gender, race, religion, locality, highest education level, and average household monthly income.

The second part of the questionnaire was used to obtain information about the respondents' knowledge of thalassaemia. The respondents were asked if they had heard of thalassaemia or a disease with low numbers of red blood cells or a deficiency of blood. The other questions addressed their knowledge of thalassaemia across several domains, including general knowledge of thalassaemia (5 items), knowledge of thalassaemia major (6 items), knowledge of thalassaemia carriers (8 items), and knowledge of the prevention of thalassaemia major (2 items). For each question, a correct response was scored as '1', and an incorrect response or 'do not know' was scored as '0', for a total possible score of 0–21, with a higher score indicating better knowledge. The maximum score of the questionnaire was 21.

The third part of the questionnaire was designed to collect information on the participants' attitude towards thalassaemia (4 items). Participants were asked for their views on premarital screening, marriage between individuals who were both carriers, pregnancy in carrier couples, and termination of pregnancies affected by thalassaemia major.

The fourth part of the questionnaire asked respondents about their intention to be screened for thalassaemia (8 items).

Screening for thalassaemia referred to screening performed in Malaysia, where initial investigation consists of a full blood count (FBC) to detect a mean corpuscular haemoglobin (MCH) value less than 27 pg.

The respondents were asked whether they would be willing to abort their baby (or their partner's baby) if it had been diagnosed with thalassaemia major or as a carrier prior to 120 days of fetal life.⁷ According to the 52nd Muzakarah Jawatankuasa Fatwa Majlis Kebangsaan Bagi Hal Ehwal Ugama Islam Malaysia⁷ that was held on July 1, 2002, for a foetus diagnosed with thalassaemia or as a thalassaemia carrier: a) it is 'makruh' (a disliked act) if abortion is performed between 1 and 40 days of foetal life, provided that it does not cause harm to the mother and both parents agree; b) it is 'harus' (a recommended act) if abortion is performed before 120 days of foetal life if the foetus is disabled or causing harm to the mother; and c) it is 'haram' (a forbidden act) if abortion is performed after 120 days of foetal life, as from the Islamic point of view, the 'roh' (soul) of the foetus has been incorporated at this point, unless the pregnancy is causing harm to the mother.

Validity and reliability

The internal consistency (Cronbach's alpha) for the 21-item, close-ended knowledge questions was 0.86.⁴

Face validation and preliminary study

A face validation study was previously conducted with 30 unmarried individuals who were over 18 years old and did not meet the exclusion criteria.

Data collection

Written consent was obtained from the participants who fulfilled the inclusion criteria. Participants who consented were provided with a set of self-administered questionnaires during the premarital course, along with an explanation of how to complete the questionnaires.

Data analysis

Data entry and statistical analyses were carried out using IBM SPSS statistics version 24.0. Simple linear regression was used to determine the potential associated factors of the mean knowledge score for thalassaemia. Multiple linear regression was used to determine two or more associated factors of mean knowledge of thalassaemia at the same time. Descriptive

analysis was conducted for attitude towards and intention regarding thalassaemia screening. A p value of <0.05 was considered statistically significant.

Results

A total of 278 participants responded to the questionnaires, for a response rate of 100%. Almost all respondents were Malay (99.6%), most were young adults with a mean (SD) age of 24.64 (4.394), and 58.6% had secondary school education. **Table 1** presents the characteristics of the respondents.

Table 2 presents a descriptive analysis of each item in the 'knowledge regarding thalassaemia' topic. The results showed that the premarital course respondents had inadequate knowledge of many aspects of thalassaemia.

Nine independent variables were tested for factors associated with a good score for knowledge of thalassaemia: sociodemographic

factors (age, gender, ethnicity, monthly average household income, highest education level, background education level, and occupation), family history of thalassaemia, and prior screening for thalassaemia (**Table 3**). Multiple linear regression showed that only professional occupation was significantly associated with adequate knowledge of thalassaemia (R^2_{adj} 13.22; 95% CI [5.37, 21.07]). No multicollinearity was detected, and the model assumption was met; therefore, the findings are valid for interpretation. The coefficient of determination (R^2) was 0.038, which implies that the model explains 3.8% of the variability. The final model equation showed that respondents with a professional occupation had a knowledge score 13.22 units higher than respondents who were unemployed.

The results regarding attitude towards thalassaemia screening are shown in **Table 4**, and **Table 5** presents the intention of respondents to be screened for thalassaemia.

Table 1. Sociodemographic features of the premarital respondents.

	Mean (SD)	n (%)
Age (years)	24.6 (4.39)	
Monthly average household income (RM)	1189.6 (1043.16)	
<i>Gender</i>		
Male		132 (47.5)
Female		146 (52.5)
<i>Ethnicity</i>		
Malay		277 (99.6)
Non-Malay		1 (0.4)
<i>Highest education level</i>		
Secondary school		163 (58.6)
Tertiary school or higher		115 (41.4)
<i>Education background</i>		
Islamic stream		86 (30.9)
Conventional/science stream		192 (69.1)
<i>Occupation</i>		
Professional		40 (14.4)
Managerial		64 (23)
Skilled worker		41 (14.7)
Unskilled worker		68 (24.5)
Unemployed		65 (23.4)

Table 2. Participant knowledge regarding thalassaemia.

Question	Correct answer n (%)
General knowledge of thalassaemia	
Thalassaemia is a hereditary disease	173 (62.2)
A person can be a thalassaemia carrier or have thalassaemia major	121 (43.5)
Thalassaemia can be divided into two groups: alpha or beta thalassaemia	90 (32.4)
Urine test can be performed to determine if a person has thalassaemia	109 (39.2)
Blood testing can be performed to determine if a person has thalassaemia	229 (82.4)
Thalassaemia major	
The life span of a thalassaemia major patient is shortened if he/she does NOT receive appropriate treatment	130 (46.8)
Red blood cells of thalassaemia major patients break down easily and cause anaemia	125 (45)
Individuals with thalassaemia major require regular blood transfusions throughout life	94 (33.8)
All thalassaemia major individuals are mentally retarded	129 (46.4)
Individuals with thalassaemia major can lead normal and healthy lives with appropriate treatment	179 (64.4)
Individuals with thalassaemia major can be cured with bone marrow transplant	61 (21.9)
Thalassaemia carriers	
The life span of thalassaemia carrier is shortened	80 (28.8)
Thalassaemia carriers appear healthy and show no symptoms	98 (35.3)
A thalassaemia carrier shows signs of anaemia (paleness), tiredness, no appetite, and is prone to infections	24 (8.6)
A thalassaemia carrier may develop thalassaemia major	36 (12.9)
A thalassaemia carrier cannot play a normal role in society with regards to working and having a family, and needs treatment for the disease	98 (35.3)
Children born to both parents who are thalassaemia carriers will be at risk of having thalassaemia major	175 (62.9)
Children born to either one parent who is a thalassaemia carrier will be at risk of having thalassaemia major	42 (15.1)
Couples where both are thalassaemia carriers will certainly give birth to thalassaemia major children; they will not conceive any healthy children	58 (20.9)
Prevention of thalassaemia major	
The partner of a thalassaemia carrier should undergo blood tests	225 (80.9)
Prenatal diagnosis for high-risk pregnancies (both partners are thalassaemia carriers) are necessary	173 (62.2)

Table 3. Independent variable differences in mean knowledge score and simple linear regression analysis of associated factors predicting knowledge of thalassaemia.

	Total knowledge score (0–21 item scale)		Simple linear regression	
	Mean score (SD)	n	ba (95% CI)	P value
<i>Age</i>				
18–24	8.2 (4.69)	156		
≥25	9.7 (5.25)	122	6.85 (1.24, 12.45)	0.017
<i>Monthly average household income</i>				
RM0–RM499	8.5 (4.78)	65		
RM500–RM999	7.7 (4.83)	53	-6.77 (-13.88, 0.34)	0.062
RM1000–RM1499	8.1 (4.74)	70	-4.68 (-11.12, 1.77)	0.155
RM1500–RM1999	10.2 (5.18)	30	7.21 (-1.80, 16.23)	0.116
≥RM2000	10.4 (5.16)	60	9.52 (2.78, 16.25)	0.006
<i>Gender</i>				
Male	8.8 (5.34)	132		
Female	8.9 (4.66)	146	0.08 (-4.80, 6.45)	0.772
<i>Ethnicity</i>				
Malay	8.8 (4.99)	277		
Non-Malay	-	1	-10.28 (-57.20, 36.63)	0.667
<i>Highest educational level</i>				
Secondary school	8.2 (4.61)	163		
Tertiary school	9.8 (5.37)	115	7.44 (1.81, 13.08)	0.010

	Total knowledge score (0–21 item scale)		Simple linear regression	
	Mean score (SD)	n	ba (95% CI)	P value
<i>Education background</i>				
Islamic stream	8.5 (4.84)	86		
Conventional/science stream	9.0 (5.06)	192	2.24 (-3.83, 8.32)	0.467
<i>Occupation</i>				
Professional	11.2 (5.53)	40	13.22 (5.37, 21.07)	0.001
Managerial	8.1 (4.67)	64	-4.48 (-11.13, 2.17)	0.186
Skilled worker	8.2 (4.43)	41	-3.52 (-11.43, 4.40)	0.382
Unskilled worker	8.8 (5.10)	68	-0.16 (-6.70, 6.38)	0.962
Unemployed	8.5 (4.86)	65		
<i>Family history of thalassaemia</i>				
No	8.8 (4.98)			
Yes	9.0 (5.50)		0.74 (-15.13, 16.62)	0.927
<i>Prior screening for thalassaemia</i>				
Yes	10.8 (4.04)			
Never	8.7 (5.02)		-9.71 (-22.51, 3.08)	0.136

^a Crude regression coefficient.

Table 4. Participant attitude regarding thalassaemia screening.

	Agreed n (%)
Premarital screening for thalassaemia is necessary for the general public.	245 (88.1)
Couples who are thalassaemia carriers should not marry	88 (31.7)
Couples who are thalassaemia carriers should not have children	74 (26.6)
Termination of pregnancy with thalassaemia major is necessary as it not only brings suffering to the affected child, but it is also a burden to the family, community, and country	92 (33.1)

Table 5. Participant intentions regarding thalassaemia screening.

Reason	n (%)
<i>Reasons for unwillingness to undergo thalassaemia screening among premarital participants who had not been previously screened (n=67)</i>	
Not at risk	44 (65.7)
Afraid of test results	13 (19.4)
Afraid of being discriminated against	1 (1.5)
Do not know about the test	6 (8.9)
Do not know where to get the test	3 (4.5)
<i>Reasons for not continuing a relationship with his or her partner if unmarried couples are thalassaemia carriers (n=81)</i>	
Do not want children with thalassaemia major	63 (77.8)
Family will not allow marriage to proceed	17 (20.99)
Others	1 (1.2)
<i>Reasons for not wanting to abort own baby/partner's baby if the baby is diagnosed with thalassaemia major before 120 days of life (n=32)</i>	
Abortion is against religion	160 (68.97)
God's fate	66 (28.4)
Others	6 (2.6)

Discussion

Thalassaemia continues to be one of the most common preventable haemolytic diseases that places a great burden on both the patient and the health care system in many countries, including Malaysia.⁸ Despite the recent move by the Malaysian Ministry of Health (MOH) to screen secondary students for thalassaemia, it is still important to assess the level of knowledge of thalassaemia, attitude towards,

and intention to screen for thalassaemia of unmarried individuals. Despite extensive health education and promotion efforts by the MOH, the results of this study showed that the level of thalassaemia knowledge remains poor. Some attitudes towards thalassaemia screening and intention to screen are also poor. It is important to analyse the possible reasons for this inadequate knowledge so that appropriate intervention measures can be taken.

In this study, most respondents had heard of thalassaemia (87.15%). In comparison, in another study on awareness of thalassaemia, only 55.3% of adults attending primary health care centres in Oman had heard of thalassaemia.⁹ Another study in Pakistan, which analysed awareness of thalassaemia among university students studying management, found that only 75.2% of respondents had heard of thalassaemia.¹⁰ These findings show that the level of awareness about thalassaemia among unmarried individuals in Kota Bharu was equivalent to the level of awareness in other Middle Eastern and Asian countries where the prevalence of thalassaemia is higher.

Most respondents in this study cited mass media as their most frequent source of information for thalassaemia (31.3%), followed by health care providers (19.8%), and school (14%). In comparison, Wong et al. noted that most of the respondents in their study cited mass media as their primary source of information (83.35%), and health care providers as a minor source (8.9%).⁴ Another study in Oman that involved Omani university students found that the students had heard about premarital screening primarily from school (36%) and less from health care providers (~31%).¹¹ A study in Pakistan involving management university students also noted that most respondents heard about thalassaemia from friends and relatives (42%) or from electronic media (26%); awareness campaigns by health authorities were only cited by 19% of respondents.¹²

The mean knowledge score of this study was 8.8 out of 21 (42.14%). This score is lower than the 11.85 out of 21 (56.43%) reported by Wong et al., who used the same questionnaire.⁴ It is interesting to note that the mean score has declined despite recent extensive health promotion and education efforts focusing on thalassaemia prevention. The possible explanation for this discrepancy could be that the youths of Kelantan are more relaxed and have different ways of viewing the hardships of life, including thalassaemia. Thalassaemia knowledge levels have been assessed in other countries. A study in Turkey noted that the knowledge score of thalassaemia among premarital couples ranged from 41–50%.¹² A study in Italy found that knowledge of thalassaemia was much higher among Italians (54.9%) than Italian-Americans (16.5%) and non-Italian-Americans (23.6%).¹³

Karimzaei et al. reported that, among Iranian marriage partners who were genetic carriers of thalassaemia, the mean knowledge score of thalassaemia was 11.48 out of 22 (52.18%).¹⁴ Another study in Pakistan involving management university students noted that 72.6% of respondents had poor to slight knowledge of thalassaemia, and only 4% had excellent knowledge.¹⁰ These findings suggest that the knowledge level of thalassaemia is still far less than satisfactory, not only in Malaysia, but also in other Asian and Middle East countries where the prevalence of thalassaemia is higher. The researcher also noted that many other studies in Middle Eastern countries assessed respondents' knowledge of premarital thalassaemia screening, rather than knowledge of thalassaemia.^{9,11,15,16}

In terms of general knowledge of thalassaemia, over half of the premarital course respondents knew that thalassaemia was hereditary (62.2%); however, most of them did not know the difference between thalassaemia major and thalassaemia carrier state. Almost all the respondents were unsure whether thalassaemia carriers would manifest symptoms of the disease (91.4%). They also wrongly believed or were unsure of the following: thalassaemia carriers developed thalassaemia major (87.1%), children born to couples where either parent is a thalassaemia carrier are at risk of having thalassaemia major (84.9%), and couples who are both thalassaemia carriers will certainly give birth to thalassaemia major children, and they are unable to conceive any healthy children (79.1%). Understanding the difference between thalassaemia major and thalassaemia carrier state may be difficult for the public, particularly for individuals with lower education levels and economic status. This study did not assess the literacy level of the respondents, but they were assumed to have a satisfactory literacy level based on their educational backgrounds.

The respondents had several misconceptions that noted in this study. Many respondents incorrectly believed or were unsure whether all thalassaemia major patients were mentally handicapped (53.6%). Some respondents also falsely believed or were unsure whether a thalassaemia carrier could lead a normal life, work, or have a family (64.3%).

Knowledge about aspects of thalassaemia major diagnosis and treatment was also found to be deficient. Although most respondents

correctly responded that blood investigation is needed to diagnose thalassaemia (82.4%), more than half falsely believed or did not know that a urine test is used to diagnose thalassaemia (60.8%). Most respondents also did not know that patients with thalassaemia major need regular blood transfusions for life (66.2%), and only 21.9% knew that thalassaemia could be definitively cured by bone marrow transplant. These findings suggested that the knowledge of the diagnosis and treatment of thalassaemia was low among the respondents. However, it is important to note that some items with a low score can be considered medical knowledge of a higher level, like the difference between thalassaemia minor and major and its cure by bone marrow transplant.

Because the mean knowledge level was found to be low in this study, efforts must be made to further improve education about thalassaemia among unmarried individuals in Kota Bharu. The Malaysian MOH has produced pamphlets about thalassaemia that are available at all local health clinics as part of their health education efforts. Other ways of educating thalassaemia should be considered.

The results of this study showed that the only associated factor that significantly predicted knowledge score was professional occupation. This finding suggests that the knowledge level regarding thalassaemia is low in unmarried individuals in Kelantan, Malaysia who are not professionals; therefore, thalassaemia health promotion efforts should be targeted towards this group. This differs from a previous study by Wong et al., who reported that average household income predicted knowledge of thalassaemia.⁴ Professional occupation seems self-explanatory; being professional corresponds to higher education level and having better access to sources of knowledge. An earlier study in Malaysia involving rural participants in Penang only analysed factors associated with awareness of thalassaemia, which were reported to be younger age group and higher level of education.¹⁷ As for studies in other countries, factors that were significantly associated with increased knowledge of thalassaemia included age, educational status, and Italian race.^{12–14}

In the multiple linear regression analysis, R^2 was 0.038, which indicated that the independent variables tested explained only

3.8% of the variability in the knowledge score. Other possible associated factors that were not analysed and could have been included in the analysis were: attitude towards thalassaemia screening; background of medical education¹⁸; location within Kota Bharu; source of thalassaemia awareness; perceived severity and susceptibility of thalassaemia¹⁴; perceived complications of thalassaemia in terms of affected patients; and perceived burden of thalassaemia on the patient, their family, and community.

Respondents were asked about their attitude towards thalassaemia screening. Most of the respondents agreed that thalassaemia screening was necessary for the general public (88.1%). Studies in Middle Eastern countries such as Oman, Turkey, and Saudi Arabia showed a high percentage of respondents agreeing that premarital screening was necessary, with the percentage of agreement ranging from 84.5% to 95.9%.^{9,11,12,19} This finding was encouraging, as the percentage of agreement in this study was similar to the value reported by other studies. This reflects the positive attitude of unmarried individuals in Kota Bharu towards premarital thalassaemia screening.

In our study, 31.7% of the respondents agreed that two thalassaemia carriers who were a couple should not get married. In studies conducted in Turkey, Oman, and Saudi Arabia, 35–50% of respondents agreed that thalassaemia carriers should not marry each other.^{11,12,19}

Only 26.6% of the respondents agreed that thalassaemia carriers should not have children. Compared with a study in Turkey, the percentage of participants that agreed that thalassaemia carriers should not have children was higher (50%).¹² The majority of premarital course respondents also did not agree with termination of pregnancy of fetuses with thalassaemia major; only 33.1% agreed. This finding implied that most respondents were not accepting of pregnancy termination, even though Islamic regulations allow termination of pregnancy for thalassaemia major cases before 120 days of gestation.^{7,20} Kelantanese individuals are known for a strong stance in practicing Islam, especially the more traditional type of Islam. It is possible that some of the clerics in Kelantan reject termination of pregnancy entirely. Regarding similar data from studies

in other countries, a study in Palestine showed that 15% of pregnant mothers diagnosed with beta thalassaemia agreed to abortion, which is low.²¹

In this study, it was found that 5% of the respondents had been screened for thalassaemia. This suggests that despite the favourable attitudes of respondents regarding premarital thalassaemia screening, unmarried individuals did not undergo screening before marriage. The reasons given by those who had not been screened included perceiving themselves as not being at risk (65.7%), being afraid of the test results (19.4%), and not knowing about the test (8.9%). These fears suggest that more education and health promotion regarding knowledge and the importance of screening for thalassaemia should be provided, particularly to unmarried individuals in Kota Bharu. A study in northern Thailand showed that, when village health volunteers engaged the community about thalassaemia education, the rate of thalassaemia screening was higher.²² Therefore, community participation can be considered an important part of thalassaemia education to encourage more voluntary thalassaemia screening.

In other countries, the percentage of premarital thalassaemia screening ranged from as low as 1.7% in Pakistan to 10.5–18.7% in Sri Lanka.^{23,24} In Oman, a country with a high prevalence of thalassaemia due to a high rate of consanguineous marriage, the percentage of premarital thalassaemia screening was still quite low at 10.5%.⁹ However, in Oman, the reasons for not undergoing premarital screening differed from

those observed in our study; the main reasons included lack of awareness, self-perception of having no hereditary diseases in the family, and lack of interest.⁹

Respondents were asked if they would separate from their partner if both were thalassaemia carriers. Most respondents indicated that they would not separate, and only 29.1% agreed that they would separate. The final item in the questionnaire focused on willingness to abort a foetus with thalassaemia major if the pregnancy was less than 120 days, to which a small proportion of respondents agreed (16.5%). The two reasons given by respondents who would have refused abortion were: abortion is against religion (68.97%), and it is God's fate (28.4%). These reasons were given even though the question had been adjusted to include a statement about abortions for pregnancies less than 120 days fitting with the Islamic ruling of abortion for babies diagnosed with thalassaemia major.^{7,20}

In conclusion, the findings of this study can be used to create further educational materials and programmes about thalassaemia, and to highlight the importance of screening. More programmes need to be designed to specifically target unmarried individuals. This study has identified various factors that influence this population, particularly in Kelantan, Malaysia.

Acknowledgments

The authors gratefully acknowledge all respondents involved in the study.

Conflicts of interest

The authors declare no conflicts of interest.

How does this paper make a difference to general practice?

- Thalassaemia is a common disease encountered in general practice.
- Primary care physicians should be aware of the issues pertaining to thalassaemia.
- Educating the youth regarding the condition is vital.
- Ensuring the application of obtained knowledge is even more important.
- This study provides all the information needed to help in guiding the society and the nation to minimise the number of children born with thalassaemia

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ORIGINAL ARTICLE

Incidence of angiotensin-converting enzyme inhibitor-induced cough in a Malaysian public primary care clinic: A retrospective cohort study

Hou Chan Loo, Fairuz Osman, Siew Lee Ho, Sing Yee An, Yim Mei Au Yong, Ee Ming Khoo

Loo HC, Osman F, Ho SL, et al. Incidence of angiotensin-converting enzyme inhibitor-induced cough in a Malaysian public primary care clinic: A retrospective cohort study. *Malays Fam Physician*. 2022;17(1):66–70. <https://doi.org/10.51866/oa.80>

Keywords:

Angiotensin-converting enzyme inhibitor, cough, incidence

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Abstract

Introduction: The incidence of angiotensin-converting enzyme inhibitors (ACEi)-induced cough has been reported between 5% and 30% but is unknown in Malaysia. This study aimed to determine the incidence of ACEi-induced cough and its associated factors in a public primary care clinic in Malaysia.

Methods: A retrospective review of electronic medical records of patients who were initiated ACEi between January 1, 2015, and December 31, 2015, and reviewed until July 31, 2016. A total of 1,091 patients were newly prescribed ACEi, and 394 patients were eligible for this study. We excluded patients who defaulted follow-ups with no further clinic visits before July 31, 2016, were transferred to the clinic without the recorded date of ACEi initiation, were transferred to other clinics during the study period, were followed up at other clinics and attended the study clinic for a short period, or were given only a stat dose of ACEi.

Results: Among the 394 patients initiated on ACEi, 225 (57.1%) were male, 369 (93.7%) were Malay, 376 (95.4%) had hypertension, and 192 (48.7%) had diabetes. The incidence of ACEi-induced cough was 24.1%, and 42 (10.7%) patients developed cough on the day of therapy initiation. There was no association between age, gender, ethnicity, type of ACEi, and cough.

Conclusion: Approximately one quarter of patients developed cough after ACEi initiation, and approximately half of them developed cough within 1 week of ACEi initiation. Doctors should consider early follow-up for patients initiated on ACEi therapy to ensure adherence, quality of life, and minimise unnecessary treatment.

Introduction

Angiotensin-converting enzyme inhibitors (ACEi) are effective in the treatment of hypertension, left ventricular systolic dysfunction, post-myocardial infarction, renal failure, and diabetic nephropathy.¹ They inhibit angiotensin II formation and block the breakdown of bradykinin, leading to vasodilation and reduced arterial pressure, preload, and afterload.² ACEi are recommended as one of the first lines of therapy for newly diagnosed uncomplicated hypertension, and are the first agent of choice for patients with hypertension and diabetes, according to guidelines.³ In Malaysia, perindopril is the most commonly prescribed ACEi, followed by enalapril.⁴

Despite the benefits of ACEi, dry cough is a troublesome side effect.^{1,5} The mechanism of how these drugs induce cough remains unclear, but it likely involves the degradation of the protussive mediators bradykinin and substance

P (a prostaglandin-like substance), leading to accumulation in the upper respiratory tract.^{1,5,6} The accumulation of these substances causes irritation of the throat and is believed to induce the dry cough, which leads to non-adherence and withdrawal from therapy. ACEi-induced cough has been shown to occur within days to months (5–180 days) after initiation of therapy.⁷

The incidence of ACEi-induced cough has been shown to range between 5% and 30% in America, Israel, and Singapore.^{8,9,10} This wide range in the incidence of ACEi-induced cough could be a result of differences in age,¹¹ gender,^{8,11} ethnicity,^{10,12,13} and genetics.^{14, 15}

As ACEi-induced cough is one of the differential diagnoses of chronic cough,¹⁶ it is important for physicians to recognise this phenomenon to avoid unnecessary investigation and treatment in patients treated

with ACEi.¹⁷ Malaysia is a multi-ethnic country. Approximately 30% and 20% of the population aged 18 years and older have hypertension and diabetes, respectively.¹⁸ A recent local paper that studied 13,784 medical records from 20 public primary care clinics found that 54.8% of patients with hypertension were taking ACEi, and 67.3% of hypertensive diabetic patients with proteinuria had been prescribed ACEi or angiotensin receptor blockers.¹⁹ Despite ACEi being widely prescribed, there is a lack of research on the incidence of ACEi-induced cough. This study aimed to determine the incidence of ACEi-induced cough and its associated factors in a public primary care clinic in Malaysia.

Methods

Study design

A retrospective review was conducted on data from the electronic medical records of patients who attended a public primary healthcare clinic in Malaysia. The study centre was a public primary care clinic in Putrajaya, Malaysia that had a daily attendance of about 1,000 patients; it was chosen as the study centre as it had an electronic record system that enabled the retrieval of records.

The study population included all patients who were initiated on ACEi at the study centre from January 1, 2015, to December 31, 2015. To define this study population, the records of patients taking ACEi were generated on the electronic medical records using keywords (drug names, dispensing date, patient name, and identification number) from January 1, 2014, to July 31, 2016. If a patient's record was present in both 2014 and 2015, it would be excluded as it meant that the patient had been initiated on ACEi in 2014; if a patient's record was present only in 2015, it meant that the patient had been initiated on ACEi in 2015 and was included in our study population. Generated records included periods in 2016 to account for the possibility of ACEi-induced cough that occurred within 6 months of therapy initiation. Perindopril, perindopril/indapamide (Coversyl Plus), enalapril, and captopril were the selected drug names, as these were the only ACEi available at the study centre during the studied period.

The following records were excluded: 1) patients who defaulted follow-ups with no further clinic visits before July 31, 2016; 2) patients who were transferred to the clinic without the recorded date of ACEi initiation;

3) patients who were transferred to other clinics during the study period; 4) patients who were followed up at other clinics and attended the study clinic for a short period; and 5) patients who were given only a stat dose of ACEi. These patients were excluded as the adverse effects from ACEi could not be determined.

Baseline clinical and demographic data were collected, and each record was independently reviewed by two researchers.

Operational definition

We adapted the World Health Organisation Uppsala Monitoring Centre causality assessment system²⁰ to define ACEi-induced cough: 1) temporal relationship of cough to initiation of treatment ('Did the cough appear after the ACEi was administered?'), 2) absence of drugs or diseases that can cause cough ('Are there alternate causes [other than ACEi] that could solely have caused the cough?'), 3) discontinuation effect ('Did the cough improve when the ACEi was discontinued?'), and 4) re-introducing effect ('Did the cough reappear when ACEi was readministered?'). We then categorised the certainty of causality of ACEi-induced cough into four categories: 'certain of causality' (all criteria were fulfilled), 'probable of causality' (all criteria were fulfilled, except reintroducing effects), 'possible of causality' (all criteria fulfilled, except discontinuation and reintroducing effects), and 'unlikely of causality' (none of the criteria were fulfilled). Operationally, ACEi-induced cough was defined as all cases that were of certain, probable, and possible causality. Patients who developed cough and had documented asthma, chronic obstructive pulmonary disease, gastroesophageal reflux disease, upper respiratory tract infection, or smoking were categorised as 'unlikely of causality' for ACEi-induced cough.

Statistical methods

Statistical analyses were performed using Statistical Package for the Social Sciences version 22 (SPSS-22). The chi-square test was used for evaluating associations between categorical variables, while the independent t-test was used for continuous variables. Statistical significance was considered if $p < 0.05$.

Ethical consideration

Ethical approval for this study was obtained from the Medical Research and Ethics Committee (MREC), Ministry of Health

Malaysia (MREC approval reference number: [5] KKM/NIHSEC/P17-1170).

Results

A total of 1,091 patients were initiated on ACEi in 2015. Only 394 patients were eligible for this study, and 697 were excluded for the following reasons: 192 defaulted follow-ups with no further clinic visits before July 31, 2016; 383 were transferred to the clinic without the recorded date of ACEi initiation; 39 were transferred to another centre; 75 were followed

up at other clinics and attended the study clinic for medication temporarily; and 8 were given only a stat dose of ACEi.

Table 1 shows the sociodemographic profile of the study population. Of the 394 patients, 93.7% were Malay, 57.1% were male, 95.4% had hypertension, and 48.7% had diabetes. A total of 386 (98.0%) patients were initiated on perindopril, 6 patients on perindopril/indapamide (Coversyl Plus), 1 patient on captopril, and 1 patient on enalapril.

Table 1. Sociodemographic profile of the study population (n=394).

Variable	No. (%)
<i>Gender</i>	
Male	225 (57.1)
Female	169 (42.9)
<i>Ethnicity</i>	
Malay	369 (93.7)
Indian	11 (2.8)
Chinese	10 (2.5)
Others	4 (1.0)
<i>Comorbidity*</i>	
Hypertension	376 (95.4)
Diabetes Mellitus	192 (48.7)
Chronic Kidney Disease	13 (3.3)
Ischemic Heart Disease	8 (2.0)
Heart Failure	4 (1.0)
Stroke	4 (1.0)

* Some patients had multiple comorbidities.

The incidence of ACEi-induced cough was 24.1% (n=95), of which 92 patients discontinued the drug, and 3 patients continued with therapy despite the cough. Of the 394 patients on ACEi, 107 (27.2%) discontinued the drug; in addition to the 92 patients who discontinued due to ACEi-induced cough, 15 discontinued for other reasons, such as pregnancy, dizziness, allergic reaction, and erectile dysfunction. Among the 95 patients who had ACEi-induced cough, 47 (49.5%) were male, 90 (94.7%) were Malay, 2 (2.1%) were Chinese, 94 (98.9%) had hypertension, 40 (42.1%) had diabetes, and 94 (98.9%) had been initiated on perindopril.

Table 2 shows the duration of ACEi therapy before the development of cough. Among the 95 patients who had ACEi-induced cough, 44.2% developed cough on the same day of initiation, 52.6% developed within 1 week, 69.4% within 1 month, and 25.3% within 1–6 months. We did not find any significant associations between age, gender, ethnicity, type of ACEi, and incidence of ACEi-induced cough.

Table 2. Duration of ACEi therapy before the development of cough.

Duration	No. (%) (n=95)*
On the same day (0–1 day)	42 (44.2)
1–6 days	8 (8.4)
7–30 days	16 (16.8)
1–6 months	24 (25.3)
>6 months	5 (5.3)
Total	95 (100.0)

* Total number of patients with ACEi-induced cough.

Discussion

We found the incidence of ACEi-induced cough to be 24.1%. This value was consistent with values reported in other studies, which ranged from 5% to 20%,^{8,9} but was lower than in other Asian countries, where 30% to 44% of patients were reported to have ACEi-induced cough.^{10,13} The reasons for this variation could be due to ethnicity^{10,12,13} or genetics.^{14, 15}

Our study population was mostly of the Malay ethnic group, in which the incidence of ACEi-induced cough had not been previously reported. A study in Singapore on mainly ethnically Chinese patients had reported that 30.4% had ACEi-induced cough.¹⁰ Studies on American and Hong Kong Chinese patients found that 34% and 44% developed ACEi-induced cough, respectively, while the general American population reported an incidence of 13%.^{12,13} Furthermore, we did not find any association between ethnicity and incidence of ACEi-induced cough. Previous studies had shown that females were more susceptible to ACEi-induced cough^{8,11} and this was related to pharmacokinetic, pharmacodynamic, or pharmacogenetic differences.¹¹ We did not find any significant association between gender and ACEi-induced cough. We cannot conclude whether there were associations between ethnicity, gender, and incidence of ACEi-induced cough, as our study cohorts of Chinese and female patients were small. Future prospective studies are needed to determine possible associations between these two factors and ACEi-induced cough.

Among the 394 patients initiated on ACEi, 42 (10.7%) developed cough on the day of therapy initiation and 50 (12.7%) developed cough within 1 week of therapy initiation. Cough may occur within hours of the first dose of medication, or its onset can be delayed for weeks or up to 6 months after the initiation of therapy.⁷ Therefore, it is desirable to conduct a follow-up for patients initiated on ACEi 1 week after initiation, to identify possible cough development that may affect compliance. The decision to discontinue ACEi therapy could then be decided cooperatively by the patient and doctor, taking into consideration the indications and benefits of the therapy and the patient's tolerance to cough.

This study was limited by record review of indications and reasons for discontinuing ACEi therapy, which may have led to bias. Approximately two thirds of the patients were excluded due to challenges during follow-ups and data retrieval; this could be attributed to the lack of continuity of care in the current primary care system, where patients are free to attend any clinic of their choice for care. A prospective study would mitigate the possible bias due to the number of records being excluded. We defined patients who had documented diseases that could cause cough as 'unlikely of causality' for ACEi-induced cough, which could have underestimated the incidence of ACEi-induced cough. The samples were from a single public primary care clinic and may not have been representative of the entire population of Malaysia. However, these findings have provided insight into the estimated incidence of ACEi-induced cough in a majority Malay ethnicity group, where this data is lacking. Future prospective studies should be conducted in more primary care clinics in areas with a higher proportion of other ethnic groups and in private primary care clinics to improve the generalisability of the results.

We found the incidence of ACEi-induced cough to be 24.1% in a majority Malay population, and approximately half of the patients developed cough within 1 week of ACEi initiation. Early review of patients 1 week after ACEi initiation would ensure adherence and minimise unnecessary treatment for ACEi-induced cough.¹⁷

Acknowledgements

We wish to express our sincere gratitude to Dr. Hamimah Binti Saad and the clinical and information technology (IT) staffs of Klinik Kesihatan Presinct-9 for facilitating the data collection of this research. We would like to thank the Director of Health Malaysia for permission to publish this paper. This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

How does this paper make a difference in general practice?

- There are no published local data on ACEi-induced cough, despite hypertension and diabetes being the most common non-communicable diseases in Malaysia, and ACEi being widely prescribed in general practice.
- There are no data on ACEi-induced cough among the Malay ethnic group, who this paper addresses, especially in Southeast Asian countries.
- We found that approximately one quarter of patients developed cough after ACEi initiation, and approximately half of them developed cough within 1 week of ACEi therapy initiation. Doctors should consider early follow-up for patients initiated on ACEi therapy to ensure adherence, quality of life, and minimise unnecessary treatment.

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CPG UPDATE

Case scenario: Management of major depressive disorder in primary care based on the updated Malaysian clinical practice guidelines

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Keywords:

Depression, major depressive disorder, primary care, screening, treatment

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Abstract

Major depressive disorder (MDD) is a common but complex illness that is frequently presented in the primary care setting. Managing this disorder in primary care can be difficult, and many patients are underdiagnosed and/or undertreated. The Malaysian *Clinical Practice Guidelines (CPG) on the Management of Major Depressive Disorder (MDD)* (2nd ed.), published in 2019, covers screening, diagnosis, treatment and referral (which frequently pose a challenge in the primary care setting) while minimising variation in clinical practice.

Introduction

MDD is one of the most common mental illnesses encountered in primary care. It presents with a combination of symptoms that may complicate its management.

This mental disorder requires specific treatment approaches and is projected to be the leading cause of the disease burden in 2030.¹ Patients experiencing this ailment are at elevated risk for early mortality from physical disorders and suicide.² In Malaysia in particular, MDD contributes to 6.9% of total Years Living with Disability.³

Ensuring full functional recovery and prevention of relapse makes remission the targeted outcome for treatment of MDD. In contrast, non-remission of depressive symptoms in MDD can impact functionality⁴ and subsequently amplify the economic burden that the illness imposes.

About the new edition

The highlights of the updated CPG MDD (2nd ed.) are as follows:

- emphasis on psychosocial and psychological interventions, particularly for mild to moderate MDD
- inclusion of all second-generation antidepressants as the first-line pharmacotherapy
- introduction of new emerging treatments, ie. intravenous ketamine for acute phase

and intranasal esketamine for next-step treatment/treatment-resistant MDD

- improvement in pre-treatment screening and monitoring of treatment
- integration of mental health into other health services with emphasis on collaborative care
- addition of 2 new chapters on special populations (pregnancy and postpartum, chronic medical illness) and table on safety profile of pharmacotherapy in pregnancy and breastfeeding
- comprehensive, holistic biopsychosocial-spiritual approaches addressing psychospirituality

Details of the evidence supporting the above statements can be found in *Clinical Practice Guidelines on the Management of Major Depressive Disorder* (2nd ed.) 2019, available on the following websites: <http://www.moh.gov.my> (Ministry of Health Malaysia) and <http://www.acadmed.org.my> (Academy of Medicine). Corresponding organisation: CPG Secretariat, Health Technology Assessment Section, Medical Development Division, Ministry of Health Malaysia; contactable at htamalaysia@moh.gov.my.

Statement of intent

This is a support tool for implementation of CPG Management of Major Depressive Disorder (2nd ed.).

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Healthcare providers are advised of their responsibility to implement this evidence-based CPG in their local context. Such implementation will lead to capacity building to ensure better accessibility of psychosocial and psychological services. More options in pharmacotherapy facilitate flexibility in prescribing antidepressants among clinicians. Further integration of mental health into other health services, upscaling of mental health service development in perinatal and medical services, and enhancement of collaborative care will incorporate holistic approaches into care.

Case Scenario

Tini is a female college student aged 24 years old. She comes to the health clinic accompanied by a friend and complains of several symptoms that she has experienced over the past 4 weeks. She reports:

- difficulty falling asleep, feeling tired after waking up in the morning and experiencing headaches
- difficulty staying focused during classes. These symptoms have led to deterioration in her study and prompted her to seek advice from the doctor.

Question 1

Will you screen her for depression?

Answer 1

Yes, because the patient presents with multiple vague symptoms and sleep disturbance.⁵
(Refer to Subchapter 2.1, page 3 in CPG.)

Question 2

What tools are used to screen for depression?

Answer 2

Screening tools for depression are:

- Beck Depression Inventory (BDI)
- Depression Anxiety and Stress Scale (DASS)
- Patient Health Questionnaire-9 (PHQ-9)
- Hospital Anxiety and Depression Scale (HADS)
- Whooley Questions

Screening for depression using Whooley Questions in primary care may be considered in people at risk.⁵

(Refer to Subchapter 2.1, pages 3 and 4 in CPG.)

- Whooley Questions on depression:

- “During the past month, have you often been bothered by feeling down, depressed or hopeless?”
- “During the past month, have you often been bothered by having little interest or pleasure in doing things?”

The doctor decides to use Whooley Questions, and Tini answers “yes” to both questions.

Question 3

How would you proceed from here to further assess for depression?

Answer 3

Assessment of depression consists of:

- detailed history taking
(Refer to Subchapter 2.2, page 4 in CPG.)
- mental state examination (MSE), including evaluation of symptom severity, presence of psychotic symptoms and risk of harm to self and others
- physical examination to rule out organic causes
- investigations where indicated – biological and psychosocial investigations

Upon further assessment, Tini reveals that she feels overwhelmingly sad. She is frequently tearful and reports feeling excessively guilty, blaming herself for not performing well enough in her studies. Her postings on social media have been revolving around themes of self-defeat. Despite feeling low, she still strives to attend classes and complete her assignments. However, her academic performance has exhibited a marked deterioration. There is no history to suggest hypomanic, manic or psychotic symptoms. She denies using any illicit substances or alcohol. Her menstrual cycle is normal and does not correspond to her mood changes.

MSE reveals a young lady who appears to be in distress. Rapport is easily established, but her eyes are downcast. Her speech is relevant, with low tone. She describes her mood as sad; she is tearful while talking about her poor results, with appropriate affect. She harbours multiple unhelpful thoughts, eg. “I’m a failure” and “I’m useless”. She exhibits no suicidal ideations, delusions or hallucinations. Her concentration is poor, and insight is partial.

Physical examination reveals no recent self-harm scars, and examination of other systems is unremarkable. Biological investigations such

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as full blood count and thyroid function test are within normal range. Corroborative history is taken from accompanying person to verify the symptoms.

Question 4

How would you arrive at the diagnosis and severity?

Answer 4

Diagnosis of depression can be made using the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or the 10th revision of the International Statistical Classification of Disease and Related Health Problems (ICD-10).⁵

(Refer to Appendix 3 and 4, pages 73-76 in CPG.)^{6,7}

In the last 2 weeks, Tini has been experiencing:

- low mood
- insomnia
- poor concentration
- lethargy
- excessive guilt

These symptoms have caused marked impairment in her academic functioning. Thus, she is diagnosed as having MDD with

mild to moderate severity in acute phase and can be treated in primary care.

Severity according to DSM-5

- Mild depression
 - Five or more symptoms are present, which cause distress but are manageable
 - Result in minor impairment in social or occupational functioning
- Moderate depression
 - Symptom presentation and functional impairment between 2 severities
- Severe depression
 - Most of the symptoms are present with marked impairment in functioning

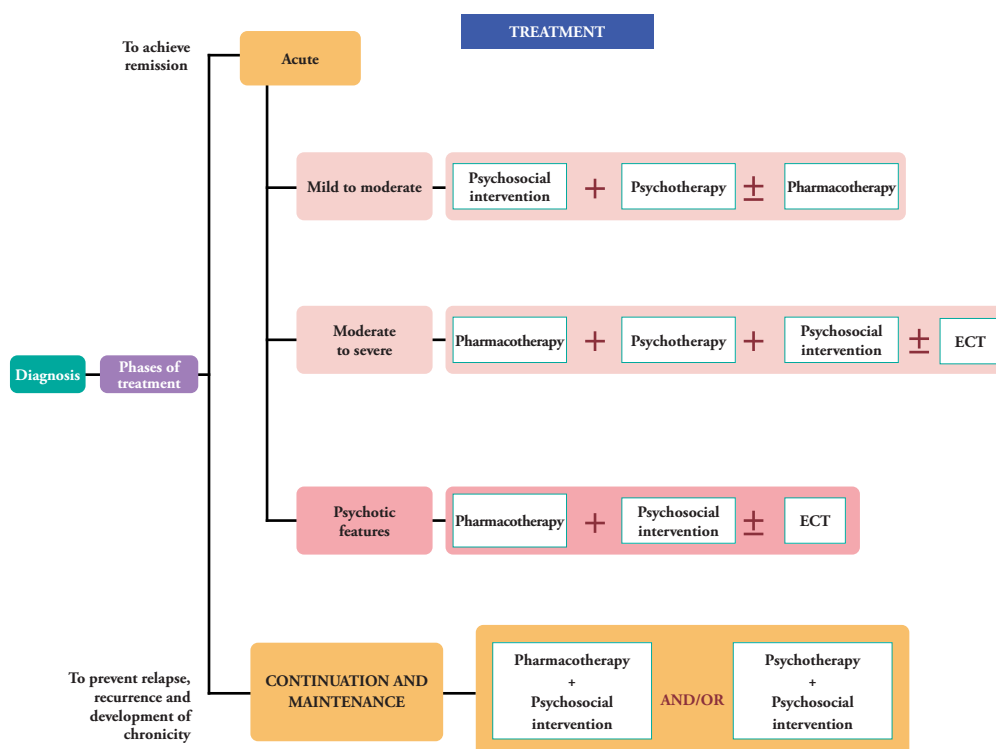
Question 5

What can be offered to this patient?

Answer 5

Psychosocial interventions and psychotherapy with or without pharmacotherapy.⁵

(Refer to Algorithm 1. Treatment of Major Depressive Disorder, page xii in CPG)

ALGORITHM 1. TREATMENT OF MAJOR DEPRESSIVE DISORDER

ECT = electroconvulsive therapy

Psychosocial interventions include the following:

- a. Psychoeducation is an important part of psychosocial intervention. It consists of topics on⁵:
 - symptoms and course of depression
 - biopsychosocial model of aetiology
 - pharmacotherapy for acute phase and maintenance
 - drug side effects and complications
 - importance of medication adherence
 - early signs of recurrence
 - management of relapse and recurrence
- b. Other components of psychosocial intervention include⁵:
 - counselling/non-directive supportive therapy – aims to guide the person in decision-making and allow to ventilate their emotions
 - relaxation – a method to help a person attain a state of calmness, eg. breathing exercise, progressive muscle relaxation, relaxation imagery
 - peer intervention – eg. peer support group
 - exercise – activity of 45-60 minutes per session, up to 3 times per week, and prescribed for 10-12 weeks
 - psychospiritual intervention – to address this treatment as part of biopsychosocial and spiritual model

(Refer to subchapter 4.1.1, pages 9-12 in CPG.)

However, the doctor may choose to start antidepressant medication as an initial measure in some situations, for example:

- past history of moderate to severe depression
- patient's preference
- previous response to antidepressants
- lack of response to non-pharmacotherapy interventions

Question 6

What are the types of psychotherapy that can be offered in mild to moderate MDD, and what factors should be considered before starting psychotherapy?

Answer 6

Psychotherapy for the treatment of MDD has been shown to reduce psychological distress and improve recovery through the therapeutic relationship between the therapist and the patient.

In mild to moderate MDD, psychosocial intervention and psychotherapy should be offered, based on resource availability, and may include but are not restricted to the following⁵:

- Cognitive behavioural therapy (CBT)
- Interpersonal therapy
- Problem-solving therapy
- Behavioural therapy
- Internet-based CBT

The type of psychotherapy offered to the patient will depend on various factors, including⁵:

- patient preference and attitude
- nature of depression
- availability of trained therapist
- therapeutic alliance
- availability of therapy

(Refer to Subchapter 4.1.1, page 17 in CPG.)

After shared-decision making, Tini receives psychosocial intervention, that includes:

- psychoeducation
- non-directive supportive therapy
- exercise
- lifestyle modification, e.g. restoring healthy sleep hygiene and adopting healthy eating habits
- relaxation, e.g. progressive muscle relaxation, imagery and breathing technique

Tini will benefit from CBT due to her multiple unhelpful thoughts, for example, "I'm a failure" and "I'm useless".

CBT helps improve understanding of the impact of a person's unhelpful thoughts on current behaviour and functioning through cognitive restructuring and a behavioural approach. By learning to correctly identify these negative thinking patterns, Tini can then challenge such thoughts repeatedly to replace disordered thinking with more rational, balanced and healthy thinking. However, she is not able to commit to regular sessions of CBT due to a demanding academic schedule and upcoming final examination. After further discussion, Tini opts for pharmacotherapy.

Question 7

What are the options for pharmacotherapy?

Answer 7

The choice of antidepressant medication will depend on various factors, including

efficacy and tolerability, patient profile and comorbidities, concomitant medications and drug-drug interactions, cost and availability, as well as the patient's preference. Taking into account efficacy and side effect profiles, most second-generation antidepressants, namely selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), noradrenergic and specific serotonergic antidepressants (NaSSAs), melatonergic agonist and serotonergic antagonist, noradrenaline/dopamine-reuptake inhibitors (NDRIs) and a multimodal antidepressants may be considered as the initial treatment medication, while the older antidepressants such as tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) may be subsequently considered for a later choice.⁵ (Refer to Subchapter 4.1.2, page 18 in CPG.)

Since Tini is being seen at a health clinic, the widely available SSRIs are sertraline and fluvoxamine. Sertraline has fewer gastrointestinal side effects and drug interactions compared with fluvoxamine. TCAs are not the treatment of choice due to prominent side effects. Tini is put on tablet sertraline 50 mg daily and educated on the anticipated onset of response and possible side effects. Short-term and low dose benzodiazepine, eg. alprazolam or lorazepam, may be offered as an adjunct to treat her insomnia. (Refer to Subchapter 4.1.2, page 24 in CPG.) Tini is given tablet lorazepam 0.5 mg at night for 2 weeks. She is asked to come in for a follow-up.

Question 8

What is her follow-up and monitoring plan?

Answer 8

The following should be done:

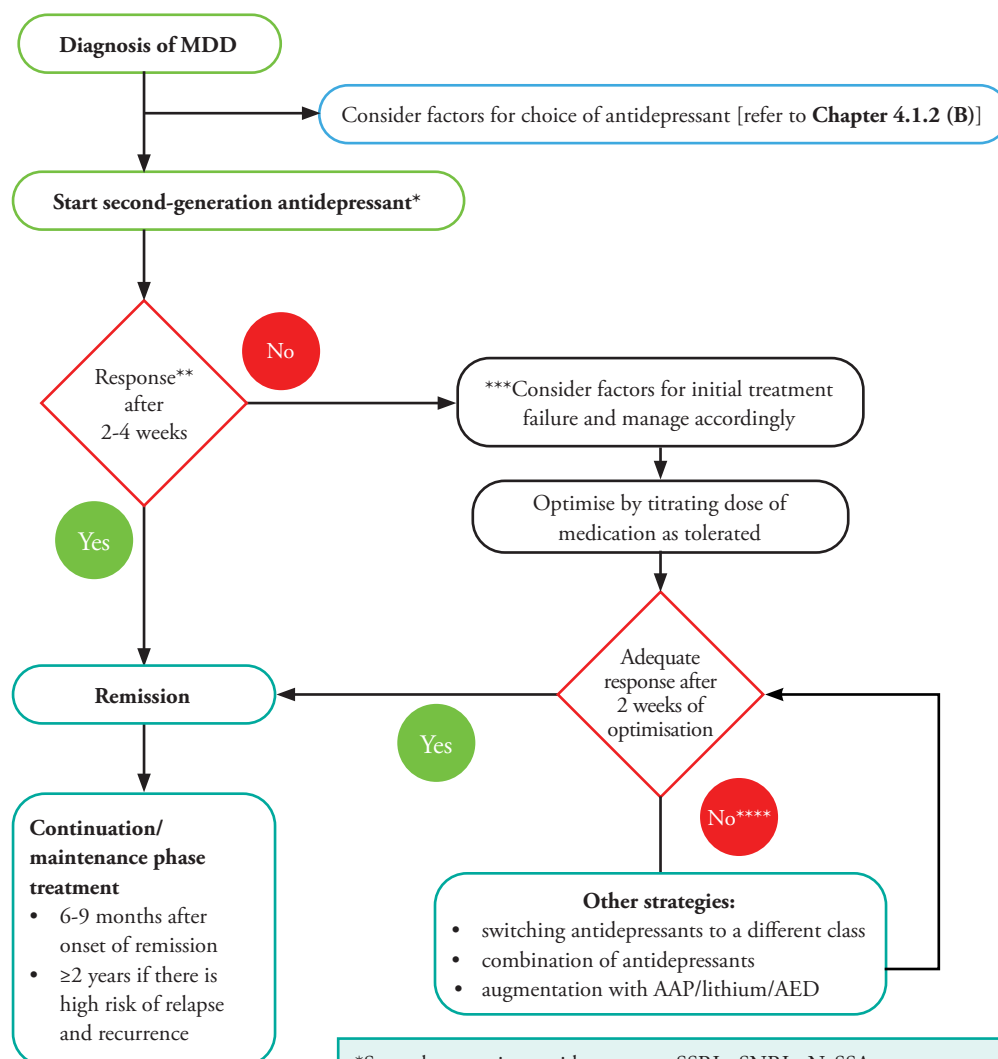
- Review response and tolerability on follow-up within 2 weeks (Refer to Appendix 8, page 81 in CPG.)
- Titrate up by 50 mg within 1-2 weeks (but may be done earlier based on clinical judgement)
- Monitor biological parameters if indicated (Refer to Table 5. Ongoing monitoring during treatment of MDD, page 57 in CPG.)

During follow-up at 2 weeks, she is noted to show partial response despite being compliant with good tolerability. She is not experiencing nausea, diarrhoea, headache, constipation, dry mouth or somnolence. She reports being less tearful. Her sleep and ability to focus have improved. Tini has started engaging in regular exercise and practises relaxation, especially before sleep. Tablet sertraline is optimised to 100 mg daily, while tablet lorazepam is reduced to 0.5 mg PRN.

Tini is reviewed again within 4 weeks; during this subsequent follow-up, she achieves full remission. Tablet lorazepam is stopped. She is then advised to continue tablet sertraline for at least 6-9 months in maintenance phase. The aim in this phase is to prevent relapse and recurrence of MDD. In view of her young age, no comorbidities and good tolerability, repeated electrolyte monitoring is not indicated.

(Refer to Algorithm 2. Pharmacotherapy for Major Depressive Disorder, page xiii in CPG.)

ALGORITHM 2. PHARMACOTHERAPY FOR MAJOR DEPRESSIVE DISORDER



*Second-generation antidepressants: SSRIs, SNRIs, NaSSAs, melatonergic agonist and serotonergic antagonist, multimodal antidepressants and NDRI

Refer to **Chapter 3

***Consider:

- Incorrect diagnosis (e.g. failure to diagnose bipolar disorder)
- Psychotic depression
- Organic conditions (e.g. anaemia or hypothyroidism)
- Co-morbid psychiatric disorder (e.g. substance abuse or dependence, panic disorder, obsessive-compulsive disorder and personality disorder)
- Adverse psychosocial factors
- Non/poor compliance

****Consider referral to psychiatrist

MDD = major depressive disorder

AAP = atypical antipsychotics

AED = antiepileptic drugs

SSRIs = selective serotonin reuptake inhibitors

SNRIs = serotonin norepinephrine reuptake inhibitors

NaSSAs = noradrenergic and specific serotonergic antidepressants

NDRI = norepinephrine/dopamine-reuptake inhibitors

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CASE REPORT

White-eyed blowout fracture, child in danger: A case report

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Rosli AH, Nordin MH, Embong Z, et al. White-eyed blowout fracture, child in danger: A case report. *Malays Fam Physician*. 2022;17(1):78–81. <https://doi.org/10.51866/cr1150>

Keywords:

White-eyed blowout fracture, diplopia, ocular motility restriction, tissue entrapment

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Abstract

A white-eyed blowout fracture is an orbital floor fracture associated with restriction of ocular motility (suggestive of orbital content entrapment) but with minimal or absence of signs of soft tissue trauma. It can lead to significant patient morbidity. This case involved an 8-year-old boy with a white-eyed blowout fracture following facial trauma. He presented with binocular diplopia and a history of recurrent episodes of vomiting after the trauma and was referred to our centre for a suspected head injury. Visual acuity in both eyes was 6/9. Examination showed minimal left periorbital haematoma with left eye motility restriction on superior and medial gaze associated with pain. CT scan of the orbit showed left orbital floor fracture with minimal soft tissue entrapment. He underwent urgent open exploration of the left orbit and release of orbital tissue entrapment. Post-operatively, the left eye motility restriction improved significantly with resolution of diplopia. In conclusion, a high index of suspicion is crucial in diagnosing paediatric white-eyed blowout fractures due to lack of external ocular signs.

Introduction

Smith and Regan et al. first described a blowout fracture – an isolated fracture of the orbital floor with an intact orbital rim – in 1957.¹ In 1998, Jordan et al. introduced the term white-eyed blowout fracture, referring to individuals presenting with ocular symptoms following a blow to the periocular area, although with minimal signs of soft tissue trauma.^{2,3} Paediatric white-eyed blowout fractures are rare and can present differently, thus offering potential for long-term complications if not recognised and treated properly.⁴ This article reports the case of a young boy with a white-eyed blowout fracture following facial trauma.

Case history

A healthy 8-year-old boy allegedly fell into a drain with the left side of his face hitting the drain's edge. There was no loss of consciousness. However, he had binocular diplopia and several episodes of vomiting after the trauma. There was no history of headache, drooping of the eyelid or sunken globe. He was referred to our emergency department for suspected head injury due to persistent vomiting.

His Glasgow Coma Scale remained full throughout admission, and he was haemodynamically stable. His visual acuity was 6/9 in both eyes. Pupillary reaction was normal in both eyes. Relative afferent pupillary defect was absent. Ocular examination revealed

minimal left periorbital haematoma with white conjunctiva and superficial abrasion wound on the left cheek. There was no ptosis, proptosis or enophthalmos of the left eye. Left eye hypotropia was present upon primary gaze. Extraocular muscle examination showed restriction in the left eye superior and medial gaze (**Figure 1A**), associated with diplopia and ocular pain on ocular movement. No tenderness or deformity of the left orbital rim was present. Both anterior segments were unremarkable. Fundoscopy revealed normal optic discs and retinas in both eyes. Hess chart test demonstrated left eye hypotropia with limited elevation. A forced duction test was not performed because the child was not cooperative.

A CT scan of the orbit and brain revealed left orbital floor fracture with extraconal fat herniation into the left maxillary sinus (**Figure 2**). No inferior rectus entrapment or retrobulbar haemorrhage was noted, nor was intracranial haemorrhage. He underwent urgent open exploration of the left orbit via a transconjunctival approach by the Oral and Maxillofacial team. Intra-operatively, exploration revealed an undisplaced fracture line near the infraorbital groove with minimal soft tissue entrapment. There was no rectus muscle entrapment. A forced duction test showed minimal mechanical restriction. The tissue entrapment was successfully released, as

evidenced by the free movement of the globe during the forced duction test at the end of the operation. No implant was placed. He also received a five-day course of oral Cefuroxime. Post-operatively, the left eye's range of movement has improved significantly. Minimal superior gaze restriction was observed with resolution of diplopia and pain (**Figure 1B**). The restriction was fully resolved after three months.

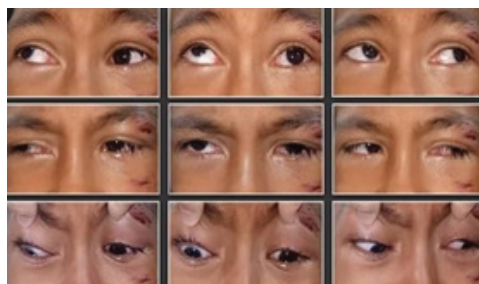


Figure 1A: Picture showing left eye hypotropia on primary gaze. There was restriction of superior and medial gaze over the left eye



Figure 1B: Picture showing significant improvement of extraocular movement post-operatively. There was minimal restriction of superior gaze over the left eye.

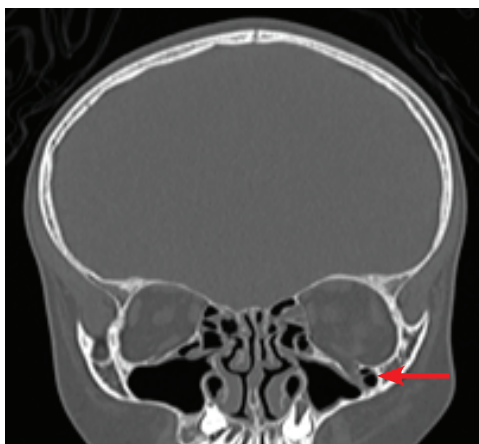


Figure 2: Coronal section of CT scan showed left orbital floor fracture with minimal soft tissue entrapment (arrow).

Discussion

The hydraulic and buckling mechanisms are two widely accepted theories explaining the

mechanism of a blowout fracture.^{1,3-5} In the hydraulic mechanism, an increased intraorbital pressure results in direct compression and fracture of the bony floor. The buckling mechanism describes any force transmitted posteriorly through the orbital rim transiently buckling and then fracturing the thin orbital floor.⁴

White-eyed blowout fractures are likely to occur in children over age 7.⁶ Younger children have thicker sinus walls, greater bone elasticity, and a thicker padding of cheek fat with a smaller and flat midface. These features are thought to be protective of the orbital floor.⁴ Commonly, paediatric white-eyed blowout fractures are caused by low-velocity, high-force crush injuries,⁴ including sport-related injuries, accidents while playing, falling, motor vehicle accidents or assault.^{4-5,7}

These fractures lead to diagnostic challenges due to a lack of clinical evidence of soft tissue injury. Even when entrapment is present, other features such as periorbital haematoma, subconjunctival haemorrhage or enophthalmos may be mild or absent.^{3,6} Common presentation of white-eyed blowout fractures includes binocular diplopia, orbital pain during superior gaze, limited extraocular motility and oculocardiac reflex.^{3-4,8,12} The symptoms of oculocardiac reflex, a potentially life-threatening condition, consist of nausea/vomiting, bradycardia, hypotension or cardiac arrest. This reflex is mediated by communication between the ophthalmic division of the trigeminal nerve and the visceral motor nucleus of the vagus nerve via the reticular formation.^{4,12} Presenting symptoms such as nausea and vomiting may lead to a head injury misdiagnosis, potentially distracting the clinician from the true aetiology. Hence, oculocardiac reflex must be considered as a cause of nausea and vomiting in patients with white-eyed blowout fractures.⁸

A CT scan of the orbital is the gold standard of imaging for a suspected orbital floor fracture.⁴ However, assessing the muscle/soft tissue entrapment clinically rather than relying on a radiologic diagnosis is vital because it is sometimes difficult in acute trauma to differentiate the entrapment from soft tissue swelling, fat stranding or haematoma.⁶ In blowout fractures, a CT scan usually shows features of trapdoor fractures, meaning a linear floor fracture with minimal displacement and little or no soft tissue herniation into the maxillary antrum.⁶ A forced duction test is

useful to assess the presence of ocular motility mechanical restriction. Mechanical gaze restriction along with a positive forced duction test and CT evidence of muscle/soft tissue entrapment are considered indications for surgical repair.⁹⁻¹⁰ At the end of surgery, a forced duction test should be performed to evaluate the globe mobility to confirm the complete release of the entrapped tissue.⁹

A white-eyed blowout fracture is recognised as a true surgical emergency. Urgent surgery within 24-48 hours to release the entrapment is recommended for a positive outcome.²⁻⁸ Early intervention can avoid ischaemic necrosis, fibrosis and scarring of entrapped muscle/ soft tissue, which can otherwise lead to permanent gaze restriction with consequent diplopia.^{5,7,12} Rather than a subciliary or lower fornix approach, a transconjunctival approach has been preferred, allowing adequate visualisation of the orbital floor and reducing the risk of postoperative ectropion and scar hyperplasia.¹⁰⁻¹¹ Implant materials vary, including autogenous materials (bone and cartilage) and alloplastic materials (titanium mesh, porous polyethylene and resorbable sheeting). The selection is determined by the patient's fracture, age and location.¹¹ In this case, the attending surgeon's decision not to place an implant was likely due to the intraoperative findings of an undisplaced fracture line over the orbital floor.

Although prescribing prophylactic antibiotics in orbital fracture has become very common, no strong evidence supports their use. A review by Reiss et al. (2017) found that the most common reasons for using antibiotics in orbital fractures included the presence of sinusitis, recommendations by otolaryngology/

ophthalmology, and presence of floor fracture. They suggested withholding antibiotics for low-risk patients (those without an upper respiratory infection and not using steroids) and recommended shorter five- to seven-day courses of an oral antibiotic, if prescribed.¹³

Persistent diplopia is the most common complication in children with white-eyed blowout fractures,^{3,4} resulting from a unique paediatric trapdoor fracture pattern that directly damages the extraocular muscle, leading to restricted motility. Another rare but devastating complication is orbital cellulitis.¹⁴

Conclusion

A high index of suspicion is crucial in diagnosing paediatric white-eyed blowout fractures due to a lack of external ocular signs. This case also highlighted a rare presentation of a white-eyed blowout fracture mimicking a head injury presentation. Notably, a delay in diagnosis can potentially lead to a life-threatening condition and delay surgical intervention.

Acknowledgement

We would like to thank the attending surgeon, Dr Abdullah Pohchi from the School of Dental Sciences, Universiti Sains Malaysia, for his extremely helpful contribution in co-managing this patient.

Conflicts of Interest

All authors declare no conflicts of interest.

Patients' consent for the use of images and content for publication

The patient and parents have provided verbal consent for the publication.

What is new in this case report compared to the previous literature?

- This paper highlights the importance of clinicians, especially those involved in the acute management of children with orbital trauma, in detecting and diagnosing a white-eyed blowout fracture.
- Due to a lack of external ocular signs, a white-eyed blowout fracture can easily be misdiagnosed as a head injury due to similar presentation, such as nausea and vomiting post-trauma, as initially happened in this case.
- We hope this paper will benefit all clinicians, especially those in primary care, such as those practising in a health clinic setting, general practitioners and emergency units. Early diagnosis and timely surgical intervention are crucial for a positive outcome and to prevent sequelae.

What is the implication to patients?

In the case of a white-eyed blowout fracture, any delay in surgical intervention can be life-threatening due to the risk of oculocardiac reflex. Furthermore, entrapped muscle/soft tissue ischaemia can lead to permanent gaze restriction with consequent diplopia in the child.

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CASE REPORT

Dizziness and syncope after subclavian steal: A case report of a rarely symptomatic, common vascular disorder

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Kamal NMFNM, Mohamad N, Yusoff BM. Dizziness and syncope after subclavian steal: A case report of a rarely symptomatic, common vascular disorder. *Malays Fam Physician*. 2022;17(1):82–85. <https://doi.org/10.51866/cr1306>

Keywords:

Subclavian steal syndrome, syncope, angioplasty

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Abstract

Subclavian steal syndrome (SSS) is a manifestation of vertebrobasilar artery insufficiency due to stenosis of the proximal subclavian artery. It is a common vascular disorder; however, most patients are asymptomatic, and the disorder is commonly found incidentally during imaging. Nevertheless, some patients may present with arm ischemia or signs and symptoms of vertebrobasilar insufficiency, such as vertigo, dizziness, diplopia, ataxia, dysarthria, and syncopal episodes. We present a case of a male patient who presented with sudden onset dizziness, syncopal episodes, and blood pressure discrepancy between his arms. Diagnosis was a challenge, and the patient underwent several investigations, including basic bloodwork, electrocardiography (ECG), echocardiography, brain computed tomography (CT), and coronary CT angiography (CTA). Narrowing in the proximal left subclavian artery was found during coronary CTA, which confirmed the diagnosis of SSS.

Introduction

Subclavian steal is a phenomenon that occurs when there is a reversal of blood flow in the ipsilateral vertebral artery due to subclavian artery stenosis proximal to the vertebral artery.¹ This phenomenon was discovered in 1960 by Contorni when he observed retrograde blood flow in a patient with an absent radial pulse.² A year later, Reivich associated this phenomenon with neurological symptoms,³ which resulted in the introduction of the term subclavian steal syndrome (SSS) by Fisher in 1961.⁴ SSS comprises a group of symptoms that arises from the consequences of reversed blood flow in the ipsilateral vertebral artery. Right and left brachial artery blood pressure (BP) discrepancy of more than 20 mmHg should raise suspicion of SSS, in addition to symptoms of vertebrobasilar artery insufficiency.

Another clinical finding associated with SSS is delayed or reduced pulse in the affected limb.⁵ The prevalence of subclavian steal phenomenon was reported to be between 0.6% and 6.4%.⁵ Not all patients with SSS are symptomatic; in a large study on extracranial artery disease, Fields et al. found that only 5.3% of SSS patients experienced neurological symptoms.⁶ We report the case of a patient with neurological symptoms who was diagnosed with SSS after a vigorous series of investigations.

Case Presentation

A 48-year-old man with multiple comorbidities, including diabetes mellitus, hyperlipidaemia, and hypertension, presented with a sudden onset of dizziness and a spinning sensation associated with palpitations. He had previously experienced multiple episodes of syncope associated with hand elevation that subsided after rest. Otherwise, there were no other aggravating factors that led to the attack; it was unrelated to postural changes or eye closure. During the attack, the patient was unable to walk due to unsteadiness. The patient reported no complaints of chest pain or neurological deficits. Upon arrival in the emergency department, his initial examination and basic blood investigations, including packed cell volume and electrolytes, were all unremarkable. There was a discrepancy between the systolic BP of his right and left arms of more than 20 mmHg, with the BP in his right arm being higher than his left. Further investigations were carried out to determine the cause of dizziness. Electrocardiography (ECG) showed sinus rhythm with no evidence of acute ischemic changes and no evidence of previous cardiac ischemia. On echocardiography, ejection fraction was normal and there was mild mitral and tricuspid valve regurgitation. No evidence

of acute brain infarction, aside from multiple old lacunar infarctions, was observed on non-contrast brain computed tomography (CT). The patient's symptoms improved throughout the hospital stay. With multiple comorbidities, cardiac CT angiography (CTA) was performed for stratification of the coronary vessels and revealed severe short-segment stenoses at the origin of left subclavian artery (approximately 95% stenosis) and just before the left vertebral artery (approximately 80% stenosis) secondary to non-calcified atherosclerotic plaques (**Figure 1** and **2**). Interdisciplinary discussions between the vascular and interventional radiology teams

agreed on a trial of angioplasty of the stenotic part. The patient subsequently underwent percutaneous angioplasty (PTA) with a transfemoral artery approach. A 6 mm x 40 mm PTA balloon (Bard Ultraverse™ 035 PTA dilatation catheter) was advanced to the stenotic part with a 0.035-inch guidewire (Terumo GLIDEWIRE® hydrophilic coated guidewire). Angioplasty was performed at the stenotic part. Post-angioplasty imaging revealed satisfactory opening of the stenotic parts; therefore, no stent was deployed. The pre- and post-angioplasty images are presented in **Figure 3**.



Figure 1. Thoracic CT angiography in coronal view. The red arrows show severe stenoses at the origin of left subclavian artery (approximately 95% stenosis) and just before the left vertebral artery (approximately 80% stenosis) secondary to non-calcified atherosclerotic plaques.

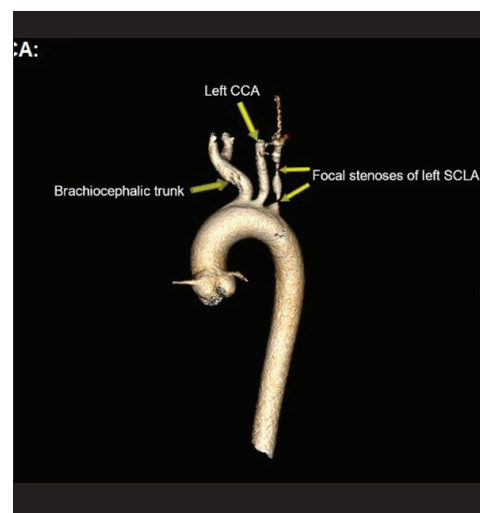


Figure 2. 3D volume rendering technique (VRT) of the main thoracic vessels. Focal stenoses at the left subclavian artery (SCLA).

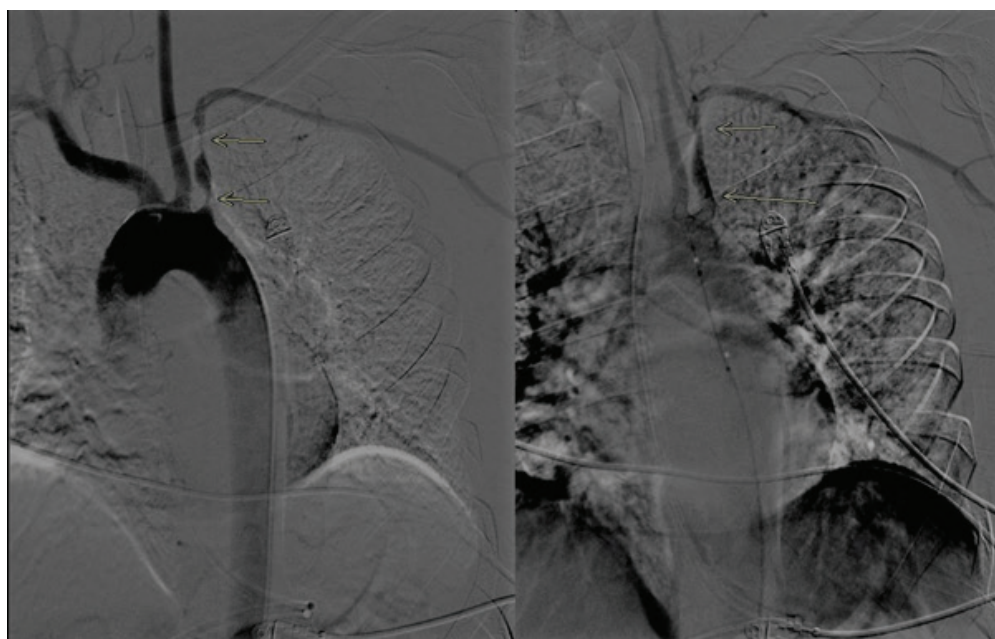


Figure 3. Pre-angioplasty digital subtraction angiography (DSA) (left) shows two significant stenoses at the proximal left subclavian artery. Post-angioplasty DSA (right) shows satisfactory re-opening of the stenotic parts.

Discussion

Whilst most of the patients who have subclavian steal phenomenon are asymptomatic, they may present with arm ischemia or neurological symptoms, such as dizziness, ataxia, vertigo, and syncope. These symptoms are due to vertebrobasilar arterial insufficiency, as blood flows retrograde from the basilar artery to the ipsilateral vertebral artery and subsequently to the distal subclavian artery. The main cause of this phenomenon is the presence of stenosis at the proximal subclavian artery, resulting in reduced blood flow distally. As a result, compensatory blood flow from the basilar artery leads to the 'steal' of blood from the brain circulation.⁷ The main aetiology of SSS is atherosclerotic vascular disease, although other causes include Takayasu arteritis, external compression of the subclavian artery, coarctation of the aorta, and congenital anomalies. Risk factors for SSS are the same as those for atherosclerotic vascular disease which include smoking, hyperlipidaemia, diabetes mellitus, hypertension, family history, and age.^{6,8}

Clinically, SSS should be suspected if there is absent or reduced ipsilateral radial pulse, a cervical or supraclavicular bruit, or an upper limb systolic blood pressure discrepancy of more than 20 mmHg.⁵ Tan et al. showed that there was a linear correlation between increasing arm blood pressure discrepancy and the occurrence of SSS symptoms.^{5,9} Further imaging with carotid duplex ultrasound, magnetic resonance (MR) angiography, or CT angiography is needed to establish the diagnosis.¹

Treatment options are either open bypass or endovascular intervention. Endovascular intervention involves angioplasty or stenting the stenotic part; it is safer than open bypass,

with low morbidity and mortality. Wang et al. reported overall survival rates of patients receiving endovascular angioplasty with stenting of 98.2 % at 12 months and 84.5% at 5 years. The main complication of stenting is intra-stent thrombosis. Inability to cross the occlusion during endovascular intervention can necessitate conversion to open axillo-axillary bypass or carotid-subclavian bypass; the latter option is preferred due to its effectiveness and improved long-term patency.¹⁰

Conclusion

Although SSS is common, it rarely presents with neurological symptoms. A thorough history of symptoms such as arm ischemia, recurrent syncopal episodes, dizziness, vertigo, diplopia, and ataxia, in addition to a BP discrepancy between arms greater than 20 mmHg, should alert general practitioners of this diagnosis. Further imaging, such as CT or MR angiography, should be performed to confirm the diagnosis.

Acknowledgements

We would like to thank the patient and all the teams involved in managing this case.

This case report received no specific grant from the government or any other funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors declare that there are no conflicts of interest.

Patients' consent for the use of images and content for publication

Written and verbal consent was obtained from the patient for publication of this case report with the accompanying images.

What is the implication to patients?

- When a patient presented with vertigo, dizziness, diplopia, ataxia, and syncopal episodes, especially when associated with strenuous activity of the hands, a physician should also be thinking of SSS as part of differential diagnosis.
- A physician must perform blood pressure measurement on both arms. A discrepancy greater than 20 mmHg has been proven to be a sensitive threshold for the detection of SSS.
- CT or MR angiography is needed to establish the diagnosis of SSS.
- SSS is now treatable with minimally invasive endovascular surgery.

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CASE REPORT

Type 2 Diabetes Mellitus with HbJ trait: A management conundrum

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Wan Yaacob WN, Yaacob LH, Draman N. Type 2 Diabetes Mellitus with HbJ trait: A management conundrum. *Malays Fam Physician*. 2022;17(1):86–89. <https://doi.org/10.51866/cr1288>

Keywords:

HbA1c, haemoglobinopathy, HbJ trait

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Abstract

Optimal glycaemic control is crucial in patients with diabetes mellitus (DM) to avoid episodes of hypoglycaemia and both micro- and macrovascular complications. Diabetic control relies mainly on the evaluation of haemoglobin A1c (HbA1c), which is unfortunately unreliable in patients with haemoglobinopathies. This case report describes a patient with type 2 DM and haemoglobin J (HbJ) trait, which resulted in erratic HbA1c values throughout her follow-up. Other approaches, such as self-blood glucose monitoring, are needed to evaluate glycaemic control instead of relying on HbA1c alone to guide the management DM in these patients.

Introduction

Haemoglobinopathies are common in many parts of the world. There are over 900 described Haemoglobin (Hb) variants, and at least 43% of all possible single-point mutations have been identified.¹ Several studies detail the impact of silent haemoglobinopathy variants on haemoglobin A1c (HbA1c) values; for example, Hb Camden, Hb Austin, and Hb N-Baltimore lead to false elevation of HbA1c values.² If an HbA1c result does not correlate with a patient's clinical condition, haemoglobinopathies and conditions affecting the lifespan of red blood cells must be considered as potential causes.³

Case Presentation

A 63-year-old woman presented to our local clinic in 2011 with fever and cough for 1 week, and she was treated for mild community-acquired pneumonia. At that time, her random capillary blood sugar (CBS) was 9.8 mmol/L. She otherwise had no symptoms of hyperglycaemia prior to the visit. Further investigations showed a fasting blood glucose of 10.7 mmol/L and an HbA1c of 37.3%; a diagnosis of type 2 diabetes mellitus (DM) was made based on these findings. The patient was started on metformin 500 mg BD. Due to the abnormally high HbA1c, a full blood picture (FBP) and Hb analysis were ordered. The FBP showed red blood cells (RBCs) containing stomatocytes and normal white blood cells (WBCs) and platelet morphology, which was suggestive of hereditary stomatocytosis. The patient's Hb was 129 g/L, MCV 93.3 fL, and MCH 31.3 pg. The results of her Hb analysis

using the capillary-CE/HPLC method showed 68.2% HbA, 1.9% HbA2, 0.7% Hb constant spring, and 29.2% HbJ, which was consistent with a possible HbJ trait. Other investigations at diagnosis noted renal impairment, with an EGFR of 41 mL/min/1.73 m² and 2+ urine albumin. The fasting lipid profile showed a total cholesterol of 4.8 mmol/L, triglycerides 1.7 mmol/L, HDL 0.82 mmol/L, and LDL 3.2 mmol/L.

Her diabetic medication was optimised with gliclazide 80 mg BD, and simvastatin 10 mg ON was added to address the elevated LDL levels. Perindopril 4 mg OD was also added for renal impairment and proteinuria. Throughout her follow-up, HbA1c levels were always erratic and mostly did not correspond with the random blood glucose readings (Table 1). The patient was adherent to all her medications and diet. The patient was also informed of the use of HbA1c in the monitoring of her illness and the difficulties that the doctor faced due to the haemoglobinopathy. She was instructed to perform self-blood glucose monitoring (SMBG); however, she was unable to do so due to financial constraints. Most of the time, the clinician relied on CBS results instead of HbA1c when evaluating the treatment, as CBS was believed to more accurately represent the patient's blood glucose control.

Despite acceptable CBS values during the initial years of treatment, the patient's diabetic control became uncontrolled and she developed further diabetic complications. Unfortunately, 5 years after diagnosis, her renal

function deteriorated from chronic kidney disease stage 3B to stage 4. She also developed bilateral eye cataracts as a complication of her uncontrolled diabetes.

Table 1. Summary of the patient's HbA1c and blood glucose readings

Year	Range of capillary blood glucose (mmol/L)	HbA1c (%)
2012	9.8–10.7 (fasting)	37.3
2013	6.7–8.3 (fasting)	Invalid result
2014	6.0–12.0 (random)	6.6
2015	6.4–7.2 (random)	Invalid result, repeated x3
2016	6.1–7.9 (random)	5.0
2017	5.7 (fasting) 6.3–10.7 (random)	26.8 (July) 33.4 (September)
2018	7.2 (fasting) 9.5–21.5 (random)	Not available
2019	8.3–9.4 (fasting) 7.5–13.8 (random)	29.7 (April) 34.3 (May) 33.6 (July)
2020	8.8–12.5 (fasting) 11.0–24.6 (random)	7.7

Discussion

The HbJ- α mutation is an alpha-chain variant found in a heterozygous state that presents a normal haematological picture.⁴ The HbJ variant is uncommon in white racial groups, and the majority of the variants are present in individuals of Asian or Southeast Asian descent.⁵ HbJ has various properties and functions and has a variable effect on HbA1c levels. HbJ Capetown ($\alpha 2$ 92Gln $\beta 2$), the most common variant of Hb J, causes erroneously elevated levels of HbA1c, as does HbJ Valencia⁶; in contrast, HbJ Baltimore and HbJ Meerut result in falsely low HbA1c values.⁷ To our knowledge, no HbJ variants have been reported to cause both abnormally high and abnormally low HbA1c estimation.

This case highlights two important points for discussion regarding HbA1c measurement in HbJ trait cases and DM management. First, the role of HbA1c in the diagnosis of DM must be discussed. HbA1c is highly sensitive to fluctuations in blood glucose levels, as a slight increase of 25–32 mg/dL in average blood glucose levels corresponds to a 1% change in HbA1c.⁸ High HbA1c levels may mislead clinicians in terms of diagnosis. A patient with the HbJ trait can be diagnosed with DM due to falsely elevated HbA1c levels and may subsequently be started on antidiabetic drugs; this can be dangerous, as the patient is at a high risk of hypoglycaemia. Therefore, a thorough history of hyperglycaemia symptoms is particularly important before making a diagnosis in these patients. It is important to not rely solely on high HbA1c to diagnose DM in patients with haemoglobinopathies.

Second, the role of HbA1c in monitoring glycaemic control must be discussed. HbA1c most accurately indicates the previous 2–3 months of glycaemic control, and it has been unequivocally demonstrated that HbA1c can predict the risk of long-term microvascular and macrovascular complications in the general population. However, some haemoglobinopathies that are clinically silent can cause biochemical aberrations that can interfere with HbA1c assays. Haemoglobin variants, such as HbS, HbC, and HbF are known to affect HbA1c assays.⁹ When the HbA1c reading is inaccurate, it affects the glucose monitoring, which leads to either overtreatment or suboptimal treatment.

The four most common methods of measuring HbA1c are affinity column immunoassay, ion-exchange high-performance liquid chromatography (HPLC), boronate affinity HPLC, and enzymatic assay.¹⁰ In cases of haemoglobinopathy, boronate affinity HPLC is the recommended method to measure HbA1c, as it can more precisely estimate HbA1c levels than other measurement methods.¹ Another alternative for monitoring glucose control is fructosamine level. Fructosamine is a measurement of the average blood glucose concentration over the past 2–3 weeks, and the value is unaffected by the presence of a haemoglobinopathy because it is dependent on protein glycation.³ Unfortunately, fructosamine was of limited value in this patient as this investigation was not provided by the clinic she attended; it is performed only at a larger healthcare centres, which leads to higher costs and delayed return of results, by which time the results have reduced value. In the absence

of other reliable methods of measuring glucose control, a correlation between clinical findings, SMBG, and HbA1c needs to be considered before reaching conclusions regarding the glycaemic control of the patient.

The presence of a haemoglobinopathy in this patient has made the management of her diabetes particularly challenging. Despite her adherence to treatment and diet, her glucose control deteriorated over the years, resulting in the emergence of diabetic complications. The main reason for her poor glucose control was failure to appropriately optimise the medications due to suboptimal glucose monitoring; this was due to inaccurate HbA1c readings and the lack of SMBG. It is recommended that, for diabetic patients with haemoglobinopathies, a reliable method for HbA1c assay must be used and supplemented with SMBG. It is especially important for primary care providers to properly educate patients about the complexity of their condition and the importance of their active

participation in the management of their illness, thus ensuring patient-centred care.

Conclusion

It is important to remember that there are many Hb variants that can interfere with routine laboratory tests. Abnormally high or low HbA1c levels in diabetic patients should prompt further investigation for haemoglobinopathies, and other methods of blood glucose monitoring should be considered.

Acknowledgements

None.

Conflicts of interest

The authors report no conflicts of interest.

Patients' consent for the use of images and content for publication

Verbal consent was obtained from the patient. No consent form was signed.

What is new in this case report compared to the previous literature?

- Rather than highlighting a new phenomenon in the literature, this case highlighted that many primary care providers might not be aware that, in the presence of haemoglobinopathy, HbA1c should be measured using ion-exchange high-performance liquid chromatography (HPLC). In addition, there is a need for other blood glucose monitoring methods for these patients.

What is the implication to patients?

- Abnormally high or low HbA1c in a patient with diabetes should alert the clinician of the presence of a haemoglobinopathy.
- In the presence of a haemoglobinopathy, HbA1c should be measured using ion-exchange high-performance liquid chromatography (HPLC).
- HbA1c readings in a patient with haemoglobinopathy should be correlated with other blood glucose parameters, and other methods of monitoring (e.g., fructosamine) should be considered.
- In the presence of a haemoglobinopathy, SMBG is required to guide insulin titration and help guide decision-making in the overall management of diabetes.

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CASE REPORT

Where are the vesicles? A case report of Ramsay Hunt syndrome

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Fader F, Gendeh HS, Goh BS. Where are the vesicles? A case report of Ramsay Hunt syndrome. *Malays Fam Physician*. 2022;17(1):90–93.
<https://doi.org/10.51866/cr1351>**Keywords:**Varicella Zoster Virus
Infection, Herpes Zoster
Oticus, Zoster Sine Herpete,
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Cheras, Kuala Lumpur, Malaysia**Abstract**

A 1-year-10-month-old child developed left-sided Ramsay Hunt syndrome (RHS) without vesicles 1 month after an episode of varicella zoster infection. No ear symptoms, including hearing loss, tinnitus, or imbalance, were reported. The external ear and otoscopic examinations were unremarkable. He achieved adequate recovery with corticosteroid treatment. This case report discusses the unusual presentation of RHS without vesicles, the diagnostic dilemma in young children, varicella zoster virus hepatitis, treatment modalities, and the role of vaccination in its prevention.

Introduction

Facial nerve palsy can be of upper motor neuron (UMN) or lower motor neuron (LMN) pathology. UMN facial nerve palsy is caused by a lesion affecting the supranuclear pathway, such as a stroke or brain tumour, and results in weakness of the lower face. In contrast, a lesion that involves the nuclear or infranuclear pathways will lead to LMN facial nerve palsy, resulting in weakness of both the upper and lower face.¹ Sudden-onset LMN facial nerve palsy may have various causes, including complications of chronic otitis media, viral infections, temporal bone trauma, or parotid pathology. In children, it is estimated that the overall incidence of facial nerve palsy is 21.1/100,000 per year. Idiopathic (Bell's palsy) and Lyme borreliosis (*Borrelia* bacterial infection transmitted via tick bite) are the most common etiologies, while Ramsay Hunt syndrome (RHS) is rare and accounts for only 2.8% of all cases of facial nerve palsy.²

RHS, also known as herpes zoster oticus, is a variant of herpes zoster (HZ). It is caused by the reactivation of varicella zoster at the geniculate ganglion causing peripheral neuralgia, and it is often associated with a vesicular papular rash around the cutaneous distribution of the 7th cranial nerve; this distribution includes the external ear canal, pinna, and sometimes the tympanic membrane.³ Occasionally, it may cause adjacent inflammation of the vestibulocochlear nerve within the internal acoustic meatus, resulting in vertigo, tinnitus, and hearing loss.⁴ Some cases may also present with lesions over

the distribution of the lingual nerve within the oral cavity, which also carries fibres for taste from the facial nerve.

This case report presents a case of RHS resulting in isolated LMN facial nerve palsy in a child without the key feature of vesicular rash.

Case Presentation

A 1-year-10-month-old boy developed sudden-onset left-sided facial weakness with the inability to close his left eye. He had no history of trauma, insect bite, or upper respiratory tract infection. He had no otologic symptoms, including ear discharge, hearing loss, or imbalance, but was seen to frequently tugging at his left pinna.

He received a 5-day course of oral prednisolone from a primary care provider, but his condition continued to worsen. He had a history of varicella infection 1 month prior to presentation, with vesicular rashes appearing over his face, trunk, and limbs, which resolved after 10 days and he had been well since. A referral to the ENT outpatient clinic was made in view of his worsening facial nerve palsy.

On examination, the patient had left-sided LMN facial nerve palsy, House–Brackmann grade V, characterised by an absence of forehead movement, inability to fully close his eye, and minimal movement of his mouth (**Figure 1**). External ear examination was unremarkable. Otoscopic examination showed bilateral intact tympanic membranes with cone

of light and absence of hyperaemia. There was no observed discharge, vesicles, lesions, or foreign bodies. Oral cavity and oropharyngeal examination were unremarkable. Eye examination revealed superficial punctate keratitis over the left cornea with Bell's phenomenon. There was no nystagmus, and the remainder of the cranial nerve examination was normal. The child was able to walk and run normally without any sign of imbalance or abnormal movement.



Figure 1. Pre-treatment shows left facial nerve palsy House-Brackmann grade V

Laboratory investigation showed an elevated total white cell count of 21.2×10^9 cells per litre, with 72.5% lymphocytes. There was also an incidental finding of elevated ALT (62 U/L), which was likely secondary to post-VZV hepatic injury. A COVID-19 polymerase chain reaction (PCR) test was also performed in view of the increasing presentation of paediatric facial nerve palsy during the COVID-19 pandemic, and Malaysia had been experiencing a second wave of the pandemic at the time. The child and his parents were negative for COVID-19 on presentation.

Differential diagnoses included left-sided RHS without vesicles in view of recent VZV infection, and Bell's palsy given that there was no indication of ear or parotid infection. Varicella zoster IgG and IgM antibody titres were available after 1 week and were positive. Therefore, the final diagnosis was a left-sided LMN facial nerve palsy secondary to RHS without vesicles and mild exposure keratopathy.

Intravenous dexamethasone was administered for 5 days with facial rehabilitation. Antiviral therapy was not initiated as it had been more than 72 hours since the onset of the symptoms. The patient's left eye was patched at night,

and he received artificial tears. He completed a 2-week course of corticosteroids and was followed up 2 weeks later at the outpatient clinic. There was significant improvement of the facial nerve palsy from House-Brackmann grade V to II. Moreover, the left eye exposure keratopathy had resolved (**Figure 2**). The liver function tests had also normalised.

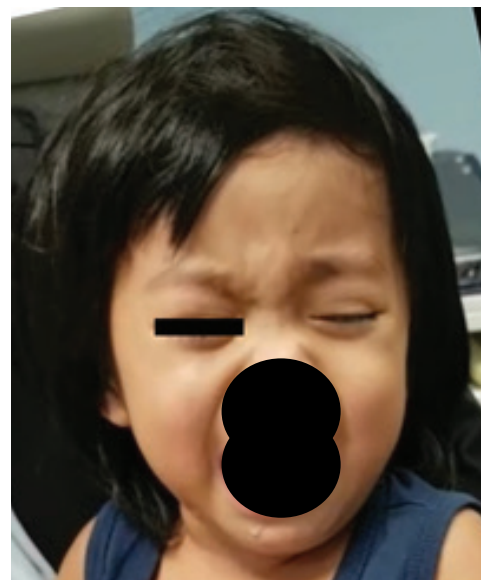


Figure 2. 2 weeks post-treatment shows left facial nerve palsy House-Brackmann grade II

Discussion

Zoster sine herpete (ZSH) is an atypical variant of HZ without vesicular skin rash. It produces atypical symptoms, such as neuropathic pain, post herpetic neuralgia, and cranial nerve palsies, such as facial nerve palsy.⁵ The infection may involve the cranial nerves, spinal nerves, visceral organs, or autonomic nerves, and may affect either motor neurons or sensory neurons that have no skin innervation.⁵ The boy in this case presented with unilateral facial nerve palsy, without the typical auricular rash of RHS. The diagnosis was difficult as there was no dermatomal skin rash, and a high level of suspicion is required when encountering atypical symptoms without any other obvious cause. In this situation, laboratory investigation helped to overcome the diagnostic dilemma with PCR detection of VZV DNA, or anti-VZV IgG and IgM antibody detection via enzyme-linked immunosorbent assay (ELISA).⁵ Other viral etiologies include Epstein-Barr virus (EBV), *Cytomegalovirus* (CMV), and herpes simplex.

With no VZV serology performed prior to presentation, the child was quickly diagnosed with Bell's palsy on his initial presentation to

the emergency department. In the strictest of definitions, Bell's palsy is an idiopathic facial nerve palsy and a diagnosis of exclusion after other possible causes of LMN facial nerve injury have been ruled out. Viral infections, including COVID-19, may cause peripheral neuropathy presenting as facial nerve palsies. Increasing numbers of children presenting to the emergency department with sudden-onset facial nerve palsies were reported in Italy during the COVID-19 pandemic; however, all patients were asymptomatic or had a negative COVID-19 diagnostic test. It is unclear whether this trend was observed elsewhere.⁶

Non-cutaneous manifestations of varicella zoster infection, such as hepatitis, are rare and are usually associated with immunocompromised states. In these patients, the condition may rapidly develop into acute fulminant hepatitis, which has a high mortality rate.⁷ In contrast, VZV hepatitis in healthy children is a mostly benign and self-limiting condition. Approximately 3% of children in this group may develop hepatitis from varicella zoster infection. Symptomatically, there is no difference between the children with VZV hepatitis and children with varicella zoster infection without hepatitis, and neither group tends to develop hepatomegaly. Most of the children will have their liver function return to normal within 1 month, without any treatment.⁸

The mainstay treatment for RHS is antiviral therapy and corticosteroids. Antiviral therapy is effective in decreasing VZV replication to prevent its proliferation and spread, but it does not eradicate the existing virus. Antivirals help to reduce the duration of viral shedding and new lesion formation while hastening rash healing. However, the therapy has a short therapeutic window and must be initiated within 72 hours of rash onset for it to be effective. Acyclovir, an antiviral agent, has become the first-line treatment for HZ on all body sites, except for the ear. Despite its wide use in RHS, there is a lack of evidence of the benefits of acyclovir being statistically significant randomised-controlled trial (RCT).⁹ Corticosteroids have anti-inflammatory properties that help to reduce oedema and minimise facial nerve damage in Bell's palsy¹⁰; they are also widely used in the treatment of RHS, given that both conditions involve inflammation of the facial nerve. However, unlike Bell's palsy, there is no significant evidence that supports the usage

of corticosteroids in RHS.¹¹ Although there have been no randomised trials that support both corticosteroids and antiviral therapy in RHS, multiple case series and cohort studies have shown that a combination of both treatments offers benefits and lowers the risk of complications.¹²

The varicella vaccine is a live-attenuated vaccine that contain the Japanese vaccine strain V-Oka.¹³ The vaccine was initially developed to prevent varicella infection and has a role in the prevention of HZ and its complications. There are some concerns regarding vaccination, as vaccine-strain VZV establishes a latent infection and can theoretically reactivate into vaccine-strain HZ. Despite the risk of vaccine-strain HZ, the overall incidence of HZ (for both wild-type and vaccine strain) in vaccinated children is 79% lower than in unvaccinated children. Therefore, varicella vaccination is an effective way to prevent HZ and its variant, RHS, in children.¹⁴ Furthermore, the rash is more likely to occur at dermatomes corresponding to the injection site, such as cervical and lumbar, and is likely to preserve other nerves, such as cranial nerves and the brain. From the history in our case, the child had not been vaccinated for VZV, but his RHS symptoms were milder than usual.

Conclusion

RHS in paediatric patients is rare and has poorer outcomes compared with the more common Bell's palsy. The lack of auricular vesicles and otologic symptoms does not rule out RHS, which presents a diagnostic dilemma for inexperienced practitioners. Despite a lack of evidence, antiviral therapy and corticosteroids remain the treatment of choice for RHS. Varicella vaccination is effective in reducing the overall risk of HZ and preventing its complications.

Acknowledgements

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Conflicts of interest

No conflicts of interest were reported.

Patients' consent for the use of images and content for publication

The patient's parents consented verbally to the use of images and case content for publication.

What is new in this case report compared to the previous literature?

- RHS may present without vesicles, which mimics Bell's palsy.
- VZV hepatitis is asymptomatic, benign, and self-limiting in healthy children.
- VZV vaccine reduces the risk of RHS.

What is the implication to patients?

Other causes of facial nerve palsy in children need to be considered before being diagnosed as Bell's palsy.

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CASE REPORT

Insulin oedema in type 2 diabetes mellitus: A case report

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Md Aris MA, Tan KF, Said AH. Insulin oedema in type 2 diabetes mellitus: A case report. *Malays Fam Physician*. 2022;17(1):94–98.

<https://doi.org/10.51866/cr.6>

Keywords:

Insulin, oedema, type 2 diabetes mellitus

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Abstract

Insulin oedema is a rare condition that may occur after the initiation or rapid intensification of insulin therapy in patients with long-standing hyperglycaemia, commonly with type 1 diabetes mellitus (DM). We reported a case of insulin oedema in a patient with type 2 DM who presented with swelling of the extremities and weight gain of 3 kg 1 week after insulin initiation. A course of furosemide was administered, but no significant immediate improvement was observed; however, the lower limb swelling resolved spontaneously after 3 months of follow-up. The patient also achieved adequate diabetic control with insulin, as shown by the reduction of her HbA1c from 10.7% to 6.9% over 6 months. Insulin oedema is a diagnosis of exclusion after ruling out other differential diagnoses, such as cardiac, renal, or liver failure. Although insulin oedema carries with it a good prognosis, physicians should be aware of the condition to avoid misdiagnosis.

Introduction

Weight gain is a common side effect seen in patients with diabetes mellitus (DM) receiving insulin therapy. However, peripheral or generalised oedema after insulin initiation is a rare condition. In most cases, oedematous conditions manifest shortly after the initiation of intensive insulin therapy. As an underdiagnosed phenomenon, the exact incidence of insulin oedema remains unknown.¹ A study published in 1966 reported 17 cases of insulin oedema between the years of 1950 to 1961, equivalent to a prevalence of 3.5% of all registered diabetic patients at the time.² In the modern era, insulin oedema is a rare occurrence due to the early detection and treatment of DM patients. Based on a few published case reports, insulin oedema was most commonly diagnosed in patients with type 1 DM.^{3–5} We report a case of a 57-year-old woman with poorly controlled type 2 DM who developed peripheral oedema after 1 week of insulin therapy. Spontaneous resolution was observed after 3 months, with no long-term complications.

Case Presentation

A 57-year-old Malay woman with type 2 DM and hypertension was diagnosed in 2017, 3 years prior to presentation. She had been prescribed oral linagliptin 5 mg OD and Twynsta (telmisartan/ amlodipine 80/5 mg) OD by a general practitioner; however, she was not followed up regularly. She had

poor compliance with oral medications due to a lack of awareness about DM and its complications. Most of the time, she would purchase the medications from the pharmacy without undergoing any follow-up or glucose monitoring. She was referred by the general practitioner to our centre for continuation of care.

At presentation, the patient reported hyperglycaemic symptoms including nocturia, polyuria, and polydipsia; otherwise, she was well and without other complaints. During the first clinic visit, her capillary glucose was 32 mmol/L, without signs and symptoms of ketoacidosis. Her previous medication, linagliptin, was discontinued and replaced with subcutaneous glargine 14 units before bed and oral metformin 500 mg BD. She returned for review of her blood investigations on the third day of insulin therapy: her capillary glucose reading remained high at 21.4 mmol/L. Therefore, subcutaneous NovoRapid (insulin aspart) 10 units three times per day was added to her medication regime.

After 1 week of intensified insulin therapy, the patient presented with bilateral swelling over her feet and hands. Her weight also increased from 75 kg to 78 kg. She mentioned noticing multiple skin lesions over her anterior shin for the past year, but had never sought treatment. Otherwise, she had no other signs or symptoms suggestive of venous thrombosis,

cardiac failure, renal failure, liver failure, or infection.

On examination, her blood pressure was 134/93 mmHg. Her heart rate was normal at 80 bpm. No elevated jugular venous pressure was noted. On auscultation, the apex beat was not displaced, and normal heart sounds were heard. Her lungs were clear. Abdominal examination was unremarkable and no organomegaly or ascites were noted. There was pitting oedema bilaterally over the lower limbs up to the anterior two-thirds of the shin. Her hands also appeared to be swollen up to the level of the wrist. A monofilament test was performed and no peripheral neuropathy was detected. The skin of the bilateral lower limbs appeared shiny, with raised purple-brown papules suggestive of diabetic dermopathy.

The patient's capillary glucose reading was 11.1 mmol/L. Chest x-ray (CXR) revealed the presence of peribronchial thickening in both lung fields with a cardiothoracic ratio (CTR) of 0.5, indicating possible bronchitis, interstitial oedema, or interstitial pneumonia (Figure 1). Blood investigations were performed, including full blood count, thyroid function test, liver function test, and renal profile. A trial of oral furosemide 40 mg OD was administered in addition to NovoRapid 10 units TDS and glargine 14 units before bed. She was instructed to return after 2 weeks to review her condition and results.

During the follow-up, her blood investigation revealed normal thyroid function (TSH 1.06 mIU/L [reference: 0.35–4.55 mIU/L], FT3 5.4 pmol/L [reference: 3.5–6.0 pmol/L], FT4 16 pmol/L [reference: 12.2–22.5 pmol/L]), normal renal profile (creatinine 58 μ mol/L [reference: 53–88 μ mol/L]) and urea 3.9 mmol/L [reference: 2.5–6.4 mmol/L]), and normal liver function (albumin 40 g/L [reference: 34–50 g/L]). No proteinuria was noted on urine FEME. Full blood count also revealed normal total white cell count (9.3×10^9 cells/L). However, lower limb swelling persisted, with only minimal improvement from the oral furosemide; the furosemide was thus discontinued. Due to the suboptimal level of self-monitoring blood sugar (SMBG), her insulin therapy was intensified to include subcutaneous glargine 16 units before bed and NovoRapid 12 units TDS. Furthermore, she was referred to a dietician for medical nutrition therapy

to improve her diabetic control. She did not experience any hypoglycaemic events throughout the treatment course. Fundus examination of both eyes revealed moderate non-proliferative diabetic retinopathy with maculopathy, and she was referred to an ophthalmologist.

During the third month of follow-up, the patient's lower limb swelling appeared to have resolved completely and she had returned to her normal weight (Figure 2); however, her SMBG was still suboptimal and was thus further intensified to NovoRapid 14 units TDS and glargine 20 units before bed. With subsequently improved control of her SMBG during the month of fasting, her insulin was tapered down to NovoRapid 10 units pre-dawn (*sahur*), 10 units pre-breakfast (*iftar*), and glargine 20 units before bed. Repeated HbA1c evaluation showed improvement of diabetic control, with an HbA1c of 6.9% after 5 months of follow-up. She continued with premeal NovoRapid 10 units TDS and glargine 20 units before bed. In addition, her blood pressure was also well controlled with a fixed dose of telmisartan and amlodipine. Her lipid profile was improved to a normal level of LDL with atorvastatin 20 mg once daily.

Throughout her follow-ups, the patients expressed concern about the lower limb oedema and diabetic control. Following reassurance from the treating physicians, she decided to continue her insulin therapy because her SMBG had indicated a marked improvement. Moreover, her daughter's participation in the diabetic consultation was a major motivating factor for her to comply with the diabetic diet and medications as prescribed.



Figure 1. Chest x-ray showed presence of peribronchial thickening in both lung fields with a cardiothoracic ratio (CTR) of 0.5, indicating possible bronchitis, interstitial oedema, or interstitial pneumonia.



Figure 2. Serial photographs showing lower limb oedema.

Table 1. Summary of clinic visits in chronological order.

Date of visit	Visit number	Clinical notes
16/11/2020	1	Glargine 14 units before bed, metformin 500 mg BD, and atorvastatin 20 mg ON were initiated.
19/11/2020	2	Blood results were reviewed. NovoRapid 10 units TDS was added.
27/11/2020	3	The patient presented with oedema. A trial of furosemide was administered. Relevant blood investigations were performed, and fundus assessment appointment was given. SMBG during this visit: 12/17.2/12.2/13.6/16.6/17.1 mmol/L. Continuation of insulin therapy regimen.
8/12/2020	4	Pedal oedema showed slight improvement. Furosemide was stopped. Pre-meal glucose levels ranged from 8.4 to 11 mmol/L, and post-meal readings were >12 mmol/L. In view of uncontrolled glucose levels, NovoRapid and glargine were increased to 12 units TDS and 16 units before bed.
14/1/2021	5	Pedal oedema completely resolved. Pre-breakfast glucose ranged from 9 to 14 mmol/L, with post-meal readings of 15 to 17 mmol/L. NovoRapid was increased to 14 units TDS while glargine was increased to 20 units before bed.
12/4/2021	6	The patient returned during the fasting month. Pre-breakfast readings ranged from 5.8 to 7.2 mmol/L. No SMBG was performed. NovoRapid was reduced to 10/-/10 units and glargine was maintained at 20 units before bed.
19/4/2021	7	HbA1c reduced to 6.9%. SMBG results: pre-sahur (5.7 to 7.4 mmol/L), post-sahur (6.3 to 8.5 mmol/L), pre-iftar (5.8 to 6.6 mmol/L), and post-iftar (6.2 to 9.8 mmol/L). Glucose was well controlled on NovoRapid 10/-/10 units and glargine 20 units before bed during the fasting month. Continuation of NovoRapid 10 units TDS and glargine 20 units before bed.

Discussion

Insulin oedema is a rare condition and an underreported physical finding. There is a wide range of oedema severity, from ankle swelling to severe generalised swelling (anasarca) that can lead to cardiac failure or massive serous effusion.⁶ However, insulin oedema can also represent a transient and benign phenomenon that may resolve spontaneously, without treatment.

Insulin oedema is a diagnosis of exclusion. The common differential diagnoses of oedema, such as cardiac, renal, and liver failure, must be ruled out before the diagnosis of insulin oedema can be made. Recent initiation or intensification of insulin therapy suggests a higher likelihood of insulin oedema. Several theories have postulated the mechanism of insulin oedema, including increased osmotic effect secondary to glycogen production, sodium retention, and increased capillary permeability.⁷ Another possible mechanism is the loss of albumin due to transcapillary leakage.⁴ However, our patient showed normal serum albumin levels and other blood parameters. CXR showed interstitial thickening over the hilar region of both lungs that might have been caused by interstitial oedema from the insulin oedema. The patient was otherwise clinically well, with no other symptoms of fluid overload.

In this patient, DM treatment was suboptimal over the years, leading to long-standing hyperglycaemia. Following the initiation of insulin therapy, there was a rapid drop in blood glucose level from 32 mmol/L to 11 mmol/L in less than 1 week. Nevertheless, the peripheral oedema could have been caused by the rapid improvement of glycaemic control, rather than the initiation of insulin therapy itself. Rapid improvement of blood sugar profile has been reported to be associated with reduced plasma osmolality that subsequently leads to intracellular water retention, i.e., oedema.⁸

To date, there is a paucity of comprehensive guidelines on the management of insulin oedema. It is important to identify patients who are at a high risk of developing severe complications of insulin oedema, namely

patients who are female, underweight, or have multiple comorbidities.⁴ Diuretic therapy can be used in severely compensated states. Aldosterone antagonists are another option in severe cases.⁹ Our patient was given oral furosemide for 2 weeks; however, no significant improvement was observed and the furosemide was discontinued. No strict fluid restriction was required in view of normal cardiac, renal and liver function, and the blood investigation results. The timing for spontaneous resolution of insulin oedema may vary; our patient achieved spontaneous recovery after 3 months. In comparison, similar conditions in children with type 1 DM resolved within 7–20 days with fluid and salt restriction, without the need for a diuretic.³

Conclusion

The rapid reduction of blood glucose level caused by initiation or intensification of insulin therapy may lead to insulin oedema. Differential diagnoses of bilateral lower limb oedema, such as renal, liver, and cardiac diseases, must be ruled out, and insulin oedema should be treated as a diagnosis of exclusion. In the clinical setting, insulin oedema should be highly suspected in patients who had recent insulin therapy initiation or intensification. A trial of diuretics is a treatment option, but it may or may not improve the patient's condition. Nevertheless, insulin oedema is associated with a good prognosis and spontaneous resolution over time. Therefore, clinicians should be confident in the continuation of insulin and provide reassurance to patients to ensure medication compliance.

Acknowledgements

The authors would like to thank the patient for her permission to publish this case report.

Conflicts of interest

The authors declared that there were no conflicts of interest related to this article.

Patients' consent for the use of images and content for publication

Informed consent was obtained from the patient before the preparation of this case report.

What is new in this case report compared to the previous literature?

1. Insulin oedema is a rare condition and an often-underreported physical finding.
2. This condition is mostly seen in patients with type 1 DM rather than type 2 DM.
3. The treating clinicians should be aware of this condition when treating DM patients.

What is the implication to patients?

Lower limb oedema may increase the patients' anxiety about their health status. It may also affect their adherence to medications. Patients should receive proper education and counselling from the treating clinicians to improve their confidence in insulin intensification therapy. In this case, the patient was concerned about her lower limb oedema. However, she was reassured that her blood sugar level had improved significantly following insulin therapy initiation and intensification. Therefore, she opted to adhere to the doctor's advice to continue with insulin injections, despite the oedema. A good doctor-patient relationship remains a crucial to ensuring the physical and psychological wellbeing of patients. In addition, the engagement of family members during diabetic consultations would also improve patient compliance to the diabetic diet, medications, and blood sugar monitoring.

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TEST YOUR KNOWLEDGE

Rash, red eyes, lip erosions and genital ulcer - What is the diagnosis?

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Evelyn Yap WY. Rash, red eyes, lip erosions and genital ulcer - What is the diagnosis?. *Malays Fam Physician*. 2022;17(1):99–102.
<https://doi.org/10.51866/tyk1371>**Keywords:**Syphilis, Chancre, HIV,
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Abstract

Maculopapular eruptions are frequently described as large areas of rash characterised by red, small, confluent bumps. They are frequently puzzling for the attending clinician due to the multiple possible aetiologies. Accurate diagnosis is important because treatment varies depending on the aetiology, and some rashes can be life-threatening if not treated promptly. Common aetiologies implicated include drug allergies, infection-related (for example: viral exanthems, scarlet fever) and autoimmune conditions (for example: Still's disease). We report a case of maculopapular eruption associated with mucocutaneous involvement and systemic symptoms. The possible differential diagnoses and approach to the management of this patient are discussed.

Case Summary

A 26-year-old male presented with a 3-week history of rash involving the face, trunk, and limbs. There was associated fever, sore throat, red eyes, painless lip erosions, and left knee pain. He had no urethritis, but reported a painless, non-healing genital ulcer for 2 months. Examination revealed widespread erythematous maculopapular rash involving the face, chest, abdomen, bilateral arms, forearms, and thighs (Figure 1). The patient had bilateral conjunctivitis. The throat was injected without tonsillar enlargement. Superficial erosions were found on the lower lip (Figure 2). A

clean-based ulcer with indurated border was seen on the penile shaft (Figure 3). He had tenosynovitis of the left knee and bilateral 'shotty' inguinal lymph nodes.



Figure 2. Well defined superficial erosions on the lower lip.



Figure 1. Widespread maculopapular rash on the trunk.



Figure 3. A clean-based ulcer with indurated border on the penile shaft.

Questions:

1. What further information would you like to elicit from history taking?
2. What differential diagnoses would you consider at this point?
3. What investigations would you like to perform?

Answers with discussion

1. What further information would you like to elicit from history taking?

- History of recurrent oral, eye, or genital ulcers
- History of recent initiation of drugs, traditional medications, or supplements
- Sexual history
- Other past medical history

The patient denied history of recurrent oral, eye, or genital ulcers. He also denied taking any medications or supplements. He admitted to being a male who had sex with males (MSM) and participated in unprotected anal and oral sex with multiple partners. His last sexual exposure was 3 months prior to presentation. He was positive for human immunodeficiency virus (HIV), which was detected 1 year prior.

2. What differential diagnoses would you consider at this point?

- Stevens-Johnson syndrome
- Disseminated gonococcal infection
- Concurrent primary and secondary syphilis
- Behçet's disease

Stevens-Johnson syndrome (SJS) is a life-threatening condition characterised by maculopapular eruption that spreads and forms blisters.¹ This condition is usually triggered by medications, such as antibiotics (penicillins and sulfonamides), anti-convulsants (phenytoin and carbamazepine), allopurinol, anti-retroviral therapy (nevirapine), and non-steroidal anti-inflammatory drugs (e.g., mefenamic acid, ibuprofen). typical exposure period is 4 days to 4 weeks. Treatment involves prompt withdrawal of the causative drug.² The rash of this patient was not characteristic of SJS. As the patient also denied recent drug initiation, SJS was an unlikely diagnosis.

Disseminated gonococcal infection (DGI) occurs 2–3 weeks after primary gonococcal infection.³ DGI is characterised by a triad of tenosynovitis, dermatitis, and polyarthralgia. Cutaneous lesions usually involve the extremities and are described as tender and sparse papulo-pustules on a haemorrhagic base.⁴ Treatment is intravenous or intramuscular ceftriaxone 1 g daily, continued

for 24–48 hours after improvement of symptoms, before switching to an oral agent for a total treatment course of at least 7 days.⁵

Concurrent primary and secondary syphilis is an uncommon presentation of syphilis. It is seen more often in HIV-infected patients due to the rapid progression of the disease from primary to secondary stage, and the delayed healing of the genital ulcer.^{6–8}

Behçet's disease (BD) is a rare and severely debilitating vasculitis that manifests as recurring orogenital ulcers and skin lesions. Diagnosis is made after excluding all other causes of orogenital ulcerations. Based on the International Study Group Criteria for BD, recurrent oral ulcerations at least 3 times in a 12-month period, plus any two of genital ulceration, eye lesions (anterior uveitis, posterior uveitis, cells in vitreous on slit lamp examination, or retinal vasculitis), skin lesions (erythema nodosum or papulopustular lesions), or a positive pathergy test supports the diagnosis of BD.⁹ As this patient denies history of recurrent oral ulcers, BD is a less likely diagnosis.

3. What investigations would you like to perform?

- Venereal Disease Research Laboratory (VDRL test) or *Treponema pallidum* haemagglutination (TPHA) test, blood culture and sensitivity
- Swab for Gram stain and culture and sensitivity from the urethral, anal, pharyngeal, and scrotal ulcers
- Urine/urethral swab for nucleic acid amplification test (NAAT)

The blood, urethral, anal, pharyngeal ulcer, and scrotal swab cultures were negative. NAAT of the urine specimen was negative for *Neisseria gonorrhoea*. These negative results ruled out disseminated gonococcal infection. VDRL was positive with a titre of 1:32, and the patient's TPHA was positive, confirming the diagnosis of syphilis. The genital ulcer represented a chancre, which is a feature of primary syphilis, whereas conjunctivitis, tenosynovitis, and maculopapular eruptions supported secondary syphilis. These findings indicated that the patient had concomitant primary and secondary syphilis. He was given a 2.4 MU stat dose of IM benzathine penicillin, which resulted in complete symptom resolution within 1 week.

Discussion

Syphilis is a common sexually transmitted disease caused by *Treponema pallidum*.¹⁰ In Malaysia, it is found mainly in HIV-positive patients and men who have sex with men (MSM).¹¹

Syphilis occurs in three phases: primary, secondary, and tertiary. Primary syphilis occurs after an incubation period of 21 days and is characterised by chancre, a painless ulcer at the inoculation site. Untreated, the chancre resolves, and the infection progresses into secondary syphilis 6 weeks later, signifying the haematogenous spread of *T. pallidum*. This secondary phase is characterised by a widespread macular rash with palmoplantar involvement and systemic symptoms.¹² *T. pallidum* may also inoculate other organs, such as the eye and musculoskeletal system. Ocular manifestations in secondary syphilis include conjunctivitis, episcleritis, scleritis, keratitis,

iritidocyclitis, anterior uveitis, posterior segment involvement, and acute posterior placoid chorioretinopathy (APPC).¹³ In the musculoskeletal system, periostitis, osteochondritis, osteitis, and less commonly, tenosynovitis and syphilitic arthritis, may occur.¹⁴ Latent syphilis follows secondary syphilis. If untreated, up to 25% of cases will progress to tertiary syphilis, characterised by cardiovascular and neurologic features and gummatous lesions.⁹

In HIV-positive patients, clinical presentation of syphilis is often atypical due to compromised humoral and cell-mediated immunity. Chancres can be numerous, large, and deep, with delayed healing, leading to persistence into secondary syphilis. Cutaneous manifestations in HIV-positive patients are also highly variable, with papulosquamous, lenticular, annular, and pustular lesions being described.¹²

Conflict of interest

The authors declare no conflicts of interest.

How does this paper make a difference to general practice?

- Syphilis in HIV-positive patients can be atypical, and it is important to have a high index of suspicion when encountering a HIV-positive patient with a skin rash.

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A MOMENT IN THE LIFE OF A FAMILY PHYSICIAN

A family physician's impossible choices & lessons learned through illness

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Liew SM. A family physician's impossible choices & lessons learned through illness. *Malays Fam Physician*. 2022;17(1);103–104.
<https://doi.org/10.51866/mol.001>

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I was recently diagnosed with bladder cancer and had to undergo four cycles of chemotherapy. After the third cycle, I was scheduled for a follow-up MRI with contrast. The medical officer (MO) conducting the pre-MRI check-up was adamant that I should not have the contrast because my reported eGFR was poor, i.e., below 30 mL/min/1.73 m². I explained that my oncologist and nephrologist had discussed the matter and that they wanted the MRI because my recalculated eGFR was better than the eGFR reported by the lab, and the scans were needed for my upcoming major operation. Following protocol, she checked with her senior, who spoke with me.

The conversation went something like this:

‘Prof, the actual reason that it might not be advisable to do the contrast MRI is due to the risk of you getting a condition known as nephrogenic systemic fibrosis that is seen only in patients with advanced renal disease. There is no treatment for this—it is rare, but it can occur.’

‘Thank you for telling me this, but I need the scans for my operation.’

‘I understand, but you need to know the risk of this condition and decide whether you are able to accept the risk.’

‘I really would prefer not to take the risk, but as I understand it, the scans are necessary for my operation. Can you discuss this with my nephrologist?’

After a telephone consultation with the nephrologist, the MO returned to inform me that they would proceed with the MRI because the adverse reaction was very rare.

I was quite affected by this consultation, and now, days later, the encounter is still being replayed in my mind. As a senior consultant in primary care medicine and an advocate for evidence-based medicine (EBM) and shared decision making (SDM), the fact that I could not make my own decision plagues my thoughts.

As a doctor, I must often discuss difficult medical decisions with patients: whether or not to proceed with an eye operation for an orbital fracture in a 90-year-old woman, to decide on end-of-life treatment for a cancer patient, to consider whether or not to start or stop preventive treatment for any patient. I would explain the choices, the pros and the cons, and the evidence—or lack thereof—underlying each decision. Patients would discuss their choices with me, but they would often simply ask: ‘What would you do, doctor?’

We give patients impossible choices, just like the choice I faced in my own experience. The two MOs, junior and senior, did the right thing and I am proud that they outlined the risks and considered my choices—but what choice did I have?

I feel that this has been a recurring theme throughout my illness. When I was first diagnosed with lupus nephritis, I was a final year medical student and was told that I had to take high-dose steroids. I knew exactly what side effects I was going to experience. My weight ballooned

from 70 kg to 120 kg within weeks. It was difficult to speak with patients about their weight problems when I, myself, was morbidly obese. Every day, my face expanded until I thought it would simply burst like an overfilled bubble. Striae blossomed on my armpits, thighs, and abdomen. The night before I took the steroids, I cried and cried—but I still had to take them.

When my bladder cancer was first diagnosed in 1999 (a result of cyclophosphamide therapy), I was devastated and could not speak of the diagnosis to anyone other than my immediate circle of family and friends. In May 2021, I was diagnosed with recurrent invasive bladder cancer, and the diagnosis was still devastating. Medical crises do not get easier to accept with time; one does not get braver or wiser. It still felt as if someone had just punched me in the gut.

At first, I could not tell anyone of my diagnosis—my latest medical crisis. In the first 2 months, I could not do anything. I realised that I lived a lot of my life in my head; my physical body had always given me problems and, to get away from them all, I read books, worked on my medical and research career and, well, lived in defiance of my symptoms and signs. But now I was being pulled back into my corporeal self, and it was difficult. I gave up many things in those first few months: my work, my teaching, my research. It was all I could do to focus on what needed to be done—scans, blood tests, scopes, chemotherapy, and the impending operation.

If I, the EBM advocate, the SDM clinician, the primary care consultant, had difficulty with this, then it must be impossible for patients—or, perhaps a little knowledge is a dangerous thing. Deep down, I know that part of my denial was that I was a preventive medicine doctor; I taught patients a healthy lifestyle, I lived a healthy lifestyle, and I felt ashamed to have renal failure and cancer, the bogeymen of complications that we tell patients they have to avoid.

This has made me realise how much we blame patients for their diagnoses. Perhaps it is because we want to think that we have some control over illness. We can reduce the risks for cancer by not smoking, maintaining the proper weight, doing check-ups, and so on, but, often these things are beyond our control. We can still be that random person for whom the treatment cures or the treatment kills.

What is the moral of the story? As I said, I am not braver nor am I wiser. If I were to speak to the younger me who wanted to do primary care medicine all those decades ago, I would tell her not to think that she can prevent illness or cure everyone, but that she can simply listen and help the patients as much as she can, and offer empathy and kindness. Sometimes that is all that is needed and is more than enough.

OBITUARY

Liew Su May (1970–2021): A champion of evidence-based primary care medicine

Editorial board members of Malaysian Family Physician

Editorial board members of Malaysian Family Physician. Liew Su May (1970–2021): A champion of evidence-based primary care medicine. *Malays Fam Physician*. 2022;17(1);105–106. <https://doi.org/10.51866/ob.001>

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On a gloomy Thursday morning, 23 December 2021, Professor Dr Liew Su May passed away at home after a long fight with SLE and cancer, surrounded by her loved ones. She leaves behind her beloved husband, Dr Saini Jeffery Freddy Abdullah, and their daughter, Elena May Saini Jeffery.

The second of three siblings, Professor Liew was born on 7 September, 1970 in Kuala Lumpur, Malaysia, to Mr Liew Yoon Loy and Mdm Teoh Ah Nya. She was educated in Convent Bukit Nanas, Kuala Lumpur, pursued her secondary education at Raffles Girls' Secondary school, and attended National Junior College for her Pre-U (A-levels) as an ASEAN scholar in Singapore before returning to Universiti Malaya to study Medicine. It was here she met Saini. She graduated with a Bachelor of Medicine and Bachelor of Surgery (MBBS) in 1994 and obtained her Masters of Medicine (Family Medicine) in 2003. She joined her alma mater at the Department of Primary Care Medicine as a lecturer in 2004, beginning her academic life. Professor Liew developed a keen interest in research after entering academia, which prompted her to pursue her PhD at the University of Oxford in the United Kingdom under the supervision of Professor Dr Paul Glasziou. She was an excellent scholar and a passionate advocate of evidence-based medicine (EBM) and was subsequently appointed as a Fellow at the Center for Evidence Based Medicine, Oxford University (2012–2016). She transferred her knowledge, skill and expertise in EBM back to Universiti Malaya and was the inaugural undergraduate EBM coordinator at the Faculty of Medicine since 2013.

Professor Liew was an insightful primary care physician and researcher with many landmark achievements to her credit. Her research interests spanned from cardiovascular disease in particular cardiovascular risk score and modelling to exploring effective ways to teach and implement EBM and, in the later stage of her academic career, respiratory diseases. She continuously searched for and addressed research gaps and topics neglected in our region, with the aim of conducting more translational research to improve patient care. She was a key researcher from Malaysia at the NIHR Global Health Research Unit on Respiratory Health (RESPIRE), University of Edinburgh. This led her to become a RESPIRE Research Fellow at the University of Edinburgh, exploring the development and implementation of Patient and Public Involvement (PPI) in Malaysia and the region at a time when PPI was still in its infancy. In Malaysia, patients and the public are not usually asked about their views regarding research, yet Professor Liew was passionate about empowering patients and the public to play an active role in research. She championed this cause by writing a section on PPI in an online research module (Manuscript Writing Made Easy), delivering a plenary talk on PPI at the UM Faculty of Medicine Research Carnival in 2021, and another plenary talk at the 7th Sabah Medical Research and Scientific Conference on Developing Patient and Public Involvement in Research in Malaysia (September 2019).

Professor Liew contributed significantly to the academic world as editor and writer, both locally and internationally. She was a member of the Editorial Board of Malaysian Family Physician since 2012. In 2016, she became the chief editor, presiding over 213 articles and ensuring they were of the highest standard. In addition, she was an Honorary Clinical Epidemiologist for the National Clinical Research Centre of Malaysia. Internationally, she contributed significantly to the International Primary Care Respiratory Group (IPCRG). She was an inspirational member of the Leadership School and Teach the Teacher programme on children with asthma of IPCRG, which continues to spread throughout Malaysia. Her

IPCRG legacy includes developing an innovative iQ&A programme, devising the research strategy, and contributing to writing the palliative care section of the massive open online course.

Professor Liew was also heavily involved in postgraduate training in family medicine. She was appointed as the Postgraduate Coordinator at the Department of Primary Care Medicine, UM in 2018 and led the development of the Malaysia National Postgraduate Medical Curriculum for Family Medicine since 2014. Despite the multiple medical conditions she lived with, her academic achievements were remarkable: she supervised and graduated 20 postgraduate Master of Family Medicine trainees and 7 postgraduate research students. Due to her personal illness experience, she embraced the importance of patient-centred care and of engaging patients in decision making. She supported research and taught EBM skills to medical students and postgraduate trainees across Malaysia, including colleagues from Hospis Malaysia and the Ministry of Health Clinical Research Centres.

Professor Liew exuded passion and enthusiasm in everything she did, from clinical practice and teaching to research. As a mentor, although uncompromising on scientific rigor and excellence, she was always kind, patient, encouraging and supportive. Her infectious laugh and enormous sense of humour, as well as her fight for justice and integrity, have left and will continue to leave an indelible mark on everyone who knew her. Beyond the professional front, she was a wonderful friend who genuinely cared for and never failed to show affection to those around her; indeed, academic conversations would often end with discussions about gardening, food, recipes or books she had read. Professor Liew's legacy – "let's address the elephant in the room" or "the most important thing is your research question" – alongside her strong sense of reasoning and relentless fight for the truth will influence us for many years to come.

