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CASE REPORTS

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Collaboration among Endocrinology Publications in Asia

For JAFES in 2010, or even before that, the overwhelming concern was how to make this journal a worthy partner among Asian and international journals. The arena was already teeming with international, regional, and country-specific journals on endocrinology. What did JAFES have to offer to the Southeast Asian endocrinologist?

Early on, we understood the extra effort and attention to detail that would be required of JAFES if we wanted to succeed. We viewed our endeavors as a form of competition, not so much with other Endocrinology journals than with ourselves, and this guided the JAFES work over the last eight years. We were always on the lookout for best practices and innovations that can be particularly suited to our Southeast Asian contexts. We were learning by doing, how to adapt with technology to drive continual improvement, committing some mistakes in the process, and celebrating successes as they came.

Through AFES society support, we teamed together, braved the journey and remained true to our ideals of representing the voice of endocrinology in Southeast Asia, eventually becoming accepted for inclusion in Scopus in 2016.

JAFES was recently invited to present at the 6th Seoul International Congress of Endocrinology and Metabolism (SICEM 2018) at a special publication session entitled "Seeking for the United Collaboration among Asian Associations through Publication." SICEM is the official scientific meeting of the Korean Endocrine Society which provides an opportunity for local and international scientists and clinicians "to share novel ideas and learn about the latest studies in the field of endocrinology and metabolism."[1] The session aimed for the cooperative development of Asian endocrine journals and featured editors of EnM, Diabetes and Metabolism, Formosan Journal of Endocrinology and Metabolism, and JAFES. We shared our respective publication's current status, successes and challenges, and future directions, and discussed, as a group, the possibility of moving forward together.

After learning much from our hands-on experience attempting to make JAFES more active and more relevant, we wish now to pay it forward. Our active participation in the Korea meeting signifies an evolution of our goals as a journal. JAFES is now a worthy partner in publication collaboration, at the national, regional, and international scenes. In an increasingly connected world, indeed collaboration in the form of mutual support to each journal's specific objectives, provides the greatest potential to promote our own publication's growth and development.

Elizabeth Paz-Pacheco
Editor-in-Chief

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Reference

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Journal of the ASEAN Federation of Endocrine Societies

ORIGINAL ARTICLE

Phenotypic Variation of 46,XX Late Identified Congenital Adrenal Hyperplasia among Indonesians

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Abstract

Objectives. To describe the phenotype variation in Indonesian 46,XX late-identified congenital adrenal hyperplasia (CAH) and the correlation between 17-hydroxyprogesterone (17-OHP) and genital virilization.

Methodology. Retrospective study of 39 cases with five salt-wasting (SW) and 34 simple virilizing (SV) types.

Results. The median age of the patients was 9.83 years (range, 0.58 to 44 years) with Prader score 2 to 5. Clitoromegaly (100%) and skin hyperpigmentation (87%) were the most common features. Lack of breast development (Tanner 1 to 2) and menstrual disorders occurred in 9 patients (teenagers and adults). Short stature (6), low voice (14), prominent Adam's apple (9) and hirsutism (4) were found only in SV types. Rapid growth (7) and precocious puberty (8) were identified in children. Male gender on admission was found in 13 patients. The mean of 17-OHP level was 304.23 nmol/L [standard deviation (SD) 125.03 nmol/L]. There was no correlation between 17-OHP levels and virilization ($r=0.19$, $p>0.05$).

Conclusion. Late-identified CAH showed severe virilization and irreversible sequelae, with clitoromegaly and skin hyperpigmentation as the most commonly seen features. Masculinization of CAH females created uncertainty with regard to sex assignment at birth, resulting in female, male and undecided genders. There is no significant correlation between 17-OHP levels with the degree of virilization in CAH females.

Key words: CAH, late-identified, phenotype, virilization

INTRODUCTION

Congenital adrenal hyperplasia is a leading cause of 46,XX disorders of sex development (DSD) resulting from a deficiency of enzymes required for cortisol and aldosterone biosynthesis. More than 90% cases have 21-hydroxylase deficiency (21-OHD) and mutations in the CYP21A2 gene, which is located on the short arm of chromosome 6 (6p21.3).[1,2] Affected females are born with various degrees of virilization, as a result of prenatal androgen exposure. Aside from 21-OHD, virilization in 46,XX individuals with CAH is also caused by 11β-hydroxylase deficiency (11β-OHD), P450 oxidoreductase deficiency (POR) and 3β-hydroxysteroid dehydrogenase deficiency (3β-HSD).[2,3,4]

Classic CAH can be further divided into salt-wasting and simple virilizing types. Virilization in a female manifests as clitoromegaly, acne, hirsutism and low voice. At puberty, normal feminization of girls fails to occur, usually presenting with lack of breast development or absence of menstruation.[3,4] Elevation of 17-OHP in CAH leads to increased androgen levels, but the relationship between 17-OHP and virilization phenotype has not been consistent as seen in previous studies.[2,5]

The incidence of CAH in the general population is approximately 1 in 16,000 on screened newborns worldwide, and carriers are present in 1:60.[6,7] Data from our center from 2004 to 2016 show that there are 84 patients with CAH, consisting of a wide age range of 3 days to 44 years old. Majority of the patients seen have never received any specific treatment for CAH. Genital ambiguity was the most common reason for physician consult in female patients.

Delayed diagnosis and treatment of CAH in children is common in Indonesia. It is frequent especially for SV or SW types who develop adrenal crises without a definite diagnosis due to the absence of newborn screening.[8] In Indonesia, newborn screening for CAH is not yet available, as basic treatment and hormonal tests are not provided in public hospitals with health insurance services. Ethically, it cannot be provided yet because

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medications such as hydrocortisone and fludrocortisone are not available. In developed countries, a patient with CAH is often diagnosed early in life by neonatal screening programs.[9]

OBJECTIVES

1. To describe the phenotype variation in Indonesian 46,XX late-identified CAH, which is rarely reported in other countries, and;
2. To identify the correlation of 17-OHP and genital virilization.

METHODOLOGY

Study design

This is a descriptive study.

Patients and methods

From 2004 to 2016, we gathered 84 patients with a diagnosis of CAH, evaluated under the clinical management of the multidisciplinary DSD team of the Dr. Kariadi Hospital and Faculty of Medicine Diponegoro University. Thirty-nine patients were enrolled in this study.

CAH was diagnosed based on the clinical manifestations and elevated serum levels of 17-OHP. The inclusion criteria were 46,XX karyotype and age 6 months or older at first visit to our center. Patients who underwent corrective genital surgery before their first visit to our center were excluded.

Medical records were reviewed to gather data including age at diagnosis, anthropometrics, appearance of genitalia, Prader score, Tanner stage, skin hyperpigmentation, acne, hirsutism, and low voice with or without Adam's apple, menstrual disorders and family history (pedigree). Details and additional information were verified with the patient or parent.

Ethical considerations

This study was approved by the Medical Ethics Committee and informed consent was obtained from all patients and parents.

RESULTS

Clinical findings

Thirty-nine patients (5 SW and 34 SV) fulfilled the inclusion criteria, with a mean age of 9.83 (SD±9.42 years). There were 9 adults and 30 children. Physician-diagnosed SW type was significantly younger compared to SV type (mean age 0.58 versus 7.25 years, $p<0.05$). The phenotype variation of late identified CAH are shown in Table 1. The most frequent clinical manifestations on both SW and SV types were clitoromegaly (100%) and generalized skin hyperpigmentation mainly around the genital area (87%). Nine patients with ages over 13 years showed lack of breast development (breast Tanner stage 1 to 2). Menstrual disorders included primary amenorrhea (67%) and late menarche occurring at age over 15 years (33%, 15 to 18 years). Precocious puberty (23.3%), defined as premature pubic hair growth, was evident by 3 years old. Fourteen patients had low voice (35.9%), 9 of which had prominent Adam's apple. Four patients had hirsutism (10.3%), all of whom were SV type. Two patients had acne problems. Eight children had height measurements above the 97th percentiles for age in the Chinese Growth chart (26.7%), the

Table 1. Phenotypic variation of Indonesian late-identified CAH[a] patients

Clinical findings	SW[b] type (n=5)	SV[c] type (n=34)	Total	p-value
Clitoromegaly (%)	5/5 (100)	34/34 (100)	39/39 (100)	0
Hyperpigmentation (%)	5/5 (100)	29/34 (85.4)	34/39 (87.2)	0.6*
Hirsutism (%)	0/5	4/34 (11.7)	4/39 (10.3)	-
Low voice (%)	1/5 (20)	13/34 (38.2)	14/39 (35.9)	-
With Adam's apple (%)	0/5	9/13 (69.2)	9/39 (23.1)	-
Acne (%)	0/5	2/34 (5.8)	2/39 (5.1)	-
Short stature				-
Children	0/5	1/25 (4.0)	1/30 (3.3)	
Adult	0/5	7/9 (77.8)	7/9 (77.8)	
Age 13 years or less				
Rapid growth	1/5 (20)	6/25 (24)	7/30 (23.3)	-
Precocious puberty	2/5 (40)	6/25 (24)	8/30 (26.7)	-
Age over 13 years				
Lack of breast development (Tanner 1 to 2)	0	9/9 (100)	9/9 (100)	-
Menstrual disorders	0	9/9 (100)	9/9 (100)	-
Genitalia status				
Clitoris/phallus length (cm)	4.8 ± 2.4	4.24 ± 1.2	4.3 ± 1.4	0.3[e]
Scrotalization	3/5 (60)	21/34 (62)	24/39 (61.5)	0.6[d]
Complete labial fusion	1/5 (20)	6/34 (17.9)	7/39 (44)	1[d]
Rudimentary labia minora	4/5 (80)	23/34 (67.6)	27/39 (61.5)	0.3[d]
Prader score	Stage 3 (60)	Stage 4 (38.2)	Stage 3 (36)	0.7[f]
Mean serum 17-OHP level, nmol/L	391.00	291.47	304.23	0.3[f]

[a]CAH, congenital adrenal hyperplasia
[b]SW, salt-wasting
[c]SV, simple virilizing
[d]Fisher exact test
[e]T-test
[f]Mann-Whitney test

Table 2. Gender assignment after final examination

Patient number	Gender and age on admission		Gender and age after final examination	
	Gender	Age (y.o**)	Gender	Age (y.o)
1	Male	17	Male	18
2	Female	11	Female	12
3	Female	33	Female	33.5
4	Female	6	Female	6.5
5	Female	7	Female	8
6	Female	7	Female	8
7	Female	4	Female	5
8	Male	3	Male	4
9	Female	1.5	Female	2
10	Female	1.9	Female	2
11	Female	10	Female	11
12	Female	3	Female	3.5
13	Female	7	Female	8
14	Female	6	Female	6.5
15	Male	24	Male	25
16	Female	7.5	Female	8
17	Female	4	Female	4.5
18	Male*	7.75	Male	8
19	Male	8	Male	8.5
20	Female	23.5	Female	24
21	Female	18	Female	18
22	**Male**	1.5	**Female**	2
23	Female	15	Female	16
24	Male	8.5	Male	9.5
25	Female	17	Female	17.5
26	Female	3	Female	3.5
27	undecided	2	undecided	3
28	Male	44	Male	46
29	**Male***	1	**Female**	1.5
30	**Male***	0.58	**Female**	1
31	Male	10	Male	10.5
32	Female	3	Female	4
33	Female	19	Female	20
34	Female*	5.67	Female	6.5
35	Female	21.5	Female	22
36	Male	8	Male	8.5
37	Female	7	Female	8
38	**Male***	5	**Female**	5.5
39	Female	1.8	Female	2

Salt Wasting type (*)
y.o = years old (**)

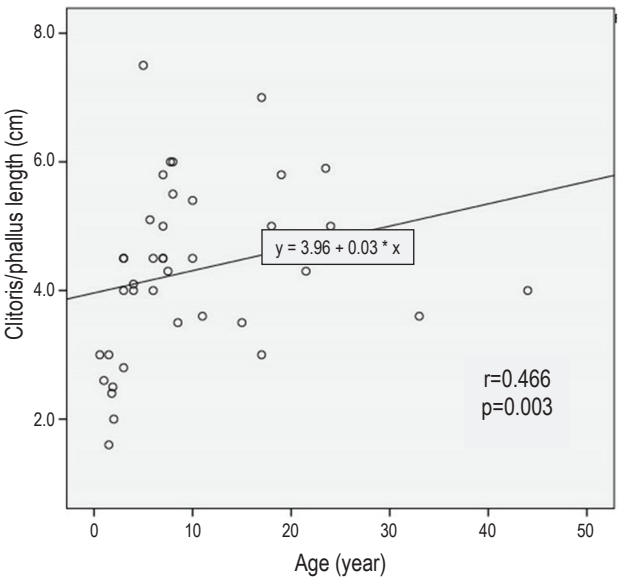

Figure 1. Relationship between age and phallus length in late-identified CAH.

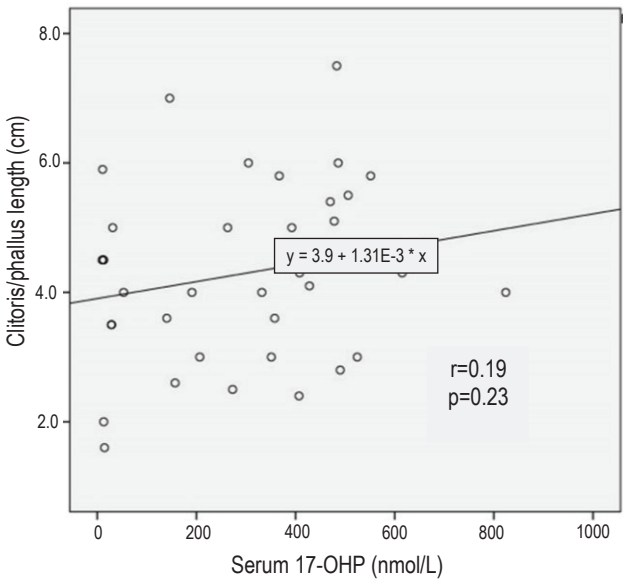

Figure 2. Relationship between serum 17-hydroxyprogesterone (17-OHP) levels and phallus length in late-identified CAH.

available reference for Asian populations, indicative of rapid growth.[10] Short stature, defined as less than the 3rd percentiles of the Chinese Growth Chart, occurred in 6 adult patients (75%). Of this group, one child had accelerated epiphyseal maturation, with bone age at 17 to 18 years.

The next most common dysmorphology was rudimentary labia minora, seen in 80% of SW and 67% of SV types (p>0.05). However, clitoral/phallus length was not significantly different between SW and SV types, with mean length 4.8 cm and 4.24 cm, respectively (p>0.05). We

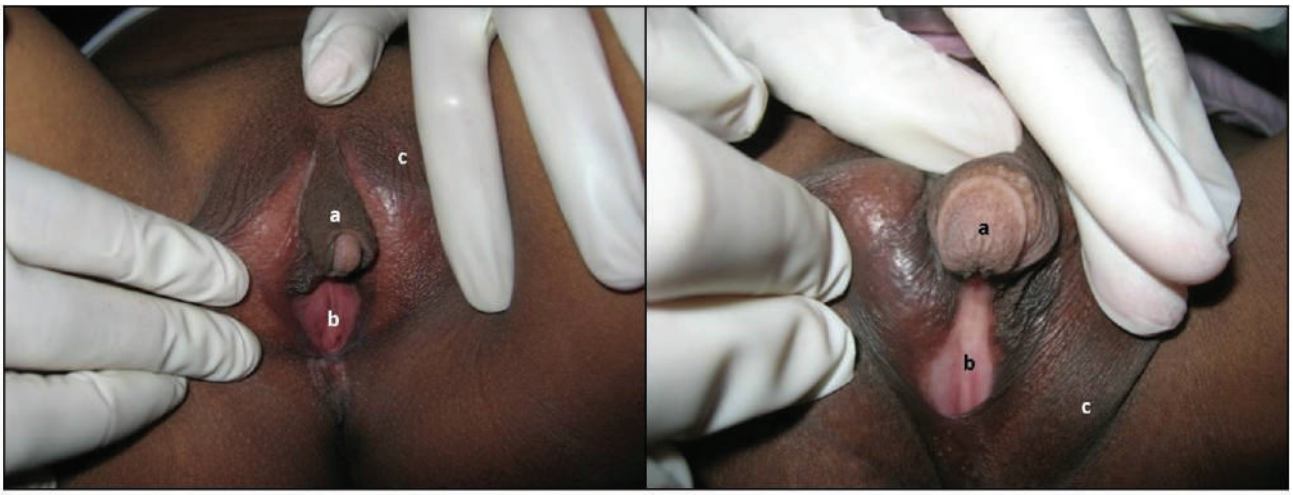

Figure 3. Virilized external genitalia in 2 female siblings showing clitoromegaly (a), presence of vaginal introitus (b), and hyperpigmentation (c).

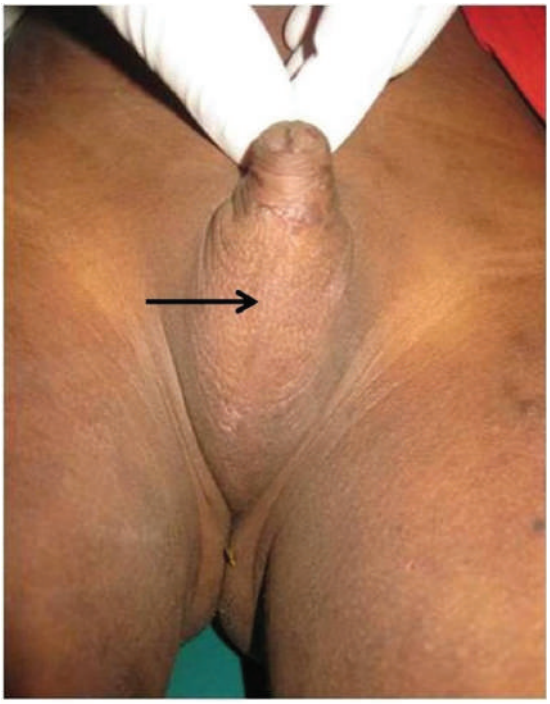

Figure 4. An 8.5-year-old child assigned to male gender with 46,XX late-identified CAH. There is complete labial fusion (*arrow*) resembling a scrotum.

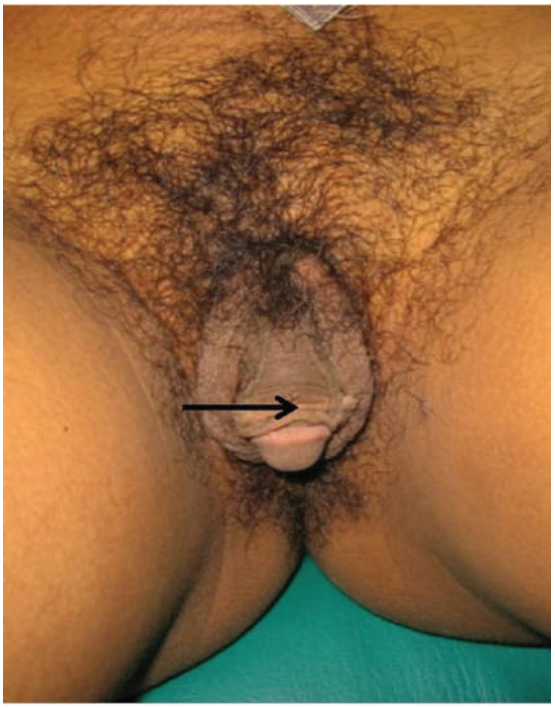

Figure 5. A 24-year-old adult assigned to male gender with 46,XX late-identified CAH. There is a big phallus (*arrow*) with scrotalization.

found a good correlation between age and phallus length in late-identified CAH (r=0.466, p<0.05) (Figure 1). More than 50% of both SW type and SV type CAH had labial scrotalization. Complete labial fusion was more frequent in SW (20%) compared to SV (17.9%) (p>0.05).

All patients had genital ambiguity, with a median Prader score of 3 and 4 in SW and SV types, respectively. Thirteen patients (33%) reveal male gender and four patients with male gender of five SW-type on their first visit and one SV type patient had undetermined gender. However, after undergoing thorough physical and laboratory examination and genetic counseling, four patients decided to change their gender from male to female (Table 2).

Correlation of 17-OHP with phallus length

All patients had elevated blood levels of 17-OHP. Based on Spearman's correlation coefficient test, there was no correlation between 17-OHP level and phallus length (r=0.19, p>0.05) (Figure 2).

DISCUSSION

The mean age of presentation of patients in our study is nine years, quite different from data from Western populations.[11] Recognition is frequently late due to lack of knowledge of medical providers, especially in remote regions; lack of awareness of parents to seek medical management; unavailability of neonatal screening in

Indonesia; and early death of affected babies before diagnosis.

There are significant differences in the number of patients and their age at diagnosis in SW and SV types in our study, in contrast to other published reports.[12] This discrepancy suggests that more of SW type CAH patients died from adrenal crises before being diagnosed. Identifying newborn girls with signs and symptoms of CAH is not difficult because of genital ambiguity and salt wasting symptoms in the SW type. In newborn boys, the diagnosis is challenging because of the absence of ambiguous genitalia, especially in the SV type. Moreover, CAH in Indonesia is still unfamiliar for many medical practitioners, such as general practitioners or midwives. Factors that may lead to late diagnosis and treatment include high cost and limited facilities for hormonal analysis to detect CAH, and the difficult access to appropriate medications.

Clinical variations depend on the degree of hormonal disruption, and timeliness and regularity of treatment.[13] Virilization is very prominent in late-identified females with CAH due to the untreated condition (Figure 3). There is a good correlation between age and phallus length in late-identified CAH, indicating that older untreated CAH females are more virilized. Androgen exposure in these girls start from the prenatal period and persist until they receive treatment.[14] In our study, androgen excess in untreated females resulted to progressive virilization of the clitoris, hyperpigmentation, lack of breast development, primary amenorrhea, delayed menarche, premature pubic hair growth, hirsutism, low voice with or without prominent Adam's apple and short stature. These observations are comparable with findings in previous studies.[15,16]

In our study, thirty-three percent of patients were considered male because of the presence of male-looking genitalia (clitoromegaly resembling penis, scrotalization with or without complete labial fusion) and the absence of treatment (Figures 4 and 5). This emphasizes the need for a thorough urogenital examination in the neonatal period for patients with DSD. Chromosomal and hormonal analyses should be performed on neonates with ambiguous genitalia to facilitate gender assignment.[17]

Precocious puberty in female CAH patients are recognized by premature pubic hair growth occurring before 8 years of age and rapid growth.[18] In the same study, patients treated after age one year have a higher risk for precocious puberty; for SV type boys, this risk was apparent even in those who received treatment at the age of 6 months.[18] We found similar findings with Hargitai et al., our SV type children showed accelerated growth patterns after 3 years old, while the final height of adult patients leading to short stature was reduced compared to the standard population and their respective target heights.[19] Bone age determination may be able to show accelerated epiphyseal maturation. Unfortunately, these results were not available in all our CAH children, due to financial constraints and limited facilities.

In our study, all late-identified CAH patients had elevated blood levels of 17-OHP. The 17-OHP levels were weakly correlated with phallus length (r=0.19). However, there was no clear relationship between 17-OHP levels and virilization of external genitalia, similar to findings by Rocha et al. [20]

Genetic counseling for families and patients is advised to explain the clinical manifestations, mode of inheritance, recurrence risk and consequences of CAH. Some challenges to our work include varied cultural beliefs within families, patient discrimination and taboos pertaining to their masculinized condition, and the unavailability of a genetic counselor.[21] Gender assignment is still a dilemma: some of the children were raised as males, females or left undecided. Late-identified CAH females with progressive virilization should undergo psychological evaluation to assess their emotional condition and gender identity.

CONCLUSION

In our study, the most common clinical features in late-identified Indonesian CAH patients were clitoromegaly and skin hyperpigmentation. Clinical features such as genital virilization, low voice, Adam's apple and short stature in adults were permanent phenotypes, indicating the severity and irreversibility of virilization despite medication. There was no correlation between of 17-OHP levels and virilization. There is a general lack of awareness of medical personnel, family members and patients regarding CAH and its effects. The high cost and limited availability of laboratory tests and difficult access to medications pose significant challenges as well. Improvement in the clinical recognition of suspected CAH patients is important in our Indonesian clinical setting. Genetic counseling is crucial in the management of CAH, especially for gender determination. Newborn screening should be included in the improvement of health policy in Indonesia.

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Author Disclosure
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Reference entries #11, 13 and 17 were not cited in the text.

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ORIGINAL ARTICLE

Self-Reported Hypoglycemia in Insulin-Treated Patients with Diabetes: Results from the Philippine Cohort of the International Operations Hypoglycemia Assessment Tool (IO HAT) Study

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Abstract

Objective. To determine the frequency of hypoglycemia in insulin-treated patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) in the non-interventional International Operations Hypoglycemia Assessment Tool (IO HAT) study.

Methodology. This sub-analysis included Filipino patients with T1DM or T2DM, aged 18 years and older, treated with insulin for more than 12 months, who completed the two-part self-assessment questionnaires (SAQ1 and SAQ2) and patient diaries that recorded hypoglycemia during retrospective (6 months/4 weeks before baseline) and prospective period (4 weeks after baseline) (ClinicalTrials.gov number: NCT02306681).

Results. A total of 671 patients were enrolled and completed the SAQ1 (62 patients with T1DM and 609 patients with T2DM). Almost all patients (100% in T1DM and 99.3% in T2DM) experienced at least 1 hypoglycemic event prospectively. The incidence of any hypoglycemia was also high in the prospective period compared to retrospective period (72.6 [95% CI: 64.8, 80.9] events PPY and 43.6 [95% CI: 37.8, 49.9] events PPY; p=0.001, respectively) in T1DM patients.

Conclusion. Among insulin-treated patients, higher rates of hypoglycemia were reported prospectively than retrospectively. This indicates that the patients in real-life setting often under-report hypoglycemia. Patient education can help in accurate reporting and appropriate management of hypoglycemia and diabetes.

Key words: International Operations Hypoglycemia Assessment Tool, insulin-treated patients with diabetes, hypoglycemia, Philippines

INTRODUCTION

The prevalence of diabetes mellitus (DM) is increasing rapidly all over the world. Asian countries account for more than 60% of the world's diabetic population.[1] The prevalence estimate published by the International Diabetes Federation reported that there were 3.5 million cases of DM in the Philippines in 2015 with a prevalence of 6.1% in adults.[2] A study conducted in six national regions of the Philippines showed that the 9-year incidence and prevalence of type 2 diabetes mellitus (T2DM) were quite high (16.3% and 28.0%, respectively).[3] Currently, there is no nationwide published data on the prevalence and incidence of type 1 diabetes mellitus (T1DM) in the Philippines.[4] International Diabetes Federation data on diabetes in young patients projected an increase in the incidence of T1DM in the coming years, with Southeast Asian countries expected to contribute the largest (24%) to the young diabetic population.[5,6]

Insulin therapy is the most common treatment option for patients with T1DM, and also in patients with T2DM, especially in cases where oral anti-diabetes therapies fail.[7] Hypoglycemia is an important complication of insulin therapy. The fear of hypoglycemia often prevents or delays the decision of patients and healthcare providers to prescribe insulin, thus adding to the burden of poor DM control.[8] Philippine practice guidelines for diabetes management also encourage patients to self-monitor blood glucose (SMBG) when they are on insulin therapy or have risks of hypoglycemia.[7] Hypoglycemia tends to increase with increased duration of insulin usage in patients, as

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was reported in the UK Hypoglycemia Study Group. A high prevalence of severe hypoglycemia (25%) was seen in patients with T2DM who were on insulin for more than 5 years.[9] Hypoglycemia impacts daily activity and productivity in patients with T1DM and T2DM. It also increases fear and anxiety in patients with DM and consequently healthcare costs.[10]

The seemingly high prevalence of DM in the Philippines and the impact of hypoglycemia on the socio-economic growth of the country necessitate detailed evaluation of hypoglycemia in the Philippine population so that steps can be taken for better management of hypoglycemia. However, no such studies (observational or clinical) has been conducted so far in the Philippines which will provide an estimate regarding incidence of hypoglycemia or its impact on daily activities and healthcare utilization. This is the first study that provides patient-reported hypoglycemic rates in Filipino patients with DM using a questionnaire data set.

The Global Hypoglycemia Assessment Tool (HAT) study collected data from insulin-treated patients with DM in 24 countries, and showed that rates of hypoglycemia were higher than had been reported previously.[11] The non-interventional International Operations HAT (IO HAT) study assessed incidence of hypoglycemia in insulin-treated patients with DM in Bangladesh, Colombia, Egypt, Indonesia, Philippines, Singapore, South Africa, Turkey and the United Arab Emirates.[12] The IO HAT study was built on the information gathered from the Global HAT study. Here we report the results of the Philippine cohort of IO HAT.

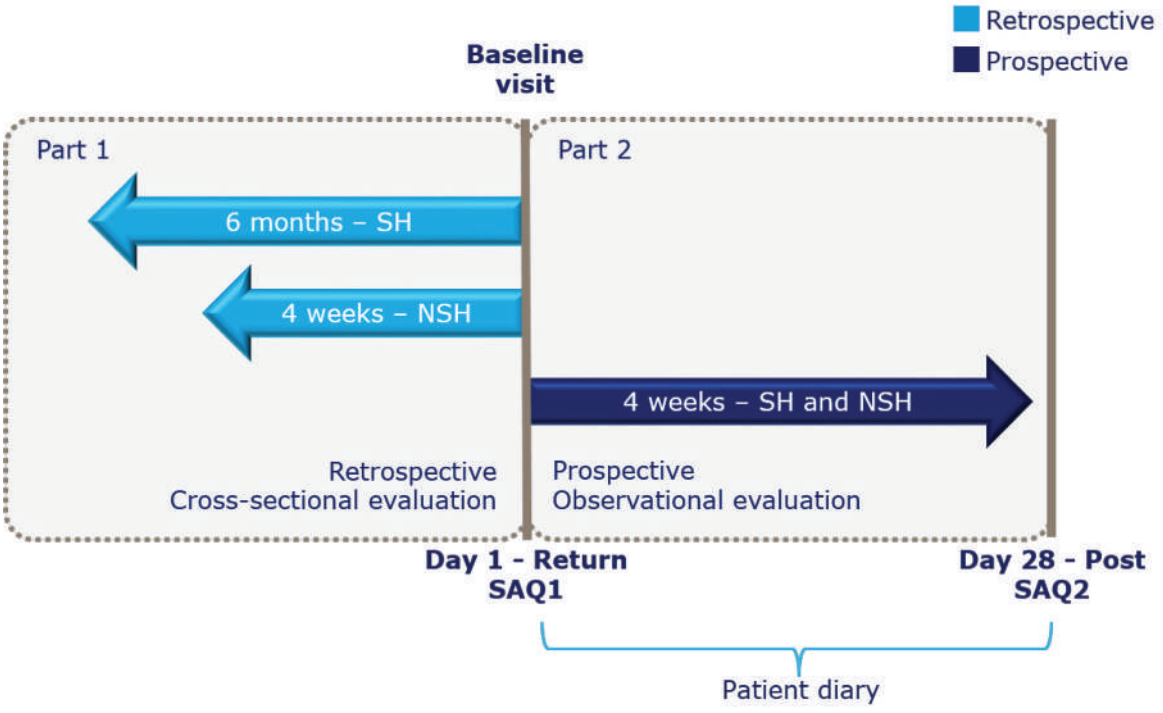
METHODOLOGY

Study design

The IO HAT study design is described in Figure 1. This is a cohort study that involved both a retrospective cross-sectional and prospective observational evaluation. In this cohort, hypoglycemia data were collected from patients recruited at 39 sites in the Philippines from 21 endocrinologists and 18 diabetes specialists between 01 Jan 2015 and 14 May 2015. This study was conducted in accordance with Good Pharmacoepidemiology Practices, Declaration of Helsinki, and Ethical Principles for Medical Research Involving Human Patients.[13,14]

Patients

Ambulatory and literate Filipino male or female patients with T1DM and T2DM, aged 18 years or older, treated with insulin for more than 12 months, and who had signed informed consent were included in this study. Participating patients were enrolled consecutively as a result of attendance to a routine clinic appointment. Participation in the study was dependent on having a sufficient duration of insulin use, but was not dependent on the use of any specific medicinal product. The investigators were primarily endocrinologists and diabetologists; however, a few internal medicine physicians (internists) also participated.



*NSH, non-severe hypoglycemia; SAQ, self-assessment questionnaire; SH, severe hypoglycemia

Figure 1. IO HAT study design. This study involved both retrospective cross-sectional and prospective observational evaluation, assessed using two-part self-assessment questionnaires (SAQ1 and SAQ2) and patient diary's that recorded hypoglycemia during retrospective (6 months/4 weeks before baseline) and prospective period (4 weeks after baseline).[12]

Study assessments

Endpoints:

This study comprised of a two-part self-assessment questionnaire (SAQ) including a retrospective cross-sectional evaluation (SAQ1) and a prospective observational evaluation (SAQ2). SAQ1 (includes 34 questions) assessed baseline demographic and treatment information, hypoglycemia unawareness and perceptions of hypoglycemia, history of severe hypoglycemia for 6 months before the baseline visit, and "any" and "nocturnal" hypoglycemia for 4 weeks before the baseline visit. SAQ2 (includes 6 questions) assessed severe and symptomatic hypoglycemia and its effect on productivity and healthcare utilization for 4 weeks from the baseline visit. Patients answered these questions using a 6-point Likert scale, with responses corresponding to agreement with each item statement ranging from ''very strongly agree" (score = 5) to ''do not agree at all" (score = 0). The validated questionnaires were translated into Filipino language with reference to WHO approved international guidelines for translation and cultural adaptation of questionnaires.

The primary endpoint of the study was the percentage of patients who experienced at least one hypoglycemic episode during the 4-week prospective period. Secondary endpoints included, difference in incidence rates of any, nocturnal, and severe hypoglycemia between two periods of observation (i.e., retrospective and prospective); relationship between diabetes treatment; glycated hemoglobin (HbA_{1c}) at baseline (HbA_{1c} <7.0%, 7.0% to 9.0%, and >9.0%); and hypoglycemic events. The patients' knowledge of hypoglycemia, hypoglycemia unawareness, fear of hypoglycemia, patients' action resulting from hypoglycemia, and its impact on work/study and health system resources were also assessed.

Hypoglycemia awareness was assessed and categorized in to the following: 'normal,''impaired,' and 'severely impaired' based on patients' responses to the question. Fear of hypoglycemia was assessed on visual analogue scale (0 to 10), where '0' denotes 'not afraid at all' and '10' denotes 'absolutely terrified,'

Hypoglycemia definition

The following definitions of hypoglycemia were employed in this study to capture the different types of hypoglycemia in SAQ and patient diary (PD):

- Severe hypoglycemia: An event requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions (as per ADA definition of severe hypoglycemia).[15]
- Nocturnal hypoglycemia: A hypoglycemic event occurring between midnight and 06:00 hours.
- Any hypoglycemia: Aggregate of all hypoglycemic events of any category, calculated based on questionnaire and PD entries.

Statistical analysis

All statistical tests were two-sided, with the criterion for statistical significance set at $p < 0.05$. No adjustment were made for multiple comparisons. For the primary endpoint, the percentage of patients who experienced at least one hypoglycemic episode during the 4-week prospective observational period was calculated together with 95% confidence interval (CI) for this percentage. For secondary endpoints, the incidence of various types of hypoglycemia was calculated as number of episodes per patient year (events PPY) (together with the 95% CI), expressed by the formula: Incidence rate (IR) = total number of events divided by total follow-up time (patient-years). Incidence rate ratio, 95% CI for incidence rate ratio, and *p*-value for incidence rate ratio were calculated using a negative binomial regression model including a single binary covariate for period (4 weeks before baseline, 4 weeks after baseline), specifying a log transformed exposure time offset term and using robust standard errors to adjust for repeated measurements on individuals. The scatter plot with regression line and 95% CI was utilized to study the relationship between HbA_{1c} at baseline and log-transformed number of events for patients experiencing hypoglycemia in the retrospective and prospective periods. Given that the majority of analyses were descriptive in nature, no imputation of missing data was performed. Baseline refers to data collected using SAQ1; follow-up refers to data collected using SAQ2 and, where applicable, PD.

RESULTS

Patient characteristics

A total of 671 patients (T1DM: 62; T2DM: 609) were enrolled from study sites in the Philippines and completed SAQ1. A total of 637 patients (T1DM: 57; T2DM: 580) completed SAQ2. Table 1 describes the baseline demographic details of Filipino cohort. The duration of diabetes in T1DM and T2DM patients was 12.3 years and 12.9 years, respectively, whereas, the mean HbA_{1c} levels in both the groups were 8.6% and 8.4%, respectively. The mean BMI was high in T2DM patients (26.8 kg/m^2) when compared to T1DM patients (21.9 kg/m^2). At baseline, in patients with T1DM and T2DM, the most common insulin treatment was pre-mixed insulin (45.2% and 40.2%, respectively) (Table 1). In this cohort, analogue insulin was used by 76.1% of patients and human insulin was used by 23.9% of patients.

Incidence of hypoglycemia by diabetes type and insulin regimen

It was observed that the rates of 'any' and 'severe' hypoglycemia were lower in the retrospective period than in the prospective period. However, the rates of nocturnal hypoglycemia were mostly comparable in these two periods.

Table 1. Distribution of participants according to sociodemographic and clinical characteristics at baseline

Characteristics	T1DM (N=62)	T2DM (N=609)
Age, years[a]	28.4 (9.2)	60.4 (11.8)
Male/ female (%)	33.9/ 66.1	30.9/ 68.0
Duration of diabetes, years[a]	12.3 (8.0)	12.9 (7.9)
Duration of insulin use, years[a]	12.3 (8.0)	5.7 (4.9)
BMI (kg/mg^2)[a]	21.9 (3.5)	26.8 (5.8)
HbA_{1c}, %[a]	8.6% (1.9)	8.4% (1.8)
FBG (mmol/L)[a]	9.2 (5.6)	8.3 (3.2)
PPG (mmol/L)[a]	9.9 (4.7)	10.5 (4.0)
Previous medical illnesses, n (%)[b]		
Myocardial infarction	0	41 (6.7)
Angina	2 (3.2)	78 (12.8)
Cerebrovascular accident	0	43 (7.1)
Transient ischemic attack	0	39 (6.4)
Angioplasty	0	15 (2.5)
Coronary artery bypass graft	1 (1.6)	12 (2.0)
Peripheral vascular disease	13 (21.0)	188 (30.9)
Nephropathy	4 (6.5)	123 (20.2)
Retinopathy	19 (30.6)	251 (41.2)
Neuropathy	21 (33.9)	362 (59.4)
None	30 (48.4)	165 (27.1)
Oral antidiabetic medications, n (%)[b]		
Metformin	4 (6.5)	305 (50.1)
Dipeptidyl Peptidase-IV	1 (1.6)	272 (44.7)
Glucagon-Like Peptide-1	0	8 (1.3)
SGLT2 Inhibitors	0	46 (7.6)
Sulphonylurea	0	69 (11.3)
Thiazoledinediones/Glitazones	0	57 (9.4)
Other	2 (3.2)	16 (2.6)
No oral medication	56 (90.3)	144 (23.6)
Insulin treatment, n (%)[b]		
Short-acting alone	1 (1.6)	10 (1.6)
Long-acting alone	7 (11.3)	195 (32.0)
Pre-mix	28 (45.2)	245 (40.2)
Both short and long acting	24 (38.7)	136 (22.3)
Both short acting and pre-mix	1 (1.6)	9 (1.5)
Both long acting and pre-mix	0	13 (2.1)
Short and long acting and pre-mix	1 (1.6)	1 (0.2)
Symptoms of hypoglycemia, n (%)[b,c]		
Any	61 (98.4)	524 (86.0)
Hunger	56 (90.3)	458 (75.2)
Weakness	56 (90.3)	411 (67.5)
Sweating	59 (95.2)	397 (65.2)
Tremor	53 (85.5)	351 (57.6)
Tiredness	50 (80.6)	353 (58.0)

[a] Data are mean (SD) unless otherwise stated; [b] Percentages based on number of patients with evaluable data; [c] Only top 5 symptoms are presented here in the table; N, total number of patients participating; n, number of patients in each category; BMI, body mass index; FBG, fasting blood glucose; HbA_{1c}, glycated hemoglobin A_{1c}; PPG, postprandial glucose; SGLT2, Sodium-glucose co-transporter 2; SD, standard deviation; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Any hypoglycemia

In patients with T1DM, all patients (100% [95% CI: 93.7%, 100.0%]) experienced at least 1 hypoglycemic event prospectively (4 weeks after baseline) (Figure 2a). The incidence rate of any hypoglycemia was significantly higher in prospective period as compared to retrospective period (72.6 [95% CI: 64.8, 80.9] events PPY vs. 43.6 [95% CI: 37.8, 49.9] events PPY; p=0.001, respectively). The incidence rate for combination of short- and long-acting insulin regimen was 76.5 events PPY and for pre-mixed regimen was 76.2 events PPY in the prospective period.

Similarly, patients with T2DM reported significantly higher incidence rates of any hypoglycemia prospectively than retrospectively (32.0 [95% CI: 30.4, 33.7] events PPY vs. 16.9 [95% CI: 15.7, 18.1] events PPY; p<0.001), with almost all (99.3% [95% CI: 98.2%, 99.8%]) patients reporting hypoglycemia in the prospective period (Figure 2b). The incidence rate for pre-mixed insulin regimen was 37.7 events PPY in the prospective period and 21.6 events PPY in the retrospective period (Figure 3a).

Nocturnal hypoglycemia

In patients with T1DM, there was no significant difference in the incidence rates between the retrospective and prospective periods (15.4 [95% CI: 12.0, 19.3] events PPY vs. 15.6 [95% CI: 12.1, 19.7] events PPY, respectively; p=0.960) (Figure 2a). The incidence rate for long-acting insulin was 22.4 events PPY in the prospective period followed by pre-mixed insulin regimen (21.0 events PPY and 19.3 events PPY) in the retrospective and prospective periods, respectively.

In T2DM patients, the incidence rates were not significantly differing from retrospective (6.2 [95% CI: 5.5, 6.9] events PPY) and prospective (4.7 [95% CI: 4.1, 5.4] events PPY, p=0.361) periods (Figure 2b). Overall, the incidence rate of nocturnal hypoglycemia was quite low in patients with T2DM for all insulin regimens (Figure 3b).

Severe hypoglycemia

In patients with T1DM, there was no significant difference in the incidence rates of severe hypoglycemia in

retrospective (16.3 [95% CI: 12.7, 20.5] events PPY) and prospective (4.8 [95% CI: 4.0, 5.6] events PPY, p=0.143) period (Figure 2a). In contrast to the observations seen for any and nocturnal hypoglycemia, the incidence rate of severe hypoglycemia was 26.1 events PPY for short-acting insulin regimen prospectively.

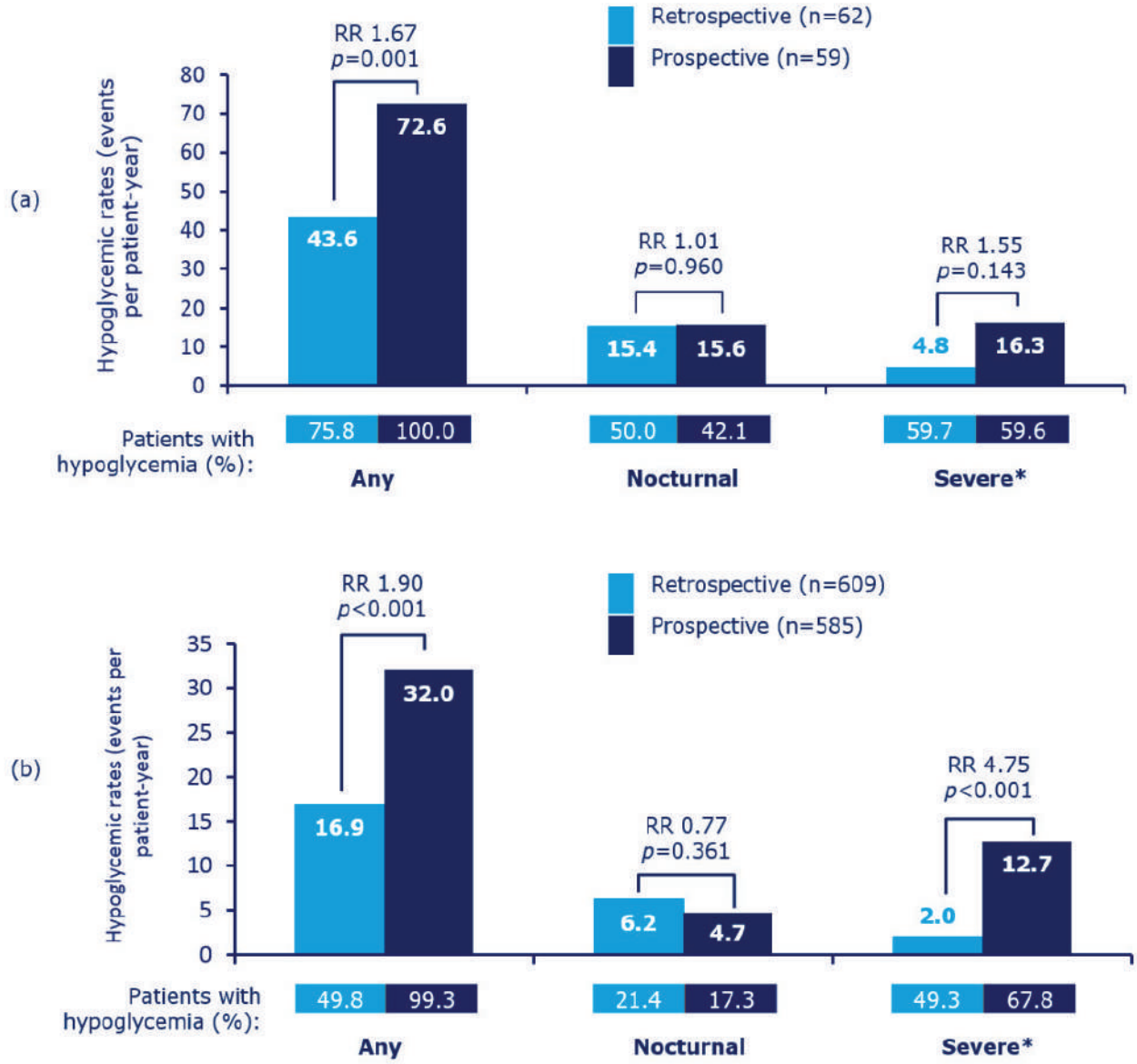
Patients with T2DM reported significantly higher rates of severe hypoglycemia prospectively than retrospectively (12.7 [95% CI: 11.7, 13.8] events PPY vs. 1.9 [95% CI: 1.8, 2.1] events PPY, respectively; p<0.001) (Figure 2b). The T2DM patients with all insulin regimens reported incidence rates of 0.9 events PPY to 2.5 events PPY and 11.6 events PPY to 14.1 events PPY with severe hypoglycemia in the retrospective and prospective periods, respectively (Figure 3c).

Relationship between HbA_{1c} at baseline and hypoglycemia rates

No notable relationship was observed between baseline HbA_{1c} (whether treated categorically or as continuous data) and the percentages of patients with hypoglycemia, in T1DM (r^2 = 0.0198) and T2DM (r^2 = 0.0023).

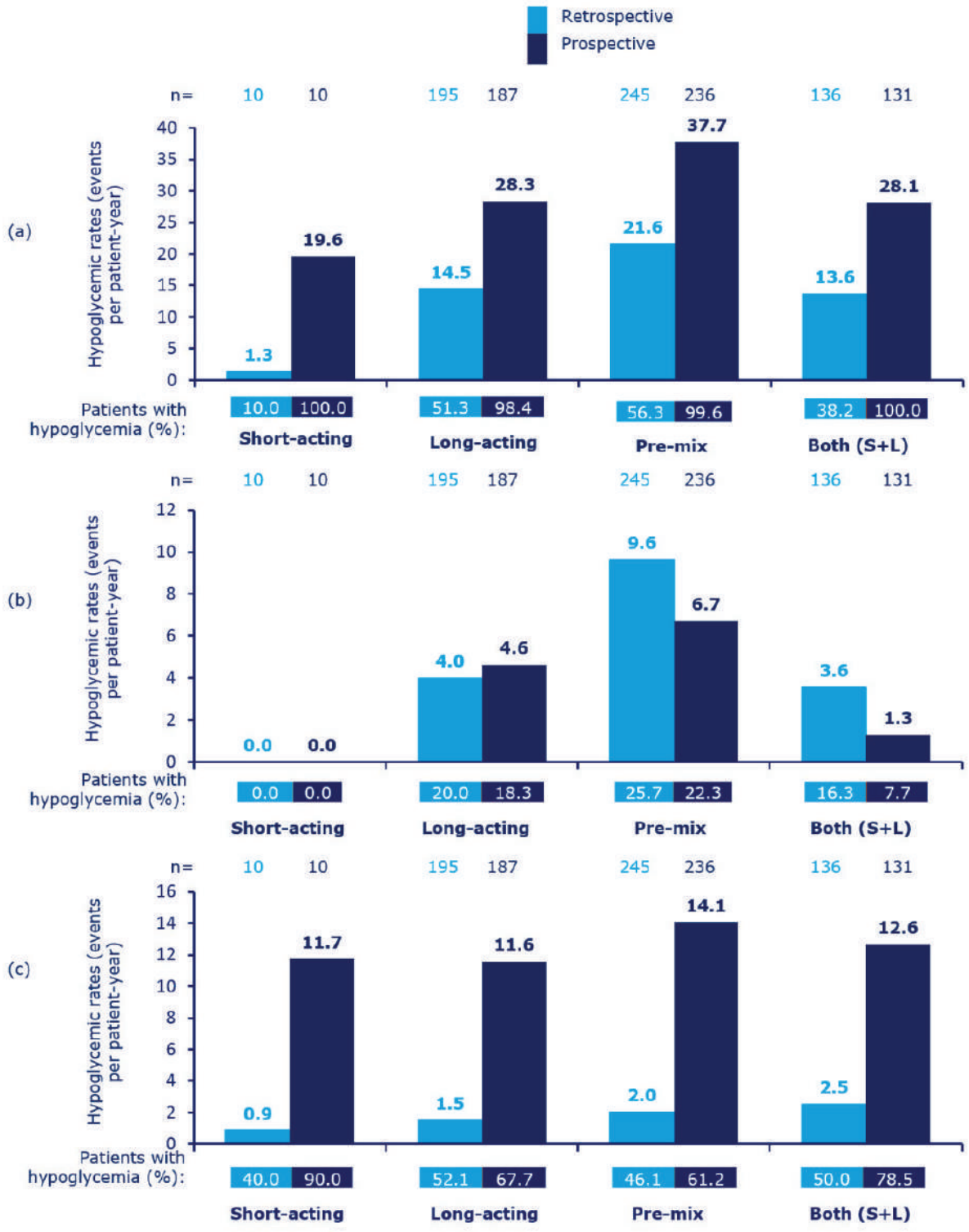
Patients' perspectives on hypoglycemia

Patients' perspectives, including patient knowledge, hypoglycemia awareness, fear of hypoglycemia, response to hypoglycemia, and impact of hypoglycemia on the medical system, are described in Table 2 and Table 3.



*RR, rate ratio; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Figure 2. Estimated rate of retrospective and prospective hypoglycemia in (a) patients with T1DM and (b) patients with T2DM. Data based on 4-week period for both retrospective and prospective analyses for any or nocturnal hypoglycemia. Retrospective data based on 6-month period and prospective data based on 4-week period for severe hypoglycemia.

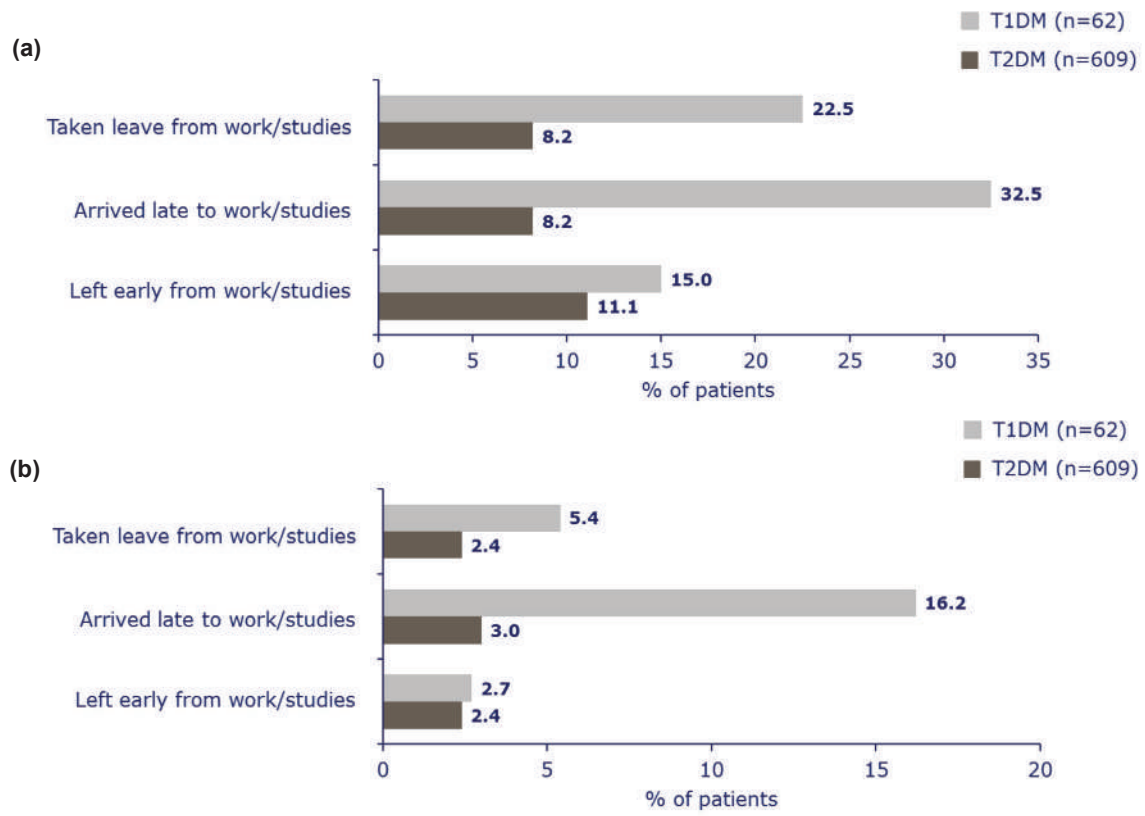


*n, total number of patients; S+L, short-acting and long-acting insulin; T2DM, type 2 diabetes mellitus

Figure 3. Hypoglycemia incidence and event rate in patients with T2DM by insulin regimen: (a) any hypoglycemia, (b) nocturnal hypoglycemia, (c) severe hypoglycemia. Data based on 4-week period for both retrospective and prospective analyses for any or nocturnal hypoglycemia. Retrospective data based on 6-month period and prospective data based on 4-week period for severe hypoglycemia.

Impact of hypoglycemic events on work and study

Prior to baseline, 40 out of 62 patients with T1DM and 171 out of 609 patients with T2DM were studying or in full- or part-time employment. A greater percentage of patients with T1DM compared to T2DM experienced hypoglycemic events that resulted in absence from work or studies (22.5% vs. 8.2%, respectively), late arrival to work or study (32.5% vs. 8.2%, respectively), or early departure from work or study (15.0% vs. 11.1%, respectively) in the retrospective period. Figure 4, represents the impact of hypoglycemic events on work and studies in retrospective and prospective period.



*T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

Figure 4. Impact of hypoglycemic events on work and study in (a) retrospective and (b) prospective periods. 'n' values represent the number of patients studying or in full or part-time employment and completed Part 1 SAQ. Bars represent proportion of subjects responding 'Yes'.

Table 2. Patient perspectives on hypoglycemia

	T1DM (N=62)	T2DM (N=609)
Knew what hypoglycemia was before reading definition provided in SAQ1 (%)	98.4	88.4
Defined hypoglycemia on basis of (%)		
Symptoms only	59.7	40.4
Blood glucose measurements only	3.2	7.9
Either	8.1	10.2
Both	22.6	20.9
Hypoglycemia awareness (%)		
Normal	54.8	25.1
Impaired	41.9	57.6
Severely impaired	1.6	12.5
Fear of hypoglycemia (scale of 0 to 10) mean score (SD)	5.2 (3.3)	4.3 (3.2)

Hypoglycemia awareness was evaluated through the self-assessment question: 'Do you have symptoms when you have a low sugar level?' where the response, 'usually' denoted impaired awareness, and 'occasionally' or 'never' denoted severely impaired awareness (unawareness); N, total number of patients; SAQ, self-assessment questionnaire; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; SD, standard deviation. Percentages are more than 100% because a single patient could have done more than 1 action resulting from hypoglycemia.

Table 3. Patient actions resulting from hypoglycemia

	T1DM		T2DM	
Actions (%)	Retrospective (n=62)	Prospective (n=57)	Retrospective (n=609)	Prospective (n=580)
Consulted their doctor/nurse	58.1	24.6	36.5	17.4
Required any form of medical assistance	61.3	26.3	37.8	17.8
Increased calorie intake	43.5	40.4	29.1	18.6
Avoided physical exercise	11.3	8.8	8.5	3.3
Reduced insulin dose	37.1	26.3	17.7	10.0
Skipped insulin injections	12.9	7.0	11.8	7.2
Increased blood glucose monitoring	29.0	15.8	26.4	15.5
Impact of hypoglycemic events on the medical system (%)	Retrospective (n=61)	Prospective (n=57)	Retrospective (n=525)	Prospective (n=578)
Required hospital admission	13.1	1.8	5.9	1.0
Attended additional clinical appointments	18.0	3.5	5.7	2.4
Made additional telephone contacts	9.8	5.3	6.9	4.8

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; n, number of patients

DISCUSSION

This study is a sub-analysis of the Philippine cohort of a multicenter, international, 6-month retrospective and 4-week prospective study with a two-part SAQ that investigated the incidence of hypoglycemia and its impact on daily activities and healthcare resources in insulin-treated adults with T1DM or T2DM. Consistent with the overall IO HAT study results, higher incidence rate of hypoglycemia was reported prospectively when compared with retrospectively, with almost all patients reporting at least one hypoglycemic event during the prospective period (T1DM: 100%; T2DM: 99.3%).[12] This could be due to the use of PD's in prospective period which assisted recall. In contrast, the retrospective data were only collected by SAQs and were, therefore, prone to recall bias. Contrary to the overall hypoglycemic data, the proportion of patients reporting nocturnal hypoglycemia was statistically equal in both retrospective and prospective periods.

The incidence rate of severe hypoglycemia was also higher during the prospective period than during the retrospective period in patients with T2DM. The recall bias for the retrospective period could be more pronounced for severe hypoglycemia since the period of recall was greater than that of any hypoglycemia (6 months vs. 4 weeks, respectively). Overall, high incidence of any or severe hypoglycemia in the prospective period could be due to combined use of PD and SAQs in this period, which act as a means for patient education, increase in knowledge and awareness of hypoglycemia. This point highlights the significance of patient education, as increased awareness will ensure better reporting of hypoglycemia and, in turn, management of DM by the healthcare providers.

The results also indicate that hypoglycemia is often under-reported by patients retrospectively, and therefore, may have been underestimated in previous studies.

Overall, the incidence of any hypoglycemia in this cohort was quite high in both the groups from retrospective period to prospective period, similar to observations seen in Global HAT study.[11] In an observation study conducted by Donnelly et al., patients with T1DM and T2DM also reported high incidence rates of overall hypoglycemia (42.89 events PPY and 16.37 events PPY, respectively); however, incidence rates of severe hypoglycemia were low (1.15 events PPY and 0.35 events PPY, respectively).[16] Data from the European cohort of PREDICTIVE study reported that overall hypoglycemic events 4 weeks before baseline were 47.5 events PPY for patients with T1DM and 9.2 events PPY for patients with T2DM.[17] The incidence rates of severe hypoglycemia in ACCORD, ADVANCE, and VADT trials with intensive treatment were quite low in comparison to what was observed in our study (0.6 to 12.0 events 100 patients/year).[18-20] As observed with Global HAT study and Canadian HAT program, the incidence rates of hypoglycemia were higher in patients with T1DM in comparison to T2DM in this cohort.[11,21] High incidence of severe hypoglycemia in patients with T2DM could be due to patient understanding of ADA definition of severe hypoglycemia, which means that patients could have misunderstood the events as severe only on the basis of assistance received rather than based on severity of symptoms.

Similar to the results from DiabCare study, majority of patients in this study were on pre-mixed insulin at baseline (T1DM: 45.2%; T2DM: 40.2%).[22] However, no statistical testing was done for insulin regimens and also for T1DM vs T2DM patients. The higher incidence rates of any hypoglycemia were reported with pre-mixed insulin in this study. This highlights the need for creating physician awareness in the region and need to shift to insulins with lower associated rates of hypoglycemia such as those based on modern insulin analogues or using insulin-pumps in conjunction with continuous glucose monitoring devices in patients with T1DM.[23-25] The results from the A1cheive sub-analysis showed that use of basal insulin analogue such as insulin detemir was associated with better glycemic control and lower incidence of hypoglycemia in patients with T2DM in the Philippines.[26]

Based on previous evidence like that from DCCT trial, it is believed that the risk of hypoglycemia was inversely associated with HbA_{1c} levels.[27] However, similar to the results from overall IO HAT study, the results from this cohort also did not report any significant relationship between HbA_{1c} levels at baseline and hypoglycemia rates. Hence, it is important for the healthcare provider to proactively screen patients for hypoglycemia regardless of their HbA_{1c} values.

Hypoglycemic events remarkably impact daily activities and productivity, and add to healthcare burden with increased utilization of resources.[11-13] Results from this study showed that the impact on productivity and medical system was greater in patients in the retrospective period compared to the prospective period, suggesting that increased awareness in prospective period may have played a role in improving the quality of life of the patients.

The results also showed that patient knowledge of hypoglycemia was high at baseline in both groups, but majority of patients with T2DM had impaired hypoglycemia awareness (57.6%). As expected, the majority of patients with impaired hypoglycemia awareness are less likely to report incidence of hypoglycemia. Another important observation was that almost all the patients in both the groups who were using blood glucose measurements to report hypoglycemia provided values consistent with standard definition. This reiterates the fact that SMBG should be encouraged in insulin-treated patients and in those at high risk of hypoglycemia. Recall bias observed during retrospective period is one of the limitations of the study, preventing

direct comparison of the data in the prospective and retrospective periods. Patient diaries used in the prospective period assist in patient recall and may also lead to over estimation of hypoglycemia rates. The findings from this study highlight that increased patient knowledge of hypoglycemia, proper tailoring of insulin or choice of insulin, and access to home glucose-monitoring equipment are important considerations that may help reduce the incidence of hypoglycemia.

CONCLUSION

Consistent with the overall IO HAT study results, higher rates of hypoglycemia were reported prospectively as compared to retrospectively. Hypoglycemic events remarkably affected daily activities, productivity, and medical system utilization and that the high incidence of hypoglycemia seen prospectively may be due to patient education. Results from this study can be used as a tool to educate patients and physicians regarding the importance of hypoglycemia recognition and management.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
Novo Nordisk was involved in the study design; collection, analysis and interpretation of data; and decision to submit the article for publication. Authors, Drs. Anand Jain and Arvind Vilas Gadekar are employees of Novo Nordisk. Dr. Roberto Mirasol is a member of the advisory board of Novo Nordisk, Eli Lilly, AstraZeneca, and Merck. Dr. Nemencio Nicodemus, Jr. is a member of the local advisory board of the following companies: Novo Nordisk, AstraZeneca, Merck, Torrent and has received speaker honoraria from Novo Nordisk, AstraZeneca, Merck, Torrent, Eli Lilly, Sanofi, LRI-Therapharma, and Servier. Dr. Susan Yu-Gan has received speaker's fee from Novo Nordisk and she has taken part in advisory boards for Novo Nordisk Philippines.

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ORIGINAL ARTICLE

The Effect of Individualised Glycemic Intervention on Wound Healing Rate in Diabetic Foot Ulcer (The EIGIFU Study)*

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Abstract

Objective. To evaluate the association of glycated haemoglobin (HbA_{1c}) reduction and wound healing in patients with diabetic foot ulcer (DFU).

Methodology. A 12-week prospective, non-controlled, interventional study in suboptimal-controlled T2DM patients with DFU was conducted. Antidiabetic medications were adjusted with the aim of at least 1% in relation to patient's individualised HbA_{1c} target. The wound area was determined by using specific wound tracing. The daily wound area healing rate in cm^2 per day was calculated as the difference between wound area at first visit and the subsequent visit divided by the number of days between the two visits.

Results. 19 patients were included in the study. There was a significant HbA_{1c} reduction from 10.33 %$\pm$1.83% to 6.89%$\pm$1.4% (p<0.001) with no severe hypoglycaemia. The median daily wound area healing rate was 0.234 (0.025,0.453) cm^2/day. There was a strong positive correlation between these two variables (r=0.752, p=0.01). After dividing the patients into four quartiles based on final HbA_{1c} and comparing the first quartile vs fourth quartile, there was a significant difference in daily wound area healing rates (0.597 vs 0.044 cm^2/day, p=0.012).

Conclusion. There was a positive correlation between HbA_{1c} reduction and wound healing rate in patients with DFU. Although this is an association study, the study postulated the benefits of achieving lower HbA_{1c} on wound healing rate in DFU which require evidence from future randomised controlled studies.

Key words: diabetic foot ulcer, individualised glycemic intervention, wound healing

INTRODUCTION

Diabetic Foot Ulcer (DFU) is a common complication of Diabetes Mellitus (DM) that has increased dramatically over previous decades.[1,2] The lifetime risk of a foot ulcer in patients with diabetes (type 1 or 2) may be as high as 25%.[3] DFU is one of the major causes of morbidity and mortality accounting for approximately two-thirds of all nontraumatic amputations performed in the United States.[3] In Malaysia, foot complications accounted for approximately 12% of all diabetic hospital admissions.[4] In Hospital Kuala Lumpur, which is the main public tertiary medical center in Malaysia, around 17% of diabetic patients were admitted because of diabetic foot ulcer (DFU).[5]

DFU is defined as a non- or poorly healing, partial or full thickness wound, located distal to the ankle in an individual with DM. The common sites involved are the sole of the foot or the toes.[6] Once DFU has developed, there is an increased risk of ulcer progression that may ultimately lead to amputation. Overall, the rate of lower limb amputation in patients with DM is 15 times higher than patients without diabetes.[7] Furthermore, DFU is responsible for substantial emotional and physical distress as well as productivity and financial losses that lower the quality of life.[8]

The primary management goal for DFU is to obtain wound closure as expeditiously as possible.[9,10] However, glucose control measured by glycated hemoglobin (HbA_{1c}) level is the most important metabolic factor.[11,12] HbA_{1c} level measures the average blood sugar concentration over a 90 day span of the average red blood cell in peripheral circulation. In the UKPDS, it was clearly shown that a 1% mean reduction in HbA_{1c} is associated with a 25% reduction in microvascular complications, including neuropathy.[13] Poor glucose control accelerated the manifestation of peripheral arterial disease (PAD) which is a primary cause of DFU.[13] Meta-analysis of nine trials enrolling 19,234 patients showed that compared with less

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intensive glycemic control, intensive control (HbA_{1c}, 6%-7.5%) was associated with a significant decrease in risk of amputation (relative risk [RR], 0.65; 95% confidence interval [CI], 0.45-0.94; I^2= 0%).[14]

One of the retrospective studies demonstrated that single blood glucose level >12.2 mmol/L on the first postoperative day was a sensitive (87.5%) predictor of postoperative infection.[15] Recently, a retrospective study showed that there was a significant association between HbA_{1c} variability and healing time in diabetic foot ulcers. Additionally, the study also highlighted that time to healing is more dependent on the mean HbA_{1c} than the variability in HbA_{1c} (p=0.007).[16]

However, to date, no prospective study has been performed to assess the effect of glycemic control to decrease HbA_{1c} levels has benefits in wound healing after a foot ulcer has developed.[17] This is a pilot study conducted with the main objective of evaluating the association of HbA_{1c} reduction and wound healing rate.

METHODOLOGY

Study design

A 12-week prospective, non-controlled, interventional study in subjects with suboptimally controlled T2DM patients with DFU was conducted from June to December 2016 at the Wound Unit, Hospital Putrajaya. The study was approved by the local institutional review board. Informed patient consent was obtained.

Study population

Majority of patients were referred by the Health Clinic from Wilayah Persekutuan Putrajaya, Malaysia to improve and optimise the risk factors for management of wound healing. The dedicated wound team consisted of 3 medical officers and 3 staff nurses. All wound treatments were performed for all patients with diabetic wounds according to the Standard Operation Procedure (SOP) of the wound clinic including removal of non-viable tissue, local dressing (antimicrobial dressings with silver), offloading with proper shoes and antibiotic treatment if infection was present. However, patients' glycaemia were not monitored at the wound clinic. Their glycaemic control and cardiovascular risk factors were managed by their respective doctors from the health clinic or specialists at the hospital.

Study patients

Eligible T2DM patients with DFU aged 20 to 75 years old who had baseline HbA_{1c} 1% higher than the target were recruited to the study. The target HbA_{1c} was determined at the first visit based on the patient's age, duration of DM, comorbid, diabetic complications, life expectancy and risks of hypoglycemia, according to Clinical Practice Guidelines – Management of Type 2 Diabetes Mellitus (5th edition).[18] Exclusion criteria were patients with acute and ongoing osteomyelitis or venous ulcer, patients with ankle brachial blood pressure ratio less than 0.5 suggesting severe limb ischemia, history (≥2 events) of hypoglycemic seizure or hypoglycemic coma within the last 6 months, patients with end stage renal disease, severe heart failure with New York Heart Association (NYHA) class IV, thromboembolic disease within the last 3 months, severe liver failure with Child–Pugh class C, history of schizophrenia, alcohol or drug abuse, and pregnant women. This study was approved by Malaysia Medical Research and Ethics Committee and was done in adherence to the Helsinki Guidelines. Written informed consent was taken during the first visit.

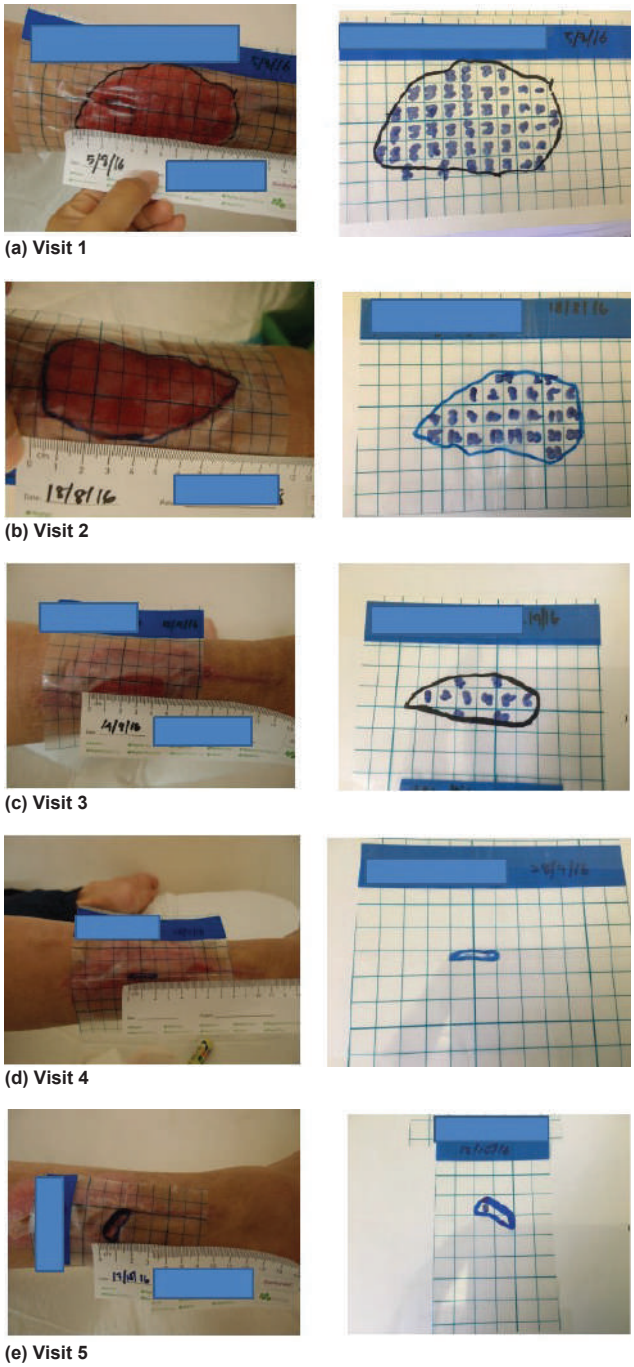
Study interventions

There were 5 visits during the study, i.e., week 0, week 2, week 4, week 8 and week 12. For each patient, demographic data, clinical data and laboratory biochemistry were collected including full blood count, renal function, liver function, HbA_{1c} and lipid profile. Biochemical investigation was obtained during the first clinic visit and week 12 of the clinic visit. Renal function was evaluated by estimated glomerular filtration rate (eGFR) using Modification of Diet in Renal Disease formula. Detailed history and physical examination were performed.

Complication assessments including microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (ischemic heart disease, stroke and peripheral vascular disease) were documented. During visits to the Wound Unit, blood pressure, pulse, and temperature were measured with the individual in a sitting position using standard clinical procedure. Associated cardiovascular risk factors including smoking, hypertension, dyslipidaemia as well as their treatment were ascertained.

Wound assessment

Detailed wound assessment was performed. Wound ulcer severity was graded by Wagner's grading system from grade 1 to 5. Any presence of foot deformity, high plantar pressure, infections, inappropriate foot self- care, trauma, fracture, callus and amputation were documented. Serial wound areas, as determined by specific wound tracing grid at each visit, were indicative of the wound healing[19] (Figure 1). Initially, the wound tracing grid was put over the wound and area was traced on the grid. The superficial layer was peeled off and placed on a piece of paper. Subsequently, the wound area would be calculated using grid in cm^2. The daily wound area healing rate in cm^2 per day was calculated as the difference between wound area at the first visit and the subsequent visits, divided by the number of days between the two visits. In order to avoid measurement bias, an accurate measurement



(a) Visit 1

(b) Visit 2

(c) Visit 3

(d) Visit 4

(e) Visit 5

Figures 1(a-e). Measurement of wound area via wound area tracing at visits 1 to 5.

of the wound size was made by the same clinician by wound tracing and validated by a third independent clinician.

Individualised glycaemic intervention

The individualised glycaemic intervention was a continuous, integrated patient-centred care involving clinicians, staff nurses, nutritionists and diabetic educators. The areas emphasized included Medical Nutrition Therapy, Exercise Therapy, Diabetic Complications, Drug Adherence, Usage of Antidiabetic agents including Insulin Therapy, Hypoglycaemia Management, Self-Monitoring Blood Sugar (SMBG) with diary record, weight control, stress management, etc. We utilised social media and electronic devices as main communication tools in educating the patients.

Antidiabetic medications including insulin therapy or oral antidiabetic agents (OADs) were adjusted or added with the aim of reducing HbA_{1c} by at least 1% in relation to patient's individualised HbA_{1c} target which was described above. Glucose meters and strips were given free to patients and SMBG with diary record was required at least 4 times per day (premeals and pre-bedtime) 3 times per week. Patients were encouraged to perform blood sugar checks whenever they were unwell or symptomatic for hypoglycemia. An ongoing insulin titration was performed actively in those patients whose glycaemia was not within the target range (including hypoglycemia) by the investigators or medical officers within the 12 weeks of their wound clinic visits. The titration of insulin was based on individualised titration protocol (based on Ministry of Health Clinical Practice Guidelines on Insulin Therapy).[18,20] Antihypertensive and lipid lowering therapies were allowed to be added or adjusted depending on investigator's discretion. The result of the glycemic intervention were expressed in absolute HbA_{1c} reduction and relative HbA_{1c} reduction rates calculated as the percentage of difference of first and final HbA_{1c} divided by first HbA_{1c}. Both were expressed in percentages (%).

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Science version 22.0 for Windows (SPSS Incorporation, Chicago, Illinois, USA). Descriptive analysis was used to explain demographic and clinical data. Numerical values for parametric and non-parametric variables were expressed as mean +/- standard deviation (SD) and median +/- Interquartile range (IQR). Categorical data were expressed as number and percentage. Spearman's correlation was used to measure the strength and direction of association between the HbA_{1c} reduction rate and the daily wound area healing rate. The patients were divided into 4 quartiles based on final HbA_{1c} and the daily wound area healing rate for the first and fourth quartiles were compared via Wilcoxon signed rank test. A p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

There were 25 patients screened and recruited. Four patients had screening failure, including three who failed to meet the HbA_{1c} criteria and two patients withdrew voluntarily from the study in the early period. Therefore, 19 patients (Table 1) completed the study. Their mean age and mean age of diagnosis of DM were 48.9$\pm$12.2 years and 37.1$\pm$9.5 years respectively. They were mainly males 15/19 (79%) and of Malay ethnicities 15/19 (79%). Their

mean duration of DM and median duration of DFU were 10.8±6.7 years and 3 (2,6.5) months respectively. Macrovascular complications were present in 3 (16%) patients with the following distribution: ischemic heart disease 1 (5%), cerebrovascular disease (stroke) 2 (11%) and peripheral vascular disease with 3 (16%). All 19 patients (100%) had microvascular complications specifically retinopathy and neuropathy, and 14 (79%) patients had nephropathy. Forty eight percent and 26% of patients had target HbA_{1c} of 6.5–7 % and 7-7.5% respectively.

Table 1. Patient demographic and clinical characteristics

Clinical Parameters	N (%) / Mean (SD)/Median (IQR)
Age (year)	48.9 (12.2)
Gender	
Male	15 (79%)
Female	4 (21%)
Ethnicity	
Malay	15 (78%)
Chinese	2 (11%)
Indian	2 (11%)
Age of Diagnosis (year)	37.1 (9.5)
Duration of Diabetes (year)	10.8 (6.7)
Duration of DFU (month)	3 (2,6.5)
Smoking history	
Active	1 (4%)
Previous/ Never	18 (96%)
Hypertension	13 (68%)
Dyslipidemia	18 (95%)
Overweight / obesity	15 (79%)
Body Mass Index (kg/m^2)	27.1(5.1)
sBP (mmHg)	128 (10)
dBP (mmHg)	80 (5)
Hb (g/dL)	11.6 (1.5)
WBC (X 10^9L)	10.8 (3.2)
Platelet (X 10^9L)	386 (121)
Albumin (g/dL)	32.5 (11.25)
ALT (mmol/L)	14.5 (12.3,22.5)
eGFR ($ml/min/1.73m^2$)	79 (23)

HbA_{1c}, glycated haemoglobin; sBP, systolic blood pressure; dBP, diastolic blood pressure; Heamogloblin; WBC, white blood cell; ALT, Alanine Aminotransferase; eGFR, estimated glomerular filtration rate

Antidiabetic agents

The patient's baseline antidiabetic medications were mainly insulin (n=18, 95 %) and Metformin (n=12, 63%). The 3 main additional antidiabetic agents were Metformin (n=6, 32%), Dipeptidyl peptidase-4 inhibitor (DPP4i) (n=4, 26%) and Sulphonylurea (n=2, 16%). During the first visit, 18 (95%) patients were on insulin therapy and 1 (5%) patient was on oral monotherapy. Among the patients on insulin, 11 (61%) were on combination of insulin therapy and one OAD. During the final visit, 2 (11%) patients were on two OADs and 17 (89%) patients were on insulin therapy. Among the patients on insulin, 12 (71%) were on combination with one OAD and 5 (29%) were on two OADs.

Wound characteristics

The median ankle-brachial pressure index for left lower limb and right lower limb was 1.07 (1,1.16) and 1.05 (0.95,1.13), respectively. Eighty four percent of patients had a single wound. Fifty three percent of patients had foot deformity or Charcot's joint and inappropriate foot care. Seventy four percent of patients had Grade 2 or 3 ulcers according to Wagner's classification of ulcer (Table 2).

Table 2. Wound characteristics

Wound numbers	
1	16 (84%)
2	2 (11%)
3	1 (5%)
Deformity / Charcot joint	10 (53%)
Inappropriate foot care	10 (53%)
Infection	6 (32%)
High plantar pressure	5 (27%)
Amputation	5 (27%)
Callus	2 (11%)
Ulcer severity (Wagner's classification)	
1	3 (16%)
2	6 (32%)
3	8 (42%)
4	2 (10%)
5	---

Glycemic intervention and wound area healing rate

Eighteen (95%) patients had HbA_{1c} reduction and 12 (63%) patients achieved the prespecified individualised target HbA_{1c}. The mean HbA_{1c} reduction rate was 31.2%±7.5% and the median daily wound area healing rate was 0.234 (0.025, 0.453) cm^2/day. There was a significant mean HbA_{1c} reduction from 10.33 %±1.83% to 6.89%±1.4% (p<0.001) and mean total daily insulin reduction from 70.4IU±19.6 IU to 41.6 IU±13.8IU (p<0.001). Spearman correlation analysis revealed that there was a strong positive correlation between the mean HbA_{1c} reduction rate and median daily wound area healing rate. (r=0.752, p=0.01) (Figure 2). After dividing the

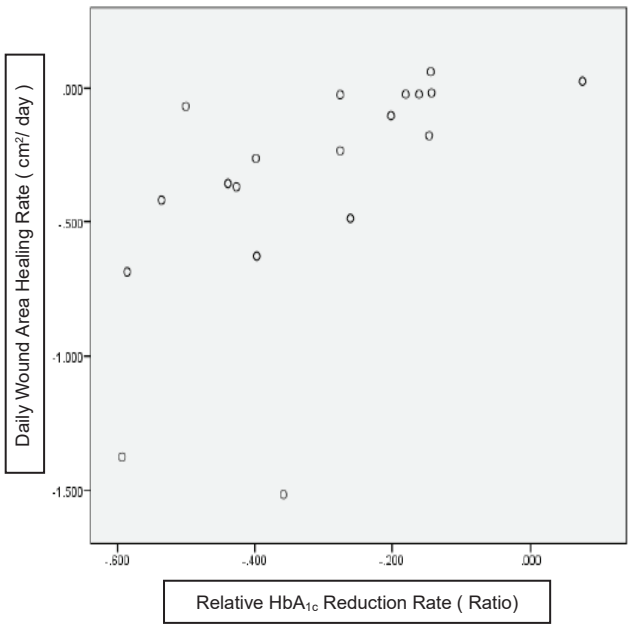


Figure 2. Correlation between the daily wound area healing rate and relative HbA_{1c} Reduction Rate. Spearman correlation analysis revealed that there was a strong positive correlation between the two variables. (r=0.752, p=0.01).

patients into four quartiles based on final HbA_{1c} and comparing the first quartile vs fourth quartile, there was a significant difference of daily wound area healing rate (0.597 vs 0.044 cm^2/day, p=0.012). (Figure 3)

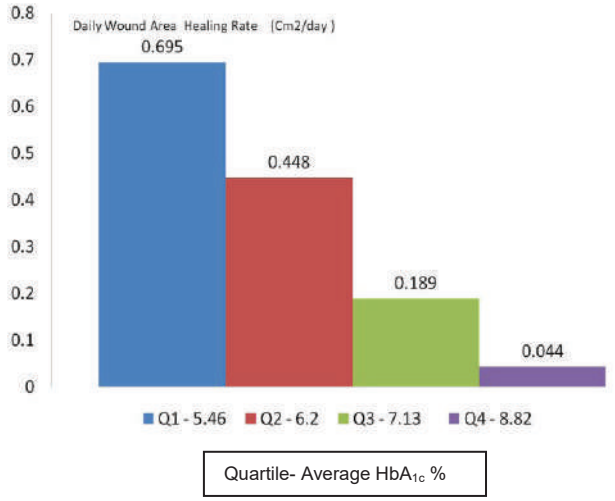


Figure 3. Daily wound area healing rate based on 1st - 4th quartiles of final HbA_{1c}.

DISCUSSION

There was a significant positive correlation between HbA_{1c} reduction rate and wound area healing rate. The lower the final HbA_{1c}, the faster the wound healed. The higher reduction of HbA_{1c} rate, the faster rate of wound healing compared to those who had lower HbA_{1c} reduction rate.

In this 12-week study, 95% and 63% of patients had HbA_{1c} reduction and achieved prespecified individualised target HbA_{1c} respectively. The mean HbA_{1c} reduction was 3.44 % and the HbA_{1c} reduction rate was 33%. Yet the insulin requirement in our study was reduced by 41% accompanied by reduction of hypoglycemia events without any significant weight changes. Their baseline antidiabetic medications were mainly insulin (95%) and metformin (63%). metformin (32%), DPP4i (26%) and sulphonylureas (16%) were the 3 main additional antidiabetic therapies during the study. Numerous randomized controlled trials and large observational studies have shown that insulin is the antidiabetic agent which has the greatest glucose lowering capacity, if compared with the other OADs.[13,21] Therefore, insulin therapy was the major therapy to achieve the significant HbA_{1c} reduction, albeit there were additions of new OADs. The only explanation of the reduction of insulin to achieve the HbA_{1c} reduction was that the patients in the study had poor compliance to insulin therapy prior to the study.

The effective communication between patient and health care provider plays an essential part in managing patients with DFU. It provided adequate time and space and promote rapport, confidence, motivation and satisfaction for both parties. Individualised glycemic intervention in patients with DFU is a holistic tailored approach adapting to patient's values, goal and preference, family, educational, socio-cultural, and occupational background. As diabetes is a multi-organ systemic disease, all comorbidities that affect wound healing must be managed by a multidisciplinary team to reduce amputation rates, lower costs, and lead to better quality of life.[22-24] Through structured education and self-management programmes, patients will be more adherent to the treatment, which have been shown to improve personal responsibility especially to their own medications.[25]

This is the pilot prospective study examining the association between individualised glycemic interventions and wound healing rate in patients diagnosed with DFU. The study was done in a specified wound clinic that allowed adequate facilities and expertise for patient care. There were certain limitations in the study including the small number of patients from a single center in a short duration of study period. Due to the reasons above, this study was designed as an uncontrolled study that would not provide a proper comparison of efficacy and safety of the intervention. The other limitation was the variable patients' clinical conditions and wound characteristics with different wound treatment that might influence the results of the study. Ideally, a large number of patients from multiple centers including primary, secondary as well as tertiary health facilities should be examined to minimize the impact of the selection bias. Individualised glycaemic intervention should be integrated into multidisciplinary team approach in order to have better wound healing in patients with DFU.

CONCLUSION

There was a positive correlation between HbA_{1c} reduction and wound healing rate in patients with DFU. Although this is an association study, the study postulated the benefits of achieving lower HbA_{1c} on wound healing rate in DFU which require evidence from future randomised controlled studies.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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ORIGINAL ARTICLE

Hypoglycaemia among Insulin-Treated Patients with Diabetes: Southeast Asia Cohort of IO HAT Study

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Abstract

Objective: To provide real-world data on hypoglycaemia incidence in patients with type 1 (T1D) or type 2 diabetes (T2D) from the Southeast Asian cohort of the International Operations Hypoglycaemia Assessment Tool (IO HAT) study.

Methodology: IO HAT was a non-interventional, multicentre, 6-month retrospective and 4-week prospective study of hypoglycaemic events among insulin-treated adults with T1D or T2D, including four countries in Southeast Asia (Singapore, Philippines, Indonesia, and Bangladesh). Data were collected using a two-part self-assessment questionnaire (SAQ1 for retrospective and SAQ2 for prospective). The primary endpoint was the percentage of patients experiencing at least one hypoglycaemic event during the 4-week prospective observational period (ClinicalTrials.gov Identifier: NCT02306681).

Results: A total of 2594 patients completed SAQ1. Nearly all patients reported experiencing any hypoglycaemic event in the 4-week prospective period (T1D, 100%; T2D, 97.3%), with all patients reporting higher rates in the prospective versus retrospective period. Severe hypoglycaemia was also reported higher prospectively (57.2% and 76.9%) than retrospectively (33.9% and 12.2%) in both T1D and T2D, respectively. Nocturnal hypoglycaemia was reported higher retrospectively than prospectively.

Conclusion: Incidence of any and severe hypoglycaemia in the Southeast Asian cohort of IO HAT was higher prospectively versus retrospectively, suggesting hypoglycaemia has previously been under-reported in this region.

Key words: *hypoglycaemia, insulin, diabetes*

INTRODUCTION

Patients with type 1 diabetes (T1D) and some with type 2 diabetes (T2D) rely on insulin therapy for survival and for glycaemic control. Prevalence of diabetes is escalating in every country, especially in developing countries, which has an impact on healthcare utilisation.[1] Developing countries in Asia have the highest population of patients with diabetes in the world[2-4] because of rapid urbanisation, unhealthy eating habits, sedentary lifestyles and increased life expectancy.[5] A meta-analysis has shown a rapid increase in the prevalence of diabetes in Southeast Asia over the past 2 decades.[6] The overall prevalence of diabetes among adults in the region was 8.5% in 2015, and this is estimated to rise to 10.7% by 2040.[3] Furthermore, there is a high prevalence of impaired glucose tolerance (IGT) in Southeast Asia and the conversion rates from IGT to diabetes are faster in Southeast Asia than in other regions.[1,7,8] Southeast Asian populations migrating from rural to urban areas that adopt unhealthy lifestyles are at a similar risk of developing diabetes as those who move from developing countries to more affluent countries.[9] High consumption of carbohydrates (especially white rice) and inertia of physical activities in Asian populations,[10] may lead to inefficient glycaemic control in those diagnosed with diabetes. An observational study that included patients from Indonesia, Thailand and Malaysia from the Southeast Asia region, found that 22% of patients with T1D and 36% of patients with T2D had never had glycated haemoglobin (HbA_{1c}) measurements.[2] Despite the predicted increase in diabetes, a literature review, which was conducted with the primary purpose of determining the known incidence and impact of hypoglycaemia in Southeast Asia, highlighted that there are limited data regarding the incidence of hypoglycaemia in this region.[11]

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Hypoglycaemia with insulin treatment is a major concern for both patients and healthcare providers and is a significant barrier to achieving good glycaemic control.[12] Real-world data and literature on the incidence of hypoglycaemia in insulin-treated patients with diabetes are scarce.[13] Results from the global Hypoglycaemia Assessment Tool (HAT) study from 24 countries worldwide showed that rates of hypoglycaemia among patients with insulin-treated T1D and T2D were higher than previously reported.[14] The non-interventional International Operations HAT (IO HAT) study was designed to assess the incidence of hypoglycaemia in patients treated with insulin (premix, short-acting and long-acting) for T1D or T2D in Bangladesh, Colombia, Egypt, Indonesia, the Philippines, Singapore, South Africa, Turkey and United Arab Emirates.[15]

This publication presents the results from the Southeast Asian cohort of the IO HAT study (Bangladesh, Indonesia, Philippines and Singapore) and aims to determine, within this cohort, whether there are any differences in the incidence rates between retrospective and prospective reporting of hypoglycaemia.

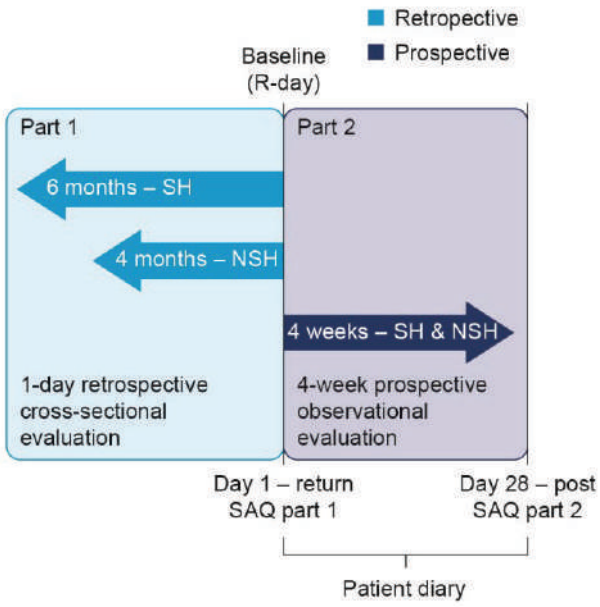
METHODOLOGY

Subjects

Eligible patients (male or female patients 18 years or older with T1D or T2D treated with insulin for more than 12 months) were enrolled consecutively after attending a routine clinic appointment.

Study design

The methods for the IO HAT study have been previously published in detail,[15] this sub-group analysis focuses on the Bangladesh, Indonesia, Philippines and Singapore cohorts from the IO HAT study. In summary, IO HAT was a non-interventional, multicentre, 6-month retrospective and 4-week prospective study of hypoglycaemic events in adult patients with T1D or T2D, treated with insulin for over 12 months (Figure 1). Retrospective cross-sectional and prospective observational evaluations took place using a two-part self-assessment questionnaire (SAQ1 and SAQ2) and the patient diary (provided at baseline and used to aid prospective reporting). There were no interventions or specific treatments recommended or provided to patients as a result of participating in this study. The trial protocol, any amendments, informed consent form and any other written information or documents, as required, were submitted to local institutional review board/ethics committees. The trial was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines.



NSH, non-severe hypoglycaemia; SAQ, self-assessment questionnaire; SH, severe hypoglycaemia; T1D, type 1 diabetes; T2D, type 2 diabetes

Figure 1. Study design.[15]

Categories of hypoglycaemia recorded in the questionnaire and patient diary included severe hypoglycaemia (defined, based on the American Diabetes Association [ADA] definition from 2005, as any hypoglycaemic event requiring assistance of another person to administer carbohydrate, glucagon or other resuscitative actions[16]) any hypoglycaemia (the sum of non-severe hypoglycaemia [any event managed by the patient alone] and severe hypoglycaemia) and nocturnal hypoglycaemia (any event occurring between midnight and 06:00 am); the reported hypoglycaemia events did not need to be accompanied by a confirmatory blood glucose measurement. Patient knowledge of hypoglycaemia was evaluated by assessing whether their definition was consistent with the ADA definition of hypoglycaemia[16] and if they knew what hypoglycaemia was before being provided with the informed consent form. Hypoglycaemia unawareness was evaluated using a previously validated question,[17] 'Do you have symptoms when you have a low sugar level?', where the responses 'always,' 'usually,' 'occasionally' and 'never' represent increasing degrees of hypoglycaemia unawareness.

Endpoints

The primary objective for the IO HAT study was to assess the percentage of patients experiencing at least one hypoglycaemic event during the 4-week prospective observational period.

Key secondary objectives included: incidence of various types of hypoglycaemic episodes; the difference in the reported incidence of severe, non-severe, nocturnal and any hypoglycaemic episodes in the retrospective and

Table 1. Baseline characteristics

Characteristic	T1D (N=154)	T2D (N=2,440)
Age (years)	**33.2 (12.5)**	**57.2 (11.2)**
Median	30.0	58.0
Upper quartile, Lower quartile	40.0, 24.0	65.0, 50.0
Male/female (%)	**44.8/55.2**	**42.7/56.7**
Country, n		
Bangladesh	25	1154
Philippines	62	609
Indonesia	17	357
Singapore	50	320
Duration of diabetes (years)	**13.6 (9.9)**	**13.2 (8.1)**
Median	12.0	12.0
Upper quartile, lower quartile	18.0, 6.0	18.0, 7.0
Duration of insulin use (years)	**12.5 (9.7)**	**5.5 (4.9)**
Median	10.0	4.0
Upper quartile, lower quartile	16.0, 5.0	7.0, 2.0
BMI (kg/m^2)	**22.4 (3.7)**	**26.4 (4.8)**
Median	22.0	25.7
Upper quartile, lower quartile	24.9, 19.7	28.7, 23.5
HbA_{1c} (%)	**8.4 (1.8)**	**8.7 (1.9)**
FBG (mmol/l)	**8.8 (4.7)**	**8.6 (3.5)**
PPG (mmol/l)	**10.2 (4.5)**	**11.4 (4.0)**
Weight (kg)	**57.9 (11.9)**	**67.3 (13.1)**
Median	56.5	66.0
Upper quartile, lower quartile	65.0, 49.0	74.0, 59.0
Height (cm)	**160.6 (9.9)**	**159.7 (8.6)**
Median	159.5	160.0
Upper quartile, lower quartile	168.0, 153.0	165.0, 153.0
Previous medical illnesses (% patients)		
Neuropathy	21.4	42.2
Retinopathy	27.9	38.2
Nephropathy	8.4	21.7
Peripheral vascular disease	14.3	19.1
Angina	4.5	12.6
Myocardial infarction	0.6	9.8
None	55.8	29.6
Method of diabetes treatment [n(%)]		
Short-acting insulin	6 (3.9)	148 (6.1)
Long-acting insulin	8 (5.2)	467 (19.1)
Pre-mix insulin	50 (32.5)	1069 (43.8)
Both short and long acting insulin	87 (56.5)	647 (26.5)
Both short acting and pre-mix insulin	2 (1.3)	70 (2.9)
Both long acting and pre-mix insulin	0 (0.0)	32 (1.3)
Short and long acting and pre-mix insulin	1 (0.6)	1 (0.0)
Missing	0 (0.0)	6 (0.2)

Data are presented as mean (SD) unless otherwise stated; BMI, body mass index; FBG, fasting blood glucose; HbA_{1c}, glycated haemoglobin; N, total number of subjects participating; n, total number of subjects; PPG, postprandial glucose; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

prospective periods; the relationship between demography, duration of diabetes, duration of insulin therapy and incidence of hypoglycaemic episode; use of healthcare resources; and patient behaviours in response to hypoglycaemia.

Statistical analyses

Statistical tests were two-sided and exploratory, with the criterion for statistical significance set at $p<0.05$. There was no adjustment for multiple comparisons, but *p*-values were interpreted conservatively, i.e. *p*-values from 0.01 to 0.05 were taken to indicate modest evidence of a difference and *p*-values of less than 0.01 were taken to indicate moderate evidence of a difference.

For the primary endpoint, the percentage of patients who experienced at least one hypoglycaemic episode during the 4-week prospective observational period among T1D or T2D was calculated together with the confidence interval for this percentage. For secondary endpoints, the incidence of various types of hypoglycaemia was calculated as the number of events per patient year.

Sample size was determined assuming a worst case scenario proportion of patients (=50%) reporting at least one hypoglycaemic episode during the 4-week prospective observation period, and that the range of the 95% confidence interval was less than 3 percentage points for the total cohort (N=6000). The sample size was calculated using 50%, which represents the largest degree of variance.

RESULTS

Patient characteristics

Patient characteristics are described in Table 1. Of the 7289 patients enrolled in the IO HAT study, 2594 (T1D, n=154; T2D, n=2440) were from Southeast Asia (Bangladesh [n=1179], Indonesia [n=374], the Philippines [n=671] and Singapore [n=370]; Table 1). Patients included in the full analysis set completed SAQ1 (2594 [T1D, n=154; T2D, n=2440]). Of these, 2483 completed SAQ2 and were included in the completer analysis set (T1D, n=138; T2D, n=2345).

Patients with T2D were older than those with T1D, with a mean age of 57.2 years compared with 33.2 years. The average duration of diabetes was similar in both patients with T1D (13.6 years) and T2D (13.2 years). On average, patients with T1D had a longer average duration of insulin use (12.5 compared with 5.5 years for patients with T2D) and lower average HbA_{1c} (8.4% [±1.8]) than those with T2D (8.7% [±1.9]). Most patients (87 patients [56.5%]) with T1D were on mixed insulin regimens (both short- and long-acting insulin), followed by pre-mix (50 patients [32.5%]), long-acting insulin (eight patients [5.2%]) and short-acting (six patients [3.9%]). Only two patients (1.3%) were on a mixed regimen of short-acting and pre-mix insulin and one patient (0.6%) was on a mixed regimen of short- and long-acting and pre-mix insulins. Most patients (1069 patients [43.8%]) with T2D used pre-mix insulins, followed by 647 (26.5%) patients on a mixed regimen of short- and long-acting insulin and 467 patients [19.1%] on long-acting insulin.

Frequency of hypoglycaemia

Any hypoglycaemia

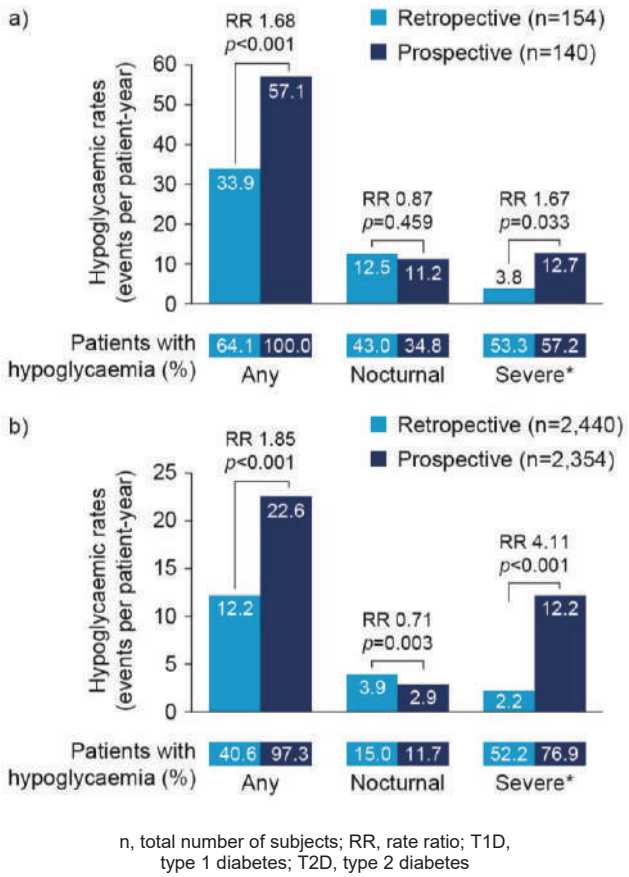
Most patients (T1D, 100%; T2D, 97.3%) reported experiencing an hypoglycaemic event during the 4-week prospective period (Figure 2). Lower rates of any hypoglycaemia were reported retrospectively compared with prospectively in patients with T1D (rate ratio [RR] 1.68, $p<0.001$) or T2D (RR 1.85, $p<0.001$; Figure 2). For any hypoglycaemia, the rates per-patient year (PPY) during the retrospective period for T1D and T2D were 33.9 (95% CI: 30.68, 37.44) and 12.2 (95% CI: 11.69, 12.70), respectively. In the prospective period, rates for T1D and T2D were higher (57.1 [95% CI: 52.63, 61.83] PPY and 22.6 [95% CI: 21.94, 23.35] PPY, respectively) than in the retrospective period.

Nocturnal hypoglycaemia

During the 4-week prospective period, 34.8% of patients with T1D and 11.7% of patients with T2D reported nocturnal hypoglycaemia. Higher rates of nocturnal hypoglycaemia were reported in the 6-month retrospective period than in the prospective period in both patients with T1D (RR 0.87, $p=0.459$) and T2D (RR 0.71, $p=0.003$; Figure 2). In patients with T1D and T2D, rates of nocturnal hypoglycaemia in the retrospective period were 12.5 (95% CI: 10.55, 14.75) PPY and 3.9 (95% CI: 3.62, 4.19) PPY, respectively. Prospectively, lower rates of nocturnal hypoglycaemia were reported for both patients with T1D (11.2 [95% CI: 9.23, 13.36] PPY) and T2D (2.9 [95% CI: 2.61, 3.12] PPY).

Severe hypoglycaemia

During the 4-week prospective period, 57.2% of patients with T1D and 76.9% of patients with T2D reported severe hypoglycaemia. Lower rates of severe hypoglycaemia were reported retrospectively compared with prospectively in patients with T1D (RR 1.67, $p=0.033$) or T2D (RR 4.11, $p<0.001$; Figure 2). In patients with T1D, rates



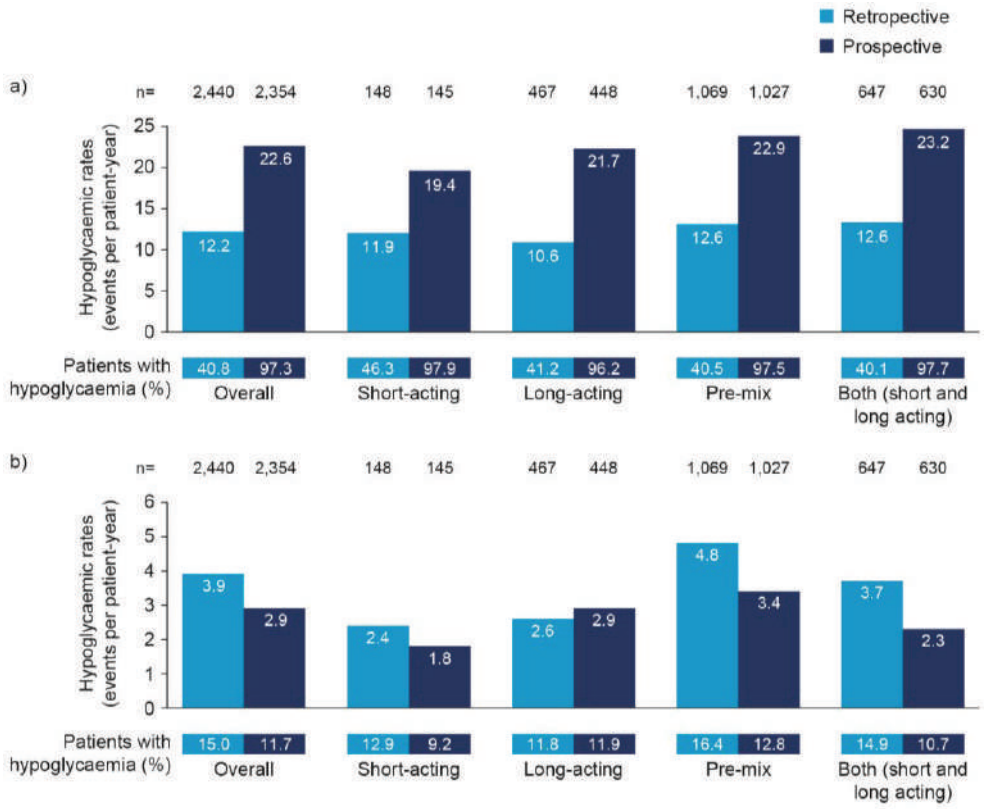
n, total number of subjects; RR, rate ratio; T1D, type 1 diabetes; T2D, type 2 diabetes

Figure 2. Retrospective and prospective hypoglycaemia rates in T1D (a) and T2D (b) 'Any' and 'Nocturnal' based on 4-week period for both retrospective and prospective analyses. *Retrospective data based on 6-month period and prospective data based on 4-week period.

of severe hypoglycaemia in the retrospective period were 3.8 [95% CI: 3.39, 4.32] PPY and in T2D, 2.2 [95% CI: 2.08, 2.25] PPY. Hypoglycaemia rates were higher in the prospective period for both patients with T1D (12.7 [95% CI: 10.61, 15.00] PPY) and T2D (12.2 [95% CI: 11.68, 12.72] PPY).

Impact of hypoglycaemia on the medical system

In the retrospective period 6 months before baseline, 7.1 and 7.3% of patients with T1D and T2D, respectively, had a hypoglycaemic event that led to hospital admission. During this time, 9.2% of patients with T1D attended additional clinical appointments as a result of a hypoglycaemic event and 7.8% made additional telephone contacts with a healthcare provider. In T2D, 6.8% of patients who experienced a hypoglycaemic event made additional telephone calls and 6.2% attended additional clinical appointments. In the 4-week prospective period, the most common effect on the medical system was making additional telephone contacts in both patients with T1D (4.3%) and T2D (5.7%), followed by attending additional clinical appointments (2.9% for patients with T1D and 1.7% for T2D) and hospital admission (0.7% for patients with T1D and 1.2% for T2D).



%, percentage; n, total number of subjects; T2D, type 2 diabetes

Figure 3. Estimated rate of any (a) and nocturnal (b) hypoglycaemic events by insulin regimen in T2D.

Rates of hypoglycaemia by insulin regimen

Lower rates of any hypoglycaemia were reported retrospectively than prospectively with all insulin regimens in both patients with T1D and T2D (Figure 3a). In patients with T1D, lower rates of nocturnal hypoglycaemia were reported retrospectively than prospectively among those treated with short-acting (4.4 compared with 10.4 PPY, respectively) and long-acting (3.3 compared with 19.6 PPY, respectively) insulin regimens. Patients on pre-mix or mixed (both short- and long-acting) insulin reported higher rates of nocturnal hypoglycaemia retrospectively than prospectively (pre-mix: 15.7 compared with 13.3 PPY, respectively; mixed: 12.3 compared with 9.5 PPY, respectively). In patients with T2D, nocturnal hypoglycaemia was reported at a higher rate retrospectively than prospectively in patients treated with all insulin regimens except long-acting insulin (Figure 3b). Lower rates of severe hypoglycaemia were reported retrospectively than prospectively with all insulin regimens in both patients with T1D and T2D, with lower rates of hypoglycaemia in patients on long-acting insulin regimens.

In patients with T1D, patients on short-acting insulin had the lowest rates of any hypoglycaemia in the prospective period (33.9 PPY). The highest rates of hypoglycaemia were reported by patients on a mixed insulin regimen (both short- and long-acting insulin; 61.3 PPY). In patients with T2D, rates of any and nocturnal hypoglycaemia (Figure 3) were also lowest with short-acting insulin regimens during the prospective period (19.4 and 1.8 PPY, respectively; Figure 3). The highest rates of any hypoglycaemia reported prospectively were in those on a mixed insulin regimen (short- and long-acting insulin; 23.2 PPY), followed by those on a pre-mix insulin regimen (22.9 PPY).

Rates of hypoglycaemia by duration of diabetes and insulin therapy

In the retrospective period, patients with T1D who had diabetes for between 12 and 17 years had the highest rates of any hypoglycaemia (40.5 PPY). In patients with T2D rates of hypoglycaemia increased with increasing duration of diabetes. Rates of nocturnal hypoglycaemia generally increased with diabetes duration for both patients with T1D and T2D, with peaks in those who had diabetes for between 12 and 17 years for T1D and between 7 and 11 years for T2D. Rates of severe hypoglycaemia generally increased with duration of diabetes for both patients with T1D and T2D. In the prospective period, for patients with T1D or T2D, rates of any, nocturnal and severe hypoglycaemia generally increased with increasing duration of diabetes.

Patients with T1D who had received insulin therapy for between 5 and 9 years reported the highest rates of any hypoglycaemia in the retrospective period. Patients who had received insulin therapy for over 10 years had the highest rates of nocturnal and severe hypoglycaemia. In

Table 2. Patient perspectives

Perspective	T1D (N=154)		T2D (N=2,440)	
Knew what hypoglycaemia was before reading definition provided [n/N total (%)]	148/154 (96.1)		2046/2390 (85.6)	
Defined hypoglycaemia on basis of [n/N total (%)]				
Symptoms only	89/154 (57.8)		1144/2440 (46.9)	
Blood glucose measurements only	6/154 (3.9)		134/2440 (5.5)	
Either	15/154 (9.7)		227/2440 (9.3)	
Both	36/154 (23.4)		500/2440 (20.5)	
Hypoglycaemia awareness (%)				
Normal	48.7		39.6	
Impaired	46.8		44.1	
Severely impaired	0.6		10.9	
Fear of hypoglycaemia (%)				
0 = no fear	14.3		18.6	
1	3.2		7.3	
2	5.2		9.6	
3	7.8		10.6	
4	9.1		9.3	
5	19.5		16.1	
6	5.8		7.7	
7	11.7		6.4	
8	11.0		5.9	
9	3.2		2.8	
10 = absolutely terrified	9.1		5.7	
Impact of hypoglycaemic events on the medical system	Retrospective	Prospective	Retrospective	Prospective
Number of hospital admission days as a result of hypoglycaemia [n, mean (SD)]	140, 0.1 (0.5)	138, 0.0 (0.1)	1947, 0.4 (2.3)	2273, 0.0 (0.5)
Number of additional clinic appointments attended [n, mean (SD)]	13, 1.8 (1.3)	4, 1.3 (0.5)	120, 1.7 (1.2)	35, 1.3 (0.6)
Number of additional telephone contacts made [n, mean (SD)]	9, 1.8 (1.6)	6, 2.0 (1.6)	123, 2.3 (2.1)	123, 1.6 (1.4)

Data are presented as mean (SD) unless otherwise stated; N, total number of subjects participating; n, total number of subjects; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

the prospective period, patients with T1D who had received insulin therapy for over 10 years reported the highest rates of any, nocturnal and severe hypoglycaemia. Patients with T2D who had received insulin therapy for over 10 years had the highest rates of any, nocturnal and severe hypoglycaemia in the retrospective and prospective periods (compared with those who had received insulin therapy for 1 to <3, 3 to <5 and 5 to <10 years).

Rates of hypoglycaemia by frequency of blood glucose monitoring

In both patients with T1D and T2D, rates of any hypoglycaemia increased with each quartile, and were highest in the upper quartile of frequency of blood glucose monitoring in both the retrospective and prospective periods. In patients with T2D, the same trend was seen for nocturnal and severe hypoglycaemia rates.

Hypoglycaemic events recorded in the patient diary

Of those who completed the patient diary (154 in T1D, 2440 in T2D) 36 patients (25.9%) with T1D and 158 (7.0%) patients with T2D had a confirmed hypoglycaemic event recorded in their diary.

Impact of hypoglycaemia on work/school

During the retrospective period, the impact of hypoglycaemia was higher on patients with T1D than T2D. In patients with T1D, arriving late to work/studies was the most common impact of hypoglycaemia on work/school, retrospectively reported by 22.1% of patients, followed by taking leave (17.3%) and leaving early (13.5%). In patients with T2D, leaving early from work was reported by 10.4% of patients, followed by taking leave (10.1%) and arriving late to work (7.6%). Of those patients who held a driver's licence (T1D, n=50; T2D, n=580), six (12.0%) with T1D and 25 (4.3%) with T2D experienced a hypoglycaemic event whilst driving in the past 6 months.

In the 4-week prospective period, arriving late to work/studies was the most common impact of hypoglycaemia on work/school, reported by 10.0% of patients with T1D, followed by taking leave (4.4%) and leaving early from work (2.2%). In patients with T2D, taking leave was reported by 3.2% of patients, with the next most common impacts being leaving early (2.8%) and arriving late (2.1%).

Patient perspectives

Patient perspectives on hypoglycaemia are described in Table 2. In T1D and T2D, 96.1% and 85.6% of patients knew what hypoglycaemia was before being provided with the definition in SAQ1. The most common method that patients used to define hypoglycaemia was based on symptoms alone (57.8% in T1D and 46.9% in T2D). More patients with T1D had normal hypoglycaemia awareness (48.7%) than those with T2D (39.6%). Patients with T2D had more hypoglycaemia unawareness than those with T1D (55% of patients with T2D had impaired or severely impaired awareness compared with 47.4% for T1D). When answering the question 'How often do you have symptoms when you have a low blood sugar measurement' 44.1% of patients with T2D and 46.8% in T1D, answered 'occasionally,' indicating impaired awareness and 10.9% answered 'never' indicating severely impaired awareness (T1D = 0.6%). Of those patients with impaired awareness, 46.9% with T1D and 45.4% with T2D experienced severe hypoglycaemia in the 6-months before baseline.

Patients reported a moderate fear of hypoglycaemia, with mean scores out of ten of five for T1D and four for T2D (where one indicated not afraid at all and ten, absolutely terrified). Retrospectively, the most common patient actions resulting from a hypoglycaemic event in T1D and T2D were requiring medical assistance (53.9% and 39.9%, respectively), consulting their doctor/nurse (51.3% and 38.8% respectively) and increasing calorie intake (40.9% and 27.3% respectively). In the 4-week prospective period, increasing calorie intake, requiring medical assistance and consulting their doctor or nurse were the most common actions taken by patients with T1D and T2D.

Associations between hypoglycaemia and continuous or predictor variables

No association was identified between HbA_{1c} level and any, nocturnal or severe hypoglycaemia.

DISCUSSION

The IO HAT study was a multicentre, international, 6-month retrospective and 4-week prospective study with a two-part SAQ that investigated the prevalence of hypoglycaemia in insulin-treated adults with T1D or T2D.

Results from the Southeast Asia cohort of the IO HAT study show that the proportion of patients who experienced at least one hypoglycaemic event was higher in the prospective period than the retrospective period for both T1D and T2D. Patients with T1D reported higher incidence rates than those with T2D in both periods for any, nocturnal and severe hypoglycaemia. Higher rates of nocturnal hypoglycaemia were reported in the retrospective period than in the prospective period, for both patients with T1D and T2D.

The higher rates of any and severe hypoglycaemia reported during the prospective period were also seen in the overall IO HAT study.[15] Despite a high proportion of patients who knew what hypoglycaemia was before learning the definition during the study (T1D 96.1% and T2D 85.6%), the most common way patients defined hypoglycaemia was based on symptoms only and nearly half of patients had impaired hypoglycaemia awareness. One review identified a high proportion of diabetes unawareness in Indonesia and suggested that patients in Southeast Asia may be poorly educated about hypoglycaemia and its management.[11] The reduced level of hypoglycaemia and diabetes awareness in this region may have contributed to the lower reporting of hypoglycaemic events by patients in the retrospective period of this study. However, the study demonstrated that when patients are properly educated about hypoglycaemia and its manifestations, patients are able to recognise the signs of hypoglycaemia themselves.

This cohort had a small number of patients with T1D (n=154). T1D is rare in Asian populations and data collection is not as systematic as in Western countries.[1] Most Southeast Asian countries do not have established registries for patients with T1D, which may contribute to the lack of data on T1D and hypoglycaemia in this region.[1] The little information available does however suggest that incidence of T1D is rising in Asia.[1]

Patient responses to hypoglycaemia increase healthcare utilisation in Southeast Asia. This may be due to seizures induced by hypoglycaemia, which can eventually lead to coma and death.[18] Hypoglycaemia may also result in patients missing doses and reactively adjusting their medication plan.[19] In the present study, most patients who experienced hypoglycaemia made contact with their doctor or nurse and required a form of medical assistance in T1D and T2D, both retrospectively and prospectively.

A study in Bangladesh found that patients with diabetes had twice the number of inpatient treatment days than those without diabetes. They also had 1.3-fold more outpatient visits and 9.7-fold more medications than those without diabetes, and the cost of their healthcare was 6.1-fold higher.[20] There is a lack of structured care management and integrated healthcare policies in the Southeast Asia region,[1,9] differences in diabetes healthcare available in rural, compared with urban areas, must be taken into consideration.

Some patients increased their calorie intake to overcome the effects of hypoglycaemia in both the retrospective and prospective periods (retrospectively: T1D, 40.9% and T2D, 27.3%; prospectively: T1D, 36.2% and T2D, 16.8%), this is in line with results from the global HAT study.[21] If patients manage hypoglycaemia themselves by increasing calorie intake, their HbA_{1c} during clinic visits may be elevated and may result in their healthcare practitioner (HCP) increasing or adding more antidiabetes agents to their treatment. More frequent monitoring and clinic visits with a duration of self-monitoring might be advised to try and achieve better glucose control. Continuous glucose monitoring has been shown to be cost-effective in patients with T1D with intensive insulin therapy[22] and in patients with T2D on oral antidiabetic drugs some of the increased costs associated with self-monitoring blood glucose are offset by reductions in diabetes complication costs.[23,24]

Pre-mix insulin is the most common method of insulin treatment in Southeast Asia and this is reflected in the results from this cohort with 32.5% of patients with T1D and 43.8% of patients with T2D on this insulin regimen at baseline. In the retrospective period, patients on pre-mix insulin reported the highest rates of any, nocturnal and severe hypoglycaemia in T1D and for any and nocturnal hypoglycaemia in T2D. This is in contrast to the overall IO HAT study, as in patients with T1D, the highest rates of any hypoglycaemia retrospectively and prospectively were reported with short-acting insulin.[15] In patients with T2D, highest rates of any hypoglycaemia were reported with a mixed insulin regimen (both short- and long-acting

insulin) retrospectively, whereas short-acting, premix and mixed regimens (both short- and long-acting insulins) had the highest rates reported prospectively.[15] The high hypoglycaemia rates identified with pre-mix insulin in Southeast Asia are similar to previous data.[11] Traditionally, the Asian diet is high in carbohydrates, and so pre-mix insulins are a suitable choice as they target post-prandial hyperglycaemia.[25] However, newer insulin analogues can provide more stable glycaemic control and effective reduction of post-prandial hyperglycaemia.

Hypoglycaemia is known to have an impact on patients' productivity. Productivity of patients in this region is clearly affected with 17.3% of patients with T1D and 10.1% of patients with T2D in this study arriving late to work/studies. In Singapore, prevalence of T2D in adults is projected to rise from 7.3% in 1990 to 15% in 2050.[5] These data suggest that this rise will have an effect on the workforce – there were 97,600 patients working and living with T2D in Singapore in 1990, which is expected to increase to 321,600 by 2050.[5] Singapore's combined Chinese, Indian and Malaysian population is representative of Asia as a whole, which makes it a useful test for healthcare research.[5] The trends observed in this study could be used to predict the future impact of hypoglycaemia on the whole of Asia. If the pattern predicted is observed over time, this may have a considerable impact on workforce productivity and workplaces may need to have the correct preparations in place to deal with employee lateness and absenteeism due to diabetes-related complications.

As the prevalence of diabetes increases and its impact on society and the economy increases, there is a real need for clear guidelines for HCPs in Southeast Asia. Use of Western guidelines in the Southeast Asia may add to the increased diabetes burden in the region, as a result of differing disease aetiology between Western and Asian diabetes populations, such as a lower BMI and younger age at time of diabetes presentation in Asian populations.[11] One of the main contributors could be the differences in diet, which is of particular importance, as a result of a higher glycemic response to carbohydrate consumption in Asian populations.[25] Other contributing factors in Asian populations include: differences in presentation of anti-insulin auto-antibodies in patients with T1D from Western compared with Asian populations,[1,26] a high proportion of patients who practice Ramadan (increased risk of hyper or hypoglycaemia) and a preference for pre-mix insulin.[11] Although some guidelines are available, there appears to be a difference between the guidelines and what HCPs do in practice in Southeast Asia.[2] This warrants the development of clear guidelines specific to the Asian population.

In a previous study, predictors for glycaemic control in Asia were lack of microvascular complications, old age, BMI <30 kg/m^2 and self-adjustment of insulin doses.[9] Lifestyle modifications can prevent diabetes and may have beneficial effects on cardiovascular risk factors, reduce the risk of microvascular complications, improve BMI and are cost-effective for both the patient and healthcare systems.[9]

Limitations to the study include the small sample size of patients with T1D, although this could reflect the smaller population of patients with T1D in general in Southeast Asia. Study bias may also have taken place, whereby patients were more likely to report hypoglycaemia after learning what the correct definition was during the study. This study may also be limited by recall bias in the retrospective period.

CONCLUSION

Through the use of the IO HAT questionnaires and patient diaries, a higher prospective than retrospective incidence of any and severe hypoglycaemia was reported in the Southeast Asian cohort of the IO HAT study. These results are consistent with those from the overall IO HAT study. As a result of lack of knowledge and awareness, any and severe hypoglycaemia may be retrospectively underestimated and under-reported by patients in this region. Patients on mixed (both short- and long-acting) insulin regimens had the highest rates of any hypoglycaemia prospectively in both T1D and T2D and hypoglycaemia rates generally increased with diabetes duration. Hypoglycaemia increased healthcare utilisation and reduced productivity. There is a need for unique guidelines, specific to the Southeast Asian population, which can help improve diabetes management and improve patient outcomes in those already diagnosed.

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All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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ORIGINAL ARTICLE

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Attitudes, Behaviors and Beliefs of Urban Adult Filipinos on Sunlight Exposure: A Qualitative Study*

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Abstract

Objective. To explore the attitudes, behaviors, and beliefs of urban adult Filipinos on sunlight exposure as an initial step in the development and validation of a culturally-appropriate questionnaire.

Methodology. Focus groups were conducted among urban Filipinos 19 years old and above (n=38). The transcribed results underwent qualitative content and thematic analyses and were used to develop a conceptual framework.

Results. Qualitative analysis revealed four main themes of sunlight exposure: internal influences, external influences, perceived benefits, and perceived risks. Both internal and external influences lead to perceived risks and benefits. Consequently, the perceived benefits (or lack) of sunlight exposure influence an individual's attitude towards vitamin D supplementation; whereas the perceived risks of sunlight exposure influence an individual's attitude towards the need for sun protection.

Conclusion. The attitudes, behaviors and beliefs of urban adult Filipinos on sunlight exposure are influenced by both internal and external factors, that in turn lead to perceived risks and benefits. An increased awareness of these factors is necessary to establish future recommendations on proper sunlight exposure in this population. The study results will be used to develop and validate a culturally-appropriate sunlight exposure questionnaire.

Key words: sunlight exposure, adult Filipinos, urban health, community health, qualitative research

INTRODUCTION

Vitamin D deficiency (VDD) affects around one billion people globally.[1] It is reflected by low levels of serum 25-hydroxyvitamin D (25-OHD), leading to calcium and phosphate imbalance, bone mineral loss and significant fracture risk. Efforts to address VDD initially focused on temperate countries where serum 25-OHD levels fluctuate to suboptimal ranges during winter and early spring.[2,3] However, there is a growing focus of concern in tropical countries, which were believed to receive adequate year-round sunlight exposure and are thus previously considered unlikely to harbor VDD. In the Philippines, a study on urban postmenopausal women revealed 36% of the subjects as having inadequate 25-OHD levels.[4]

Ultraviolet ray (UVB) exposure is the main source of Vitamin D in humans.[5] It is assessed by different methods such as observation, skin reflectance with colorimeters, skin swabbing with spectrophotometers, dosimetry with polysulfone films, sunlight diaries and mole inspection. However, these procedures are either not readily available or expensive, or prone to inter-observer variability.[6] In population-based studies, questionnaires remain the most cost-effective way of measuring sunlight exposure.[7] Although no universally-validated version is available for routine use to quantify sunlight exposure, several questionnaires have been formulated and validated in different countries. Of these, only 2 were validated in Asian populations (Hong Kong and Pakistan), and only 3 were done in the context of VDD by correlating questionnaire results with serum 25-OHD.[7-10]

Currently, there is no existing sunlight exposure questionnaire validated for use in tropical countries such as the Philippines. This study used focus group

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Table 1. Summary profile of the FGD participants, N=38, Manila, Philippines

	Group Description	Number of individuals	Median age in years (range)	Highest educational attainment	Religion	Occupation
1.	Male, some education, mostly outdoor work	8	34 (20-39)	College undergraduate	Christian	Telephone repairman, construction workers, messengers, delivery boy
2.	Female, some education, mostly outdoor work	7	32 (22-47)	High school graduate	Christian	Store-to-store merchandiser, street and market vendors, delivery girl, outdoor washerwoman
3.	Male physicians, mostly indoor work	8	28 (26-29)	Post-graduate	Christian	Physicians
4.	Female physicians, mostly indoor work	8	27 (25-32)	Post-graduate	Christian	Physicians
5.	Elderly	7	63 (61-69)	High school graduate	Christian	Retired (Not in healthcare prior to retirement)

Table 2. Guide questions for the FGD

Topic	Questions
Duration and intensity of sunlight exposure	How do you describe your skin when it is exposed to the sun? What is your usual clothing when you go out in the sun? How long are you usually exposed to the sun each day?
Factors affecting sunlight exposure	What are the different factors affecting sunlight exposure? Do these factors positively or negatively impact sunlight exposure?
Benefits of sunlight exposure	What are the benefits of sunlight exposure? What are the risks of not getting enough sunlight exposure? Do you believe in the benefits of Vitamin D supplements? Why or why not?
Risks of sunlight exposure	What are the risks of getting too much sunlight exposure? What methods do you use to protect yourself from too much sunlight exposure?

discussions (FGDs) to explore the attitudes, behaviors and beliefs of urban adult Filipinos on sunlight exposure as an initial step towards the development and validation of a culturally-appropriate sunlight exposure questionnaire.

METHODOLOGY

The study included individuals 19 years old or older, who are able to speak and understand the Filipino *(Tagalog)* language, and who are either living in or working at least 5 days a week in Metro Manila for at least the past 5 years. The FGDs were conducted separately with 5 groups: Group 1, working age (19-60 years old) males with some education and outdoor work; Group 2, working age females with some education and outdoor work; Group 3, working age male physicians with indoor work; Group 4, working age female physicians with indoor work; and Group 5, elderly (60 years and older) individuals. Seven to 8 participants were recruited for each FGD, the recommended number in literature.[11] The participants were recruited from the Philippine General Hospital by two study investigators (MGY and ABU). Table 1 shows the summary profile of the FGD participants.

All FGDs were conducted in Filipino (*Tagalog*) and took place in a quiet room with a facilitator (MGY) and a note-taker (ABU) who did both manual transcription and digital audiotaping of the sessions. Written informed consent was obtained from all participants. Each session commenced with the facilitator first explaining the purpose and outline of the FGD, after which the participants were asked to introduce themselves. The guide questions were formulated by a panel of three endocrinologists, two dermatologists, a health social scientist, an internist and a community medicine physician. These were constructed in a semi-structured, open-ended format (Table 2). Each participant was given a chance to speak, and both verbal and non-verbal responses were noted. The FGDs concluded with the facilitator summarizing the discussion.

The accuracy of the manual transcripts was verified and cross-checked with the digital audio recordings. The transcribed responses of the participants then underwent qualitative content analysis with quotations being listed anonymously. Both manifest and latent analysis of content data were done. Manifest analysis was first performed by identifying key themes and concepts in the transcripts, after which latent analysis was performed by putting data into categories, with relationships being generated and modified. Emerging themes and sub-themes were further identified by clustering the different categories.[12] The integration of data was based on words, context, frequency, intensity and extensiveness of comments, and specificity of responses. The analyzed FGD results were reviewed by the panel and were used to develop a conceptual framework. The version approved by the majority of the panel (50% + 1, or at least 5 members) was accepted as the final conceptual framework (Figure 1). All qualitative analyses were performed manually.

Ethical Considerations

The protocol was approved by the University of the Philippines Manila Research Ethics Board (UPMREB) prior to study commencement. A monetary incentive was provided to all participants as token honorarium.

RESULTS

The 5 FGDs included 38 participants. Each session lasted from 60 to 80 minutes, with the participants being generally cooperative. Females were observed to be more responsive than males; Group 5 participants (elderly) were noted to be the most responsive among all groups while

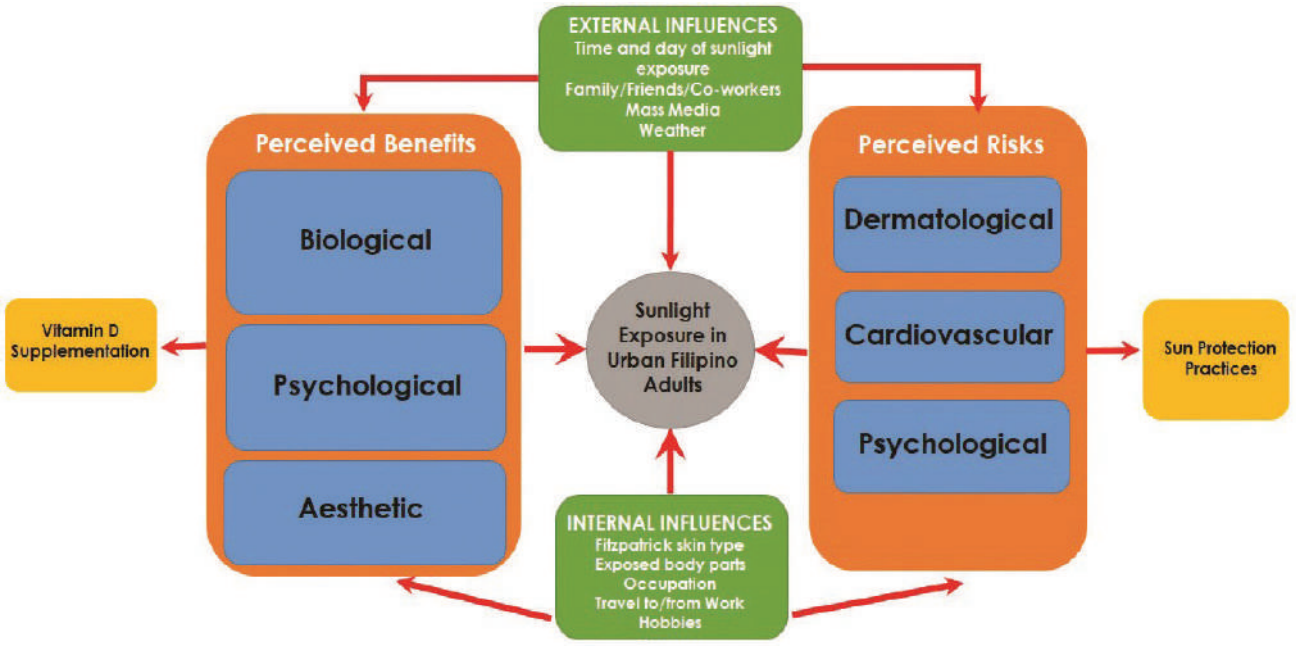

Figure 1. Conceptual framework on sunlight exposure in urban adult Filipinos.

Group 1 participants (outdoor males) were relatively more reserved. Those who attained higher levels of education (Groups 3 and 4) were more open in discussing their opinions. In terms of nonverbal responses, the female and elderly participants used more hand and arm gestures and eye contact while speaking compared to the male participants who were more soft-spoken.

The results of the FGDs are listed below using representative quotes to illustrate the way in which individuals participated in the discussions. Qualitative analysis revealed 4 key themes, each with 4 to 5 sub-themes (Table 3).

Table 3. Themes and sub-themes in the FGD

Theme	Subtheme
Internal influences on sunlight exposure	Fitzpatrick skin classification
	Amount of skin exposed to the sun
	Occupation
	Travel to/from work
	Hobbies
External influences on sunlight exposure	Time of the day exposed to sunlight
	Day of the week exposed to sunlight
	Family, friends, coworkers
	Mass media
	Weather conditions
Benefits of sunlight exposure	Biological benefits
	Psychological benefits
	Aesthetic benefits
	Vitamin D supplementation
Risks of sunlight exposure	Dermatological risks
	Cardiovascular risks
	Psychological risks
	Sun protection methods

Internal influences on sunlight exposure

Fitzpatrick skin type. Answers regarding skin type were elicited using the phrase *"kapag ang balat ay naaarawan"* ("when the skin is exposed to the sun"). These roughly corresponded to the Fitzpatrick skin phototype classification, which categorizes the response of different skin types to UV light.[13] The participants appeared to possess four Fitzpatrick skin types: Majority had Type IV ("sometimes burn, always tan") and Type VI ("never burn, always tan") skin types, while a few had Type I ("always burn, never tan") and Type III ("sometimes burn, sometimes tan") skin types.

Amount of skin exposed to the sun. When going out in the sun, males preferred short-sleeved shirts and either shorts or long pants while females preferred either sleeveless tops or short-sleeved shirts and either skirts or long pants. Thus, the face, neck, arms, and sometimes the legs were usually exposed. Some participants believed that this depended on the prescribed work attire.

> *"Sa kumpanya namin, bawal magtrabaho sa konstruksyon kapag hindi nakasuot ang* long sleeves, *bota, at* helmet.*"* ("In our company, it is forbidden to work at the construction site when not wearing long sleeves, boots, and a helmet.") (Male, Outdoor No. 3)

Occupation. A significant difference was seen in the duration of sunlight exposure between the outdoor (Groups 1 and 2) and the indoor and elderly (Groups 3, 4 and 5) participants. The former spent 30 minutes or more to five hours each day exposed to the sun due to the nature of their work. The latter spent as little as 5 minutes each day exposed to the sun and attributed their limited sunlight exposure merely to travel to/from work and errands, respectively.

> *"Dahil sa trabaho ko bilang* repairman *sa kumpanya ng telepono, nakabilad ako sa ilalim ng init nang halos buong araw."* ("Because of my work as a telephone company repairman, I am exposed under the heat for almost the entire day.") (Male, Outdoor No. 1)

Travel to/from work. Travel to work was considered a positive influence on sunlight exposure as most participants walked to work early in the morning and walked back home during late afternoon. Public transport was also perceived to allow more sunlight exposure than private transport.

> "*Pag nag-aantay ka ng* jeep, *nakabilad ka sa araw. Ganun din kapag sasakay ka ng* LRT. *Ang haba kasi ng pila."* (When you are waiting for a jeepney, you are exposed to the sun. The same is true when you are taking the LRT [light rail transit]. The line is so long.") (Male, Indoor No. 4)

Hobbies. Most participants preferred indoor activities such as shopping, watching television, and surfing the internet, making these a negative influence on sunlight exposure. Only a few engaged in outdoor hobbies such as jogging and outdoor sports.

External influences on sunlight exposure

Time and day of sunlight exposure. For all groups, sunlight exposure took place predominantly during early morning. For the working groups (Groups 1, 2, 3 and 4), this was due to travel from home to work. For the elderly group, this was due to daily activities such as going to the market and bringing grandchildren to school. Most participants reported no significant difference in sunlight exposure between weekdays and weekends.

> *"Mga* 7:00 *ng umaga, lumalabas ako para ihatid ang mga apo ko sa paaralan at mamamalengke pagkatapos noon."* ("Around 7:00 in the morning, I go out to bring my grandchildren to school and then proceed to the market after.") (Elderly No. 1)

Family, friends, and coworkers. The influence of family, friends, and coworkers on sunlight exposure was overwhelmingly negative, with most participants being advised to avoid the sun due to its harmful effects. A recurring theme was the risk of getting darker complexion in the female groups (Groups 2 and 4).

> *"Sabi ng nanay ko, huwag daw magpaaraw dahil nakakaitim. Dapat panatilihing maputi ang kutis kapag babae."* ("My mother said, don't get exposed to the sun because it causes darker skin. You need to maintain a fair complexion if you are female.") (Female, Indoor No. 2)

The elderly participants stated that sunlight exposure was heavily dependent on the type of activities they accompanied their younger family members to.

> *"Depende sa gustong gawin ng mga anak at apo ko. Kung gusto nila magpaaraw, sasama ako. Kung gusto nila pumunta sa* mall, *sasama din ako."* ("It depends on what my children and grandchildren want to do. If they want to go out in the sun, I would go with them. If they want to go to the mall, I would also go with them.") (Elderly No. 3)

Mass media. The influence of mass media on sunlight exposure was similarly negative. The participants believed that this is significant in Philippine society where fair skin is valued.

> (Verbatim in English): "They always advertise whitening products on TV. That's why no one goes out in the sun anymore." (Male, Indoor No. 1)

Weather. Most participants were willing to be out in the sun more during cloudy weather as opposed to extremely sunny weather, as they tried to avoid the heat.

> "*Mas maaliwalas kapag maulap. Ayokong lumabas kapag masyadong maaraw."* ("It's more comfortable when it's cloudy. I don't want to go out when it's too sunny.") (Female, Outdoor No. 5)

Perceived benefits of sunlight exposure

The perceived benefits of sunlight exposure fell under three categories: biological, psychological and aesthetic.

Biological benefits. For the participants, the purported biological benefits of sunlight exposure included favorable effects on bone health and faster recovery from illness. Conversely, many of them believed that lack of sunlight exposure is a detriment to the immune system and makes one sicklier.

> "*Kapag hindi ka nagpapaaraw, lalo kang madaling kapitan ng ubo't sipon."* ("When you don't get exposed to the sun, you'll be more prone to cough and colds.") (Elderly No. 6)

Psychological benefits. The psychological benefits of sunlight exposure included feeling happier and livelier. Some participants believed that this is due to increased physical activity when one is outdoors.

> "*Pakiramdam ko mas nagiging malungkot at matamlay ako kapag hindi naaarawan.*" ("I feel more sad and lethargic when I do not go out in the sun.") (Male, Outdoor No. 7)

Aesthetic benefits. The aesthetic benefits of sunlight exposure included getting a rosier complexion, which the participants attributed to improved circulation. Some participants with skin types that tan also believed tanning gave them a better and more "exotic" appearance.

> (Verbatim in English): "I look thinner and sexier. I also like the beauty of a tan." (Female, Indoor No. 3)

Vitamin D supplementation. Almost all participants did not take Vitamin D supplements, which they attributed to the abundance of sunlight in the Philippines. Some believed that supplements are effective only if partnered with sunlight exposure.

> "*Hindi ako umiinom ng* supplement *kung hindi naman kailangan. Maaari pa itong magdulot ng 'di magandang epekto sa katawan."* ("I don't take supplements if these are not necessary. They can

even cause harmful side effects to the body.") (Female, Outdoor No. 1)

"*Kailangan ng balanse. Magpapaaraw ka sa umaga at iinom ka ng* supplement *sa gabi."* ("There should be balance. You get exposed to the sun during the day and take supplements at night.") (Elderly No. 5)

Perceived risks of sunlight exposure

Similar to the perceived benefits, the perceived risks of too much sunlight exposure can also be classified under biological and psychological categories. However, the biological risks clearly fell under two sub-categories: dermatological and cardiovascular.

Dermatological risks. Most of the participants were familiar with and used English terms for the different dermatological conditions caused by too much sunlight exposure, such as "sunburn," "skin cancer," and "skin allergy." The exceptions were prickly heat rash (termed "*bungang-araw"*) and photoaging (termed *"pangungulubot ng mukha"* or "wrinkling of the face" by the participants.)

Cardiovascular risks. The cardiovascular risks of too much sunlight exposure included hypertension, dizziness and heat stroke. Some participants believed that this is caused by unfavorable changes in the body's circulatory system.

"*Kapag masyadong matagal sa ilalim ng araw, lalapot ang dugo mo at magiging* high blood." ("When you are under the sun for too long, your blood will become more viscous, leading to hypertension.") (Female, Outdoor No. 1)

Psychological risks. The psychological risks of too much sunlight exposure included discomfort from sweating and fear of getting darker skin. These were especially emphasized in the indoor female group (Group 4).

(Verbatim in English): "I feel uncomfortable when I am sweaty. I also develop low self-esteem when I get darker skin because in the Philippines, you can get bullied for that." (Female, Indoor No. 7)

Sun protection methods. The participants utilized different methods of sun protection. The use of caps and hats was a common feature of outdoor males. This group was also the only one not using sunscreen, as many thought these were only for women. Umbrella use, meanwhile, was found in most females. Active shade-seeking was a common feature of the outdoor groups due to the nature of their work. Shades or sunglasses were the least commonly-employed form of sun protection and were mostly worn for fashion purposes instead.

"Hindi ako gumagamit ng sunblock. *Di ba pangbabae lang 'yun?"* ("I don't use sunblock. Isn't it only for girls?") (Male, Outdoor No. 4)

(Verbatim in English): "It's a cultural thing to not actively seek shade because we are in a tropical country." (Female, Indoor No. 5)

Conceptual framework

The end result of the FGDs was a conceptual framework explaining the attitudes, behaviors, and beliefs of urban adult Filipinos on sunlight exposure (Figure 1). In general, sunlight exposure in urban adult Filipinos was influenced primarily by two main factors: internal and external. Internal factors included the Fitzpatrick skin type, amount of body parts exposed to sunlight, type of occupation, travel to/from work and hobbies. External factors included the time of the day and day of the week exposed to sunlight, weather conditions, mass media, and the influence of other people such as family, friends and colleagues. Both internal and external factors, in turn, led to perceived risks and benefits. Perceived benefits were biological, psychological or aesthetic; whereas perceived risks were dermatological, cardiovascular or psychological. The perceived benefits (or lack of) of sunlight exposure influenced an individual's attitudes towards Vitamin D supplementation, whereas the perceived risks of sunlight exposure influenced an individual's attitudes towards the need for sun protection.

DISCUSSION

In this study, we explored the attitudes, behaviors, and beliefs of urban adult Filipinos on sunlight exposure. Our study is unique in so far as no other qualitative research has been conducted in a similar setting and population to investigate concepts and notions about sunlight exposure. Urban residents were prioritized as air pollutants in cities absorb UVB, thus reducing the amount that reaches the earth's surface.[14] This may partly explain the lower serum 25-OHD levels consistently found in urban populations across Asia.[15,16]

The first theme involved internal influences on sunlight exposure in the participants, which are factors usually inherent to the individual. In terms of Fitzpatrick skin type, the participants' responses conformed to the general perception of Southeast Asian people being darker-skinned compared to Caucasians. Since melanin is known to absorb UVB, the former may require a greater degree of sunlight exposure to synthesize a comparable amount of Vitamin D.[17] Indoor occupations and hobbies negatively impacted sunlight exposure, while public transport positively impacted sunlight exposure. The influence of public transport was striking given the generally perceived lack of transport infrastructure in the Philippines.[18]

The second theme involved external influences on sunlight exposure, which are extrinsic to or non-modifiable by the individual. The relative constancy of the participants' sunlight exposure duration, regardless of day of the week or month of the year, conformed to the flat seasonal profile of tropical countries, in contrast to temperate countries with distinct seasons and climates. Family and friends, mass media and sunny weather negatively impacted

sunlight exposure, while cloudy weather positively affected sunlight exposure. The significant influence of family attested to the strong kinship and social ties of Filipinos.[19] The considerable influence of mass media, on the other hand, can be explained by urban residents having better access to technology compared to their rural counterparts.

The third theme involved the perceived benefits of sunlight exposure. These were grouped into three main categories: biological, psychological and aesthetic. One observation was the lack of a local term equivalent for VDD, as many participants attempted to come up with concepts such as "*kakulangan ng bitamina"* ("lack of vitamins") and "*panghihina ng buto"* ("weakening of the bones"). The fact that most participants did not take Vitamin D supplements was also another interesting observation given the widespread advertising of supplements in the Philippines.

The last theme involved the perceived risks of sunlight exposure, also grouped into three categories: dermatological, cardiovascular and psychological. While the dermatological and cardiovascular risks were consistent with scientific literature, the psychological fears of getting darker skin highlighted the common Filipino psyche of wanting to attain fairer skin, which is perceived as superior.[20] Sun protection practices, as a whole, were also more common in hotter climates. We found noticeable sex differences, with men preferring to use caps and women preferring umbrellas. Many participants, however, were not aware of the concept of sunlight protection factors (SPF) for sunscreens, given that a mere potency of SPF 8 has been shown to reduce Vitamin D production by as much as 90%.[21]

Member homogeneity is important to focus groups as it allows the individual participants to be more comfortable with each other, and in turn, achieve a high degree of group interaction.[22] However, the pressure to conform to the ideas of others may have also induced socially desirable behavior, which has been termed the "acquiescence effect" in literature.[23] In Filipinos, this is called *"pakikisama"* ("to go along"), and is evident in the fact that few dissenting opinions were noted in the FGDs.[24] Furthermore, the responses may have also been influenced by the fact that the sessions were conducted in the proximity of a health center, and as such, the participants possessed a relatively strong health-seeking behavior (although we did not have any data regarding health resource use). Strong health-seeking behavior is usually associated with higher levels of self-management.[25]

Aside from the physicians, the rest of the participants were also relatively well-educated (being at least high school graduates) and hence were relatively familiar with the concepts discussed. Many terms were expressed verbatim in English regardless of FGD group.

The study utilized both manifest and latent analyses of content data. Manifest data refers to the tangible or concrete surface content, while latent data involves the underlying meaning behind the actual information. The advantages of manifest analysis are its ease of use and reliability (as it is evaluated at face value), but at the expense of lower validity. Latent analysis, on the other hand, possesses stronger validity but requires greater comprehension skill. It also has lower reliability due to the possibility of multiple interpretations. Hence, combining the two analysis types enables qualitative researchers to draw from the strengths of both techniques.[26]

One limitation of the study was the lack of a pretest of the focus group instrument prior to the actual FGDs. Another was the performance of manifest and latent analyses by only one investigator, although the final analyzed results were reviewed, revised and eventually approved by the entire panel. Due to health reasons and logistic difficulties, we were also unable to recruit very elderly (above 70 years old) participants, one of the groups most at risk for VDD. Since serum 25-OHD levels were not tested prior to the FGDs, we were likewise unable to determine whether any of the participants have known VDD. Moreover, none of the FGD participants were night shift workers, and we were unable to recruit participants of other religions, such as *hijab*-wearing female Muslims.[27] According to the National Commission on Muslim Filipinos in 2012, Muslims are estimated to comprise 10.7% of the country's population.[28]

CONCLUSION

The attitudes, behaviors and beliefs of urban adult Filipinos on sunlight exposure are influenced by both internal and external factors that in turn lead to perceived risks and benefits. An increased awareness of these factors is necessary to establish future recommendations on proper sunlight exposure in this population. The study results will be used to develop and validate a culturally-appropriate sunlight exposure questionnaire.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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Endocrinology and Environment

27th – 30th September 2018
Royal Ambarrukmo Hotel, Yogyakarta-Indonesia

JOINTLY ORGANIZED By The ASEAN Federation of Endocrine

WELCOME MESSAGE

It is my honor and great pleasure to invite you to join us at The 16th Asia - Oceania Congress of Endocrinology (AOCE) that will be held on 27th - 30th September, 2018 at Ambarrukmo Hotel, Yogyakarta, Indonesia. The theme chosen for this important meeting is Endocrinology and Environment.
We are expecting a great number of attendees from all the member of FESAO (Federation of Endocrine Societies of Asia and Oceania) and also from other continents. Let's meet up and enhance our contact and friendship in this ancient city.

The scientific committee is currently putting together the program contents and it is going to be rich, inspirational and exciting. The conference aims to provide updated information and challenging evidences to all topics relating to endocrinology. In addition to the main sessions, we will be presenting a concurrent session designed specifically for family physicians, addressing their role in the treatment of endocrinology diseases. We will also be looking at current controversies and some special case considerations. To round out our program, we would like to also invites abstract(s) submissions that will be competed in form of oral and poster presentation.

Yogyakarta is truly a unique meeting destination. This and ancient city located in central Java and its ornate 18th - century royal complex, or kraton, encompasses the still-inhabited Sultan's Palace. The great Borobudur and Prambanan temple is easily reach from Yogyakarta City.

Since March 2016 Indonesian government has granted 169 countries for FREE Visitor Visa. Please check the list of countries and further details in Visa section. Block the dates and confirm your participation in one of the most unique spot in the world.

Looking forward to see you soon.

Chairman
President of PB PERKENI

IMPORTANT DATES

Deadline for Early Bird Registration	: 31st July, 2018
Deadline for Accommodation Reservation	: 30th June, 2018
Deadline for Abstract Submission	: 22nd July, 2018
Pre-conference Workshops & Courses	: 27th September, 2018
Opening Ceremony	: 28th September, 2018
Free Paper Session	: 28th – 29th September, 2018
AOCE Dinner	: 29th September, 2018
AOCE Business Meeting	: 27th September, 2018
Exhibition	: 28th – 30th, September 2018

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AGENDA

Pre Conference Workshops:

1. Diabetes	2. Thyroid	3. Osteoporosis	4. Obesity	5. Dynamic Function Tests in Endocrinology

CONFERENCE

1. Environmental influences of endocrine system:
   a. Nutrition, gut microbiotas and diseases
   b. Plastic-BPA: is it real threat to human
   c. Environmental obesogenic
   d. Endocrine disruptors impact on thyroid hormone function
2. Endocrinology of life cycle:
   a. Healthy aging: andropause and menopause
   b. Antioxidant
3. Reproduction:
   a. Transgender: where are we now
   b. Endocrine disruptor and infertility
   c. Diagnosis and management of infertility
   d. Endocrine problems in pregnancy
4. Emergencies in endocrinology:
   a. Acute adrenal insufficiency
   b. Diagnosis and management of hyponatremia and hypokalemia
   c. Myxedema coma overlooked: loop holes in diagnosis
   d. Endocrine problems in critically ill patient
5. Metabolic syndrome and Diabetes Mellitus:
   a. Young and very young DM
   b. Thinking like pancreas
   c. Bionic pancreas
   d. Erectile dysfunction: what is new
   e. Contraception choices in patient with endocrine problems
6. Thyroid:
   a. Anti thyroid drug vs I-131 ablation
   b. AITD: new finding of stimulating and blocking antibodies
   c. A risk based approach of thyroid nodule
7. Adrenal and pituitary:
   a. Growth hormone and steroid controversies
   b. Perioperative management of pituitary tumor
   c. Endocrine hypertension: diagnostic approach and treatment
8. Endocrinology Malignancies (Genetics and Epigenetics)
9. Endocrinology Educations:
   a. International Standardized in Endocrinology: is it possible
   b. Primary Health Care services of endocrine disorders
10. Endocrinology Therapy in the future:
    a. Beta stem cell therapy and telemedicine for endocrine disease
    b. Robotic Surgery
11. Bone and Calcium Metabolism
    a. Osteoporosis from endocrine perspective
    b. Hyperparathyroidism: new approach and treatment
    c. Vitamin D supplementation: what is new
12. New drugs development for DM/insulin new generation

CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Transient Pseudohypoaldosteronism in an Infant: A Case Report*

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Abstract

Transient pseudohypoaldosteronism is strongly linked to urinary tract infections complicating structural urinary tract anomalies. A 3-month-old baby girl with hyponatremia, hyperkalemia and metabolic acidosis associated with urinary tract infection and structural urinary tract anomalies was diagnosed with transient pseudohypoaldosteronism following elevated serum aldosterone and normal 17-hydroxyprogesterone level. Electrolytes normalized with corrections and antibiotic therapy. Clinicians should have a high index of suspicion for transient pseudohypoaldosteronism in an infant presenting with hyponatremia, hyperkalemia and urinary tract infection with or without associated urinary tract anomalies.

Key words: pseudohypoaldosteronism, urinary tract infection (UTI), urinary tract anomalies

INTRODUCTION

Electrolyte imbalances, such as hyponatremia and hyperkalemia, are emergencies, especially in small infants. These abnormalities may be due to impaired mineralocorticoid secretion or response. Some causes to be considered are congenital adrenal hyperplasia (CAH) or hypoplasia, isolated aldosterone deficiency, certain medications or pseudohypoaldosteronism (PHA), a rare syndrome of mineralocorticoid resistance.[1]

PHA can be classified into Type 1 and Type 2. Type 1 PHA is a rare condition characterized by renal resistance to the actions of aldosterone and is further sub-classified into primary and secondary (transient) PHA.[2] In Type 1 primary PHA, there is mutation in the mineralocorticoid receptor that causes end organ resistance to mineralocorticoids. Type 1 secondary or transient PHA is strongly associated with urinary tract infections (UTI) complicating structural urinary tract anomalies.[2,3]

We report a case of transient PHA in a 3-month-old baby with hyponatremic hyperkalemic metabolic acidosis to highlight that although rare, transient PHA should be considered as a differential diagnosis of hyponatremia and hyperkalemia in infants with UTI complicating structural urinary tract anomalies. Furthermore, it also points out that the existence of urinary tract infection complicating urinary tract malformations is a powerful predisposition for the development of transient aldosterone resistance.

CASE

A 3-month-old, previously well Chinese girl, presented with one-week history of diarrhoea followed by one episode of afebrile seizure. She was referred from a district hospital for further work up and management. Her birth history was also unremarkable. She was delivered at term with birth weight of 3.72 kg (75th centile) and length of 55 cm (97th centile) (Figure 1). She had been on exclusive breastfeeding for 1 month and then changed to infant formula. She was on multiple different brands of cow's milk formula in view of recurrent episodes of loose stool and excessive flatulence.

On examination, she was moderately dehydrated and tachycardic. Her weight was 6.2 kg (above 75th centile) and length of 61 cm (75th centile). Examination revealed ballotable right kidney. Initial laboratory investigations showed hyponatremia (117 mmol/L), hypochloremia (90 mmol/l), hyperkalemia (9 mmol/L) with metabolic acidosis. She required intravenous (IV) normal saline bolus (10 ml/kg) given at the district hospital and IV hydration with 5% correction over 12 hours. She was given one cycle of lytic cocktail with calcium resonium 6 hourly to correct the hyperkalemia. Her electrolytes normalized after 4 days of treatment. Stool culture for rotavirus and reducing sugar were negative. In view of the possibility of cow's milk protein allergy, she was commenced on extensive hydrolysed milk formula and subsequently responded well with resolution of

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**This case was presented as a poster at the Malaysian Endocrine and Metabolic Society Annual Meeting in Hilton Hotel, Kuala Lumpur, Malaysia, 19-21 May 2017.*

diarrhoea. She had no recurrent episode of seizure and her neurological examination was unremarkable with normal ultrasound scan of the brain.

Her urine culture grew *Enterobacter* and therefore, she was treated with 7 days course of cefuroxime. Ultrasound of kidney, ureter, and bladder (USG KUB) showed right duplex kidney with gross hydronephrosis and hydroureter, while a micturating cystourethrogram (MCUG) showed grade 5 vesicoureteric reflux on the right side.

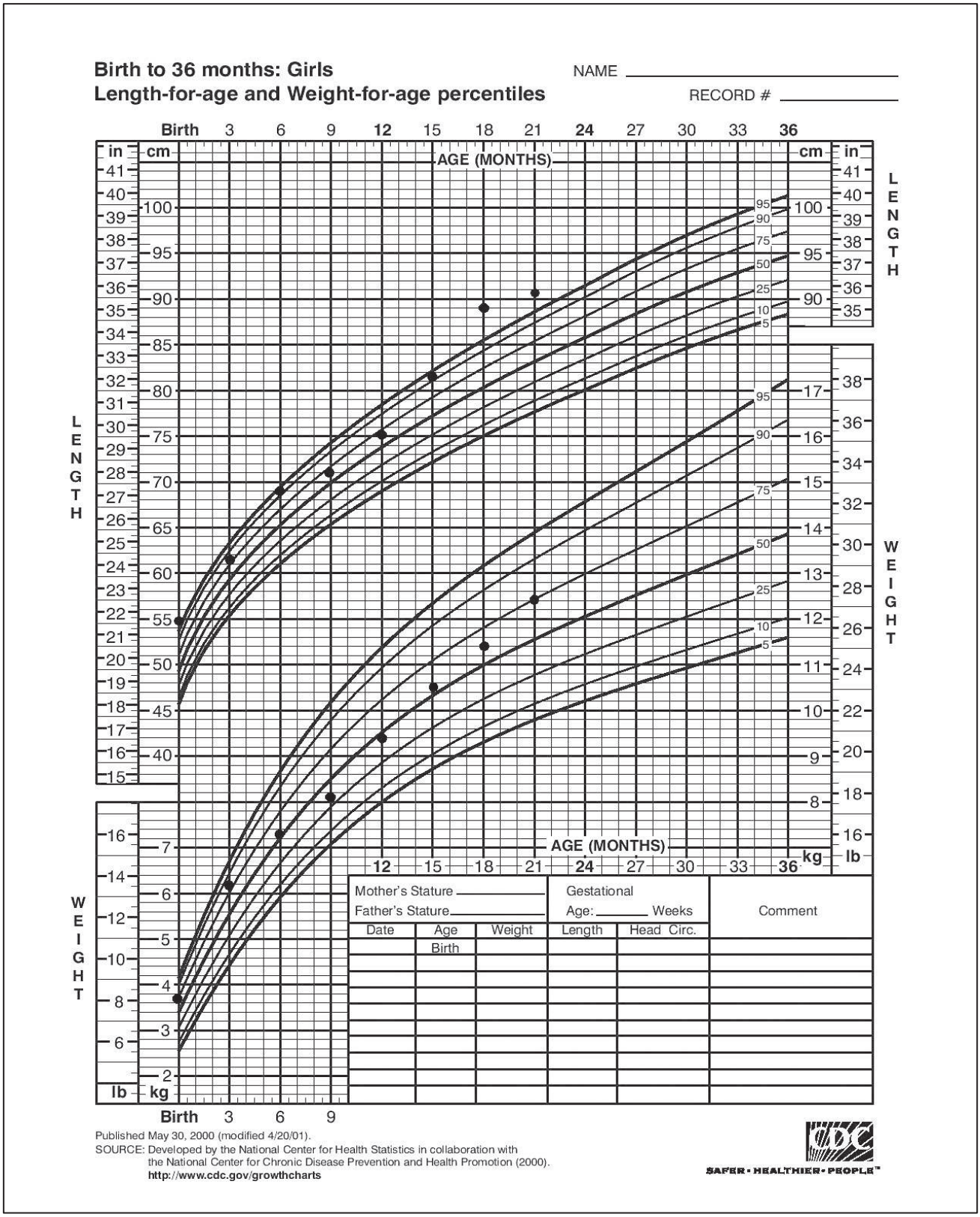

Figure 1. Growth chart from birth to 2 years old (downloaded from https://www.cdc.gov/growthcharts/clinical_charts.htm).

Routine screening for CAH is not done in our country. The diagnosis of transient PHA became apparent when the serum aldosterone level obtained on admission was elevated at 3700 pmol/l (normal range <1109 pmol/L) with normal 17-hydroxyprogesterone (17-OHP) level (0.8 nmol/L, reference range 1.0-14.12 nmol/L). Adrenocorticotropic hormone (ACTH) stimulation test was also normal. She was commenced on oral trimethoprim for urinary tract prophylaxis prior to discharge. She has no subsequent recurrent episode of electrolyte disturbances nor urinary tract infection as evidenced by negative urine culture post treatment. She is now two years old and currently under our follow up. Her growth is satisfactory with weight 12.4 kg (above 50th centile) and height 90 cm (90th centile). Her developmental milestones are appropriate and she is currently awaiting urethral implantation.

DISCUSSION

The primary function of aldosterone is reabsorption of sodium and water at the expense of potassium in the distal renal tubule. Deficiency of aldosterone or end organ resistance to its actions leads to hyponatremia, hyperkalemia, hypovolemia and metabolic acidosis. An elevated serum aldosterone level with hyponatremia and hyperkalemia in the absence of elevated 17-OHP level are the key findings to suggest Type 1 PHA. Type 1 PHA was first described in 1958 by Cheek and Perry.[4] Since then, reports on type 1 PHA have been published and genetic analysis has recently identified two different forms of type 1 primary PHA: Renal PHA 1 or autosomal dominant-PHA and Systemic PHA 1 or autosomal recessive-PHA 1.[1,2,5]

On the other hand, transient PHA with obstructive uropathy was first described by Rodriguez-Soriano et al., in 1983.[6] Watanabe in his review documented that all patients were younger than 7 months and 80% of them suffered from both urinary tract malformation and associated UTI similar to our case.[7] Some cases of transient PHA in infants with UTI who had urinary tract abnormalities were previously documented.[8,9] Schoen et al., also discussed that the resolution of all hormonal and electrolyte abnormalities was followed by successful treatment of UTI in infants, which was similar to our case.[10] Development of aldosterone resistance may be predisposed by the development of UTI complicating urinary tract structural anomalies.

Our case presented with afebrile seizure and dehydration due to diarrhoea and urinary tract infection. The most likely cause of her seizure was hyponatraemia. Diarrhoea usually causes hypokalemic metabolic acidosis with varying levels of serum sodium; hyponatremic or hypernatremic or normal depending on the loss of water and sodium. However, the result of her investigations revealing hyponatremic hyperkalemic metabolic acidosis had alerted us that there might be underlying urinary and endocrine pathologies. Thus, we proceeded with further laboratory and imaging studies to obtain a final diagnosis. Normal 17 hydroxyprogesterone level and ACTH stimulation test excluded CAH. The diagnosis of type 1 PHA was strongly suggested by an elevated serum aldosterone.

However, prompt diagnosis of transient PHA may be difficult since the aldosterone assay is normally sent to a reference laboratory and takes several days to obtain the results. Measurement of urinary sodium level prior to treatment may reveal excessive urinary sodium excretion which suggests aldosterone deficiency or resistance. Patient's presentation, laboratory studies, the existence of urinary tract anomalies and family history may help to differentiate between type 1 primary PHA from type 1 secondary, or transient PHA.

Our patient was diagnosed to have urinary tract infection with underlying gross hydronephrosis and hydroureter due to grade 5 vesicoureteric reflux on the right side and exhibited transient renal tubular resistance to aldosterone. After aggressive treatment, she has no subsequent recurrent episode of electrolyte disturbances nor urinary tract infection. We hypothesize that renal inflammation may cause transient tubular resistance to aldosterone independent of structural anomaly. The aldosterone resistance leading to salt wasting and high risk of recurrent urinary tract infection if the structural anomaly is not corrected may lead to failure to thrive in the future. However, our patient did not show any sign of failure to thrive with reasonably good growth. Treatment of transient PHA involves sodium chloride replacement, normalization of potassium level, antibiotic therapy and surgical intervention if indicated.

CONCLUSION

In conclusion, clinicians should have a high index of suspicion in diagnosing transient PHA in an infant presenting with hyponatremia, hyperkalemia and urinary tract infection with or without associated urinary tract anomalies typically if diagnosis of CAH was not found. Furthermore, in infants presenting with salt wasting, urine cultures should be obtained to investigate for underlying UTI.

Acknowledgments
The authors thank the parents and the patient for giving consent to use the patient's data.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

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None.

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Communicating Hydrocephalus in a Case of Long-Term Primary Hyperparathyroidism

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Abstract

We present the rare case of a 47-year-old woman with protracted primary hyperparathyroidism complicated by communicating hydrocephalus and cerebellar tonsillar herniation secondary to calvarial thickening. The parathyroid glands remained elusive, despite the use of advanced preoperative imaging modalities and three neck explorations. The serum calcium was optimally controlled with cinacalcet and alfacalcidol. Awareness of this rare complication is essential for early diagnosis and prompt intervention to prevent fatal posterior brain herniation.

Key words: cinacalcet, hydrocephalus, hypercalcemia, hyperparathyroidism, primary, osteitis fibrosis cystica

INTRODUCTION

Although hypercalcemia caused by primary hyperparathyroidism (PHPT) is common, advanced hyperparathyroid skeletal manifestations are now rarely encountered, due to the higher rate of early diagnoses and successful definitive surgical treatments.[1] Unfortunately, PHPT secondary to elusive parathyroid adenomas has remained a challenging entity, presenting a dilemma to endocrinologists managing these patients.[2] Here, we present a rare complex case of PHPT with elusive parathyroid adenomas complicated by florid advanced skull manifestations causing communicating hydrocephalus.

CASE

A 47-year-old female presented to our clinic with a 40-year history of persistent hypercalcemia secondary to PHPT. During the time that she was followed up in the endocrine clinic, corrected serum calcium ranged from 2.52 to 2.89 mmol/L [normal value (NV) 2.14-2.58], serum phosphate from 0.76 to 1.32 mmol/L (NV 0.74-1.52) and serum parathyroid hormone (PTH) from 9.73 to 13.9 pmol/L (NV 1.3-7.6). Her menstruation was regular.

She presented with facial deformities caused by multiple mandibular swelling at 8 years old. The investigations did not suggest McCune-Albright syndrome, familial hypocalciuric hypercalcemia or multiple endocrine neoplasia type 1 or 2a. There was no significant family history. She underwent two corrective surgeries for her mandibular deformities. Histopathologic examinations of the excised mandibular tissues confirmed the presence of brown tumors.

Preoperative imaging modalities included neck ultrasonography; angiography to assess the neck vasculature; selective parathyroid venous sampling; radioisotope bone scintiscan (with 12 mCi of technetium-99m methylene diphosphonate) or sestamibi imaging; and sestamibi imaging with single-photon emission computed tomography (SPECT). However, the discordant results of these advanced imaging modalities were not helpful in localizing the parathyroid glands. These issues provided valuable insights into the challenges during her three unsuccessful neck explorations at age 8, 12 and 40.

This patient was lost to follow up in 2000. Ten years later in 2010, she was admitted with acute cholecystitis secondary to cholelithiasis. She had an uneventful cholecystectomy. During admission, she was also assessed for complications of PHPT. Bilateral nephrocalcinosis, corneal calcifications and worsening skeletal manifestations of PHPT were found. The skeletal changes included periosteal bone resorption and acro-osteolysis of the hands (Figure 1). There was no evidence of fractures and renal dysfunction. A subnormal 25-hydroxycholecalciferol [25(OH)D] level of 41.1 nmol/L (NV 60.0-160.0) was also noted. Dual energy x-ray absorptiometry (DEXA) scan of the lumbar vertebrae and left hip demonstrated normal bone mineral density with z-scores of 0.4 and 2.8, respectively.

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At the time when the patient was diagnosed with PHPT, sodium dihydrogen phosphate was the medical treatment for persistent hypercalcemia. Subsequently, cinacalcet was added when it became available. Unfortunately, she experienced adverse adverse effects from cinacalcet: persistence of poor appetite, nausea and vomiting led discontinuation of the drug for one month. When cinacalcet was reinitiated, the dose was titrated upward gradually to the optimal dosage of 25 mg twice daily without severe adverse gastrointestinal effects. Ergocalciferol (vitamin D2), at a dosage of 0.25 μg daily (titrated based on the calcium level) was also started for her subnormal serum 25(OH)D level.

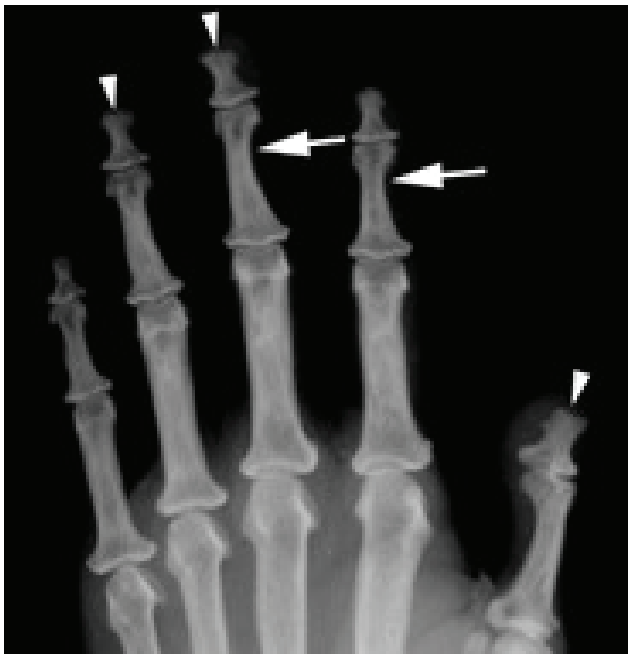

Figure 1. AP radiograph of the left hand, cropped to accentuate osseous detail. Areas of subperiosteal resorption are seen markedly at the radial aspect of the third middle phalanx, and subtly at the radial aspect of the second middle phalanx *(arrows)*. Acro-osteolysis is also evident at the distal phalanges *(arrowheads)*.

The patient was closely monitored for recurrent swelling and purulent discharge associated with mandibular osteomyelitis. Her alkaline phosphatase (ALP) levels remained relatively stable (600 to 870 U/L) for the first 24 years (NV 40-150 U/L). The subsequent two-fold to three-fold rise in the ALP (1,600 to 2,000 U/L) correlated with recurrent osteomyelitis in the mandible. Computed tomography (CT) showed thinning and sclerotic changes in the mandible with multiple lucent areas (Figure 2). Cystic lesions with well-circumscribed sclerotic margins were suggestive of brown tumors. However, in view of persistent osteomyelitis, no biopsy was carried out.

Hydrocephalus on CT was an incidental finding while monitoring the chronic mandibular osteomyelitis. Clinically, she was asymptomatic. She had no papilledema, neurological deficit nor any gait abnormality. Subsequent magnetic resonance imaging revealed a communicating hydrocephalus and diffuse calvarial thickening with intracortical tunnelling (Figure 3). This calvarial thickening caused a reduction in the posterior cranial fossa, including the foramen magnum. The resulting compression on the cerebellum and anterior cervico-medullary junction caused cerebellar tonsillar herniation. A ventriculo-peritoneal shunt was inserted with an uneventful post-surgical course.

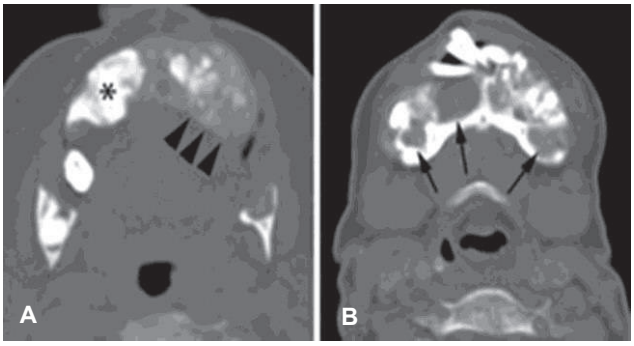

Figure 2. Cross-sectional CT of the mandible in bone algorithm at the level of the mandibular angles **(A)** and symphysis menti **(B)**. There is a loss of cortical and marrow differentiation. This has been replaced by a ground glass density, with areas of irregular osseous expansion *(arrowheads in A)* and patchy regions of osteosclerosis *(asterisk in A)*. Cystic lesions with well-circumscribed sclerotic margins *(arrows in B)* are likely Brown tumours, with evident dental displacement.

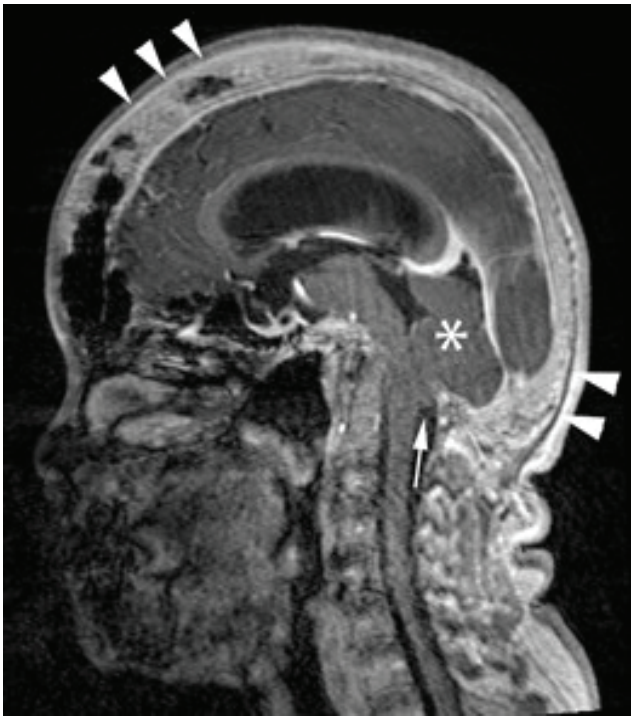

Figure 3. T1 post-gadolinium MRI in midsagittal reconstruction. Calvarial thickening, a known effect of hyperparathyroidism, is apparent *(arrowheads)*. Note the ventricular dilatation and the small posterior fossa *(asterisk)*. Cerebellar tonsillar herniation is depicted *(arrow)*.

DISCUSSION

The patient exhibited a complex clinical course with multiple disease complications due to elusive abnormal parathyroid glands. The most unusual and significant complication was the complex florid osteitis fibrosis cystica change in the skull. Diffuse calvarial thickening of the skull reduced the posterior cranial fossa and obliterated the foramen magnum, causing local compression on the cerebellum and anterior cervico-medullary junction, leading to cerebellar tonsillar herniation and communicating hydrocephalus. In contrast, the other only case of hydrocephalus was due to the local compression of a brown tumor secondary to PHPT in the maxilla.[3] In addition, the presentation of multiple mandibular brown tumors secondary to asymptomatic PHPT in a child of less than 10 years old has not been reported. Although the previous series of skull brown tumors consisted predominantly of women, they were young and middle-aged adults.[4] In a review of 16 cases involving brown tumors of the skull base, the mean age was 32 years old, and 75% of the patients were women.[5] In another case series of 22 patients with maxillo-facial brown tumors, 91% were women, with a mean age of 51 years old.[6]

The mechanism pertaining to these florid skull changes is not clear. Excess PTH results in an increase in osteoclastic resorption with subsequent fibrous replacement and reactive osteoblastic activity.[7] Osteosclerotic changes are an unusual feature of PHPT, and only 3 cases of multiple skull osteosclerotic lesions in PHPT patients have been reported. One was a 26-year old man with PHPT, while 2 women had coexisting vitamin D deficiency.[7,8] Diffuse and patchy osteosclerosis has been described in cases of secondary hyperparathyroidism in renal osteodystrophy and vitamin D deficiency.[9,10] This phenomenon has been postulated to be a disproportionate increase in the osteoblastic response after prolonged osteoclastic activity.[11] Our patient exhibited vitamin D insufficiency. In a previous cross-sectional study, vitamin D deficiency did not suggest any impact on the bone microarchitecture.[12] Therefore, the coexistence of vitamin D insufficiency (41.1 nmol/L) and prolonged PTH exposure could not fully account for the marked skull and skeletal manifestations.

Although the clinical presentation of PHPT has changed over the years due to early detection and treatment, the challenges of localizing and surgically removing elusive parathyroid adenomas have remained, as in our patient.[13] Abnormal parathyroid glands, variable anatomy and ectopic location of adenomas account for most of surgical failures.[14] In cases like ours, localization of the parathyroid gland is essential for preoperative planning.[15] Despite the availability of different advanced imaging modalities for targeted parathyroidectomies, there is still no clear consensus on the preferred imaging strategy.[16] Ultrasonography of the parathyroid glands has sufficient sensitivity (76 to 82%) to detect a single parathyroid enlargement in the neck, but has limited use in multiple gland hyperplasias, double adenomas, the presence of concomitant thyroid nodules and ectopic gland locations.[16] Therefore, ultrasonography alone was not sufficient in our patient given the presence of thyroid nodules, abnormal parathyroid glands, and the possible ectopic or unusual location.

Selective venous sampling has been available since the 1980s. Since our patient initially underwent an unsuccessful parathyroidectomy, angiography of the neck vasculature and selective venous sampling may have been beneficial. Unfortunately, together with the dual phase sestamibi scan and sestamibi scan with SPECT imaging modalities, the location of the parathyroid glands remained undetermined. Unusual anatomical location, multiple glands, and coexistent thyroid nodules may reduce the sensitivities of all these imaging modalities.

Inevitably, in such cases, medical treatment plays an essential role in lowering the serum calcium level and in bone protection.[17] Unfortunately, most pharmaceutical options have only been available in the last decade, with limited long-term outcome data. Sodium dihydrogen phosphate was the first oral therapy available before cinacalcet.[18] However, large and frequent dosing affected compliance, explaining the fluctuation of serum calcium levels in our patient. During the period when the patient was lost to follow up, her calcium control was suboptimal.

Cinacalcet has only been available recently. It appears to stabilize and maintain normocalcemia over time, but has no effects on the bone.[19] Moreover, adverse gastrointestinal effects may affect the optimization of the cinacalcet dose. In addition, a low vitamin D status has been shown to be associated with specific features reflecting more severe biochemical hypercalcemia in postmenopausal women.[12,20] Supplementing with high dose vitamin D has been shown to be safe in PHPT cases in a randomized controlled trial (RCT), with improvement in vitamin D status and decrease in PTH levels without increasing serum calcium levels.[21] While there have been no RCT evaluating the combination of cinacalcet and vitamin D supplementation, our patient benefited from this combination with an optimal reduction in her serum calcium level without adverse effects.

CONCLUSION

Severe calvarial osteosclerosis compressing the posterior fossa and causing communicating hydrocephalus due to persistent PHPT is rare. To the best of our knowledge, rare florid diffuse bony changes in the posterior fossa causing brain tissue compression and communicating hydrocephalus have not been previously reported in the literature. An awareness of this rare skull manifestation

causing posterior brain compression and communicating hydrocephalus is essential for early diagnosis and prompt intervention to prevent fatal posterior brain herniation.

The available medical options offer both advantages and drawbacks. Moreover, the considerable variation in protracted PHPT presentations necessitates individualized management. Continual active surveillance for unusual complications is essential for early detection and prompt treatment.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

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Successful Modified Desensitization Therapy with Analog Insulin in an Individual with Severe Allergy to Multiple Insulin Preparations: A Case Report*

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Abstract

We present a case of a 27-year-old female with T2 DM who developed allergic reactions after commencement of insulin therapy. Trial with different types of insulin resulted in a series of allergic reactions ranging from urticarial rash to development of angioedema, bronchospasm and anaphylactic shock. She was successfully treated with a modified insulin desensitization protocol using rapid-acting insulin.

Key words: insulin allergy, desensitization, excipients, T2 DM, insulin preparations

INTRODUCTION

Allergy to insulin has become rare with the advent of human insulin and its analogues. The incidence of insulin allergy is less than 1% in patients with diabetes. The diagnosis is based on clinical presentation and supported by skin or serological testing if available.

Insulin preparation requires additives such as protamine or zinc, which may act as a potential allergen. Therefore, allergy to insulin can be precipitated by the insulin molecule itself or carrier proteins.

Treatment options for insulin allergy include symptomatic therapy with antihistamines and use of alternative insulin preparation. Other therapeutic actions which have been reported include insulin desensitization using small doses of insulin or through a continuous subcutaneous insulin infusion (CSII), use of monoclonal antibodies (Omalizumab) and even pancreatic transplantation for severe, resistant cases.[1] We report a case of insulin allergy successfully treated using a modified insulin desensitization protocol.

CASE

A 27-year-old female with Type 2 Diabetes Mellitus (T2 DM) was initiated on insulin therapy for glucose optimisation for pre-pregnancy care. She was diagnosed with diabetes at the age of 25 years old and treated with Gliclazide (Diamicron MR) 90 mg daily and Metformin 1 gram bid. She has poor glycaemic control with a recent HbA_{1c} of 9.5%. There was no evidence of diabetes retinopathy, nephropathy or neuropathy.

Her initial insulin therapy included short-acting human insulin (Actrapid) and basal insulin (Detemir). She developed generalised urticarial rash 20 minutes after administration of short-acting insulin (Actrapid) and basal insulin (Detemir). She discontinued her insulin after developing similar reaction with subsequent insulin injections and resumed her oral antidiabetic agents. Her insulin regimen was switched to rapid acting insulin (Aspart) and basal insulin (Glargine) a month later during the clinic visit. Unfortunately, it resulted in anaphylactic shock, angioedema and bronchospasm requiring a hospital admission. She responded to rescue therapy with intravenous antihistamine, hydrocortisone and intramuscular adrenaline. While in the ward, trial with pre-mixed human insulin (Mixtard) resulted in bronchospasm which was relieved with intravenous hydrocortisone and antihistamine chlorpheniramine.

Further history revealed that she had previous allergies to gliclazide 80 mg tablet form, paracetamol and seafood. However, these allergies were confined to skin manifestation described as pruritus and urticarial rash. There was no similar history of allergy among her family members. None of her family members has asthma.

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During the trial period of insulin initiation, she was concomitantly maintained on oral antidiabetic agents. After unsuccessful attempts to initiate patient on different types of insulin (insulin Actrapid, Insulatard, Mixtard, Aspart, Detemir and Glargine), she was referred to our centre for insulin desensitization therapy.

Initial blood test in our centre showed eosinophils count of 0.4 (reference range <0.4) with a total IgE of 78 kU/L (reference range <70). Unfortunately, skin prick testing or allergy testing for insulin was not available at our centre.

In view of the previous history of anaphylactic reaction, her insulin regimen was commenced at a very low dose of rapid-acting insulin (Glulisine). Rapid-acting insulin (Glulisine) was diluted to achieve a dose of 0.0001 IU. The initial 4 doses (0.0001, 0.0001, 0.001 and 0.005 IU) was given as an intradermal injection at a 30-minute interval. Pre-medication therapy included antihistamine loratadine. She developed transient erythema and itchiness at the site of injection which subsided within few minutes. There was no further development of urticaria. Subsequent insulin doses were administered subcutaneously at an incremental dose of 0.01 IU every 30 minutes, achieving a dose of 0.1 IU on Day 1.

After successful desensitization with a very low dose of rapid-acting insulin (Glulisine) on Day 1 and considering patient's intention to conceive in near future, we switched her insulin to rapid-acting insulin (Lispro) as it has more safety data for use in pregnancy and better availability of rapid-acting insulin (Lispro) in the primary and secondary healthcare formulary near her hometown.

Desensitization therapy was continued using rapid-acting insulin (Lispro) at Day 2. We initiated low dose of rapid-acting insulin (Lispro) at 0.1 IU with an incremental dose of 0.05 IU every 30 minutes. Once her insulin dose reached a level of 0.5 IU, her incremental dose was given at 0.1 IU every hour achieving a maximum dose of 1 IU of insulin per injection. The incremental dose was given at 30 to 60 minute- intervals over a 12- hour duration for the first 2 days.

On day 3, rapid-acting insulin (Lispro) was given at 1 IU, 2 IU and 3 IU at 30- minute intervals. She was able to tolerate the slow increment of low insulin doses over the 3-day period without any allergic reactions.

On day 4, rapid-acting insulin (Lispro) was titrated to 4 IU tid and intermediate-acting human insulin (Insulatard) 10 IU was added at bedtime. A daily allowance of 12 IU of rapid-acting insulin (Lispro) and 10 IU of intermediate-acting insulin (Insulatard) combined with gliclazide (Diamicron MR) 90 mg od and metformin 1 g bid was achieved with blood sugar ranging between 7 to 13 mmol/L throughout the day.

The patient was referred back to her local clinic doctor with further titration of rapid-acting insulin (Lispro) and discontinuation of gliclazide (Diamicron MR) within 2 weeks.

DISCUSSION

Allergy to insulin is rare with a prevalence of 2% worldwide.[1] Although most allergic reactions are local and confined to the site of injection, systemic reactions involving generalized urticarial rash and anaphylaxis have been reported. These allergens include insulin molecule or excipients such as preservatives (i.e., metacresol), retardants (i.e., protamine sulphate), stabilizers (i.e., zinc), acid and base buffers, and isotonic agents (i.e., glycerol).[1,2]

The advent of analog insulin has reduced the incidence of insulin allergy. Allergenicity of insulin has been proposed by chemical changes in terminal B chains which have been modified in analog insulin.[1] It has been reported that the ability of analog insulin to reduce immunogenicity is associated with its rapid absorption rather than changes in the immunogenic epitopes itself.[1]

Treatment of insulin allergy includes antihistamine and use of alternative insulin preparation.

Allergy to insulin excipients is more common than allergy to the insulin molecule itself. Treatment includes replacing it with insulin without the suspected allergenic excipients. However, this may be difficult.

Wheeler et al., found that metacresol is universally present in available commercial insulin.[2,3] Metacresol is present in all insulin preparations (insulin Aspart, Detemir, Glargine, Actrapid, Insulatard, Mixtard, Lispro) tested on our patient, which suggests that it acts as a potential allergen. Previous reports have shown a dose-response relationship: the lowest reaction was seen with intermediate-acting Humulin NPH® (metacresol 1.6 mg/mL) and the most severe reactions were seen with rapid-acting insulin (Lispro and Glulisine) (metacresol 3.15 mg/mL).[2] A further intradermal test or specific IgE test would help to identify the allergen involved[5] but these tests were not available in our centre.

Options for treatment of metacresol allergy are limited. Past insulin preparations which did not contain metacresol, such as porcine insulins Monotard®, and Ultratard® are no longer available. However, since metacresol is present as a preservative in almost all commercially available insulins, desensitisation protocol is a reasonable approach.

The most common type of insulin allergy is related to an IgE-mediated Type 1 allergic reaction of the Coombs and Fell classification.[2] Type III Arthus type reaction is less frequent. In addition, insulin hypersensitivity can be

related to a T-cell mediated Type IV reaction. Desensitization is usually successful in IgE-mediated type 1 reaction, as in our case.[3,4]

There is no standard protocol for insulin desensitization regimen. Insulin desensitization can be in the form of micro doses of insulin, subcutaneous continuous insulin infusion (SCII) or low basal rate of intravenous insulin infusion running between 0.1 IU/hour to 0.3 IU/hour.[1]

The mechanism for tolerability of intravenous insulin infusion is unclear. Suggested mechanism includes different responses of the immune system to the route of insulin administration.[2] A simple mechanical explanation is due to the rapid distribution of the relatively small volume of insulin into a larger central venous circulation.[2]

A report by Pfohler et al., recommended an ultra-rush protocol with subcutaneous insulin application (0.004, 0.01, 0.02, 0.03, 0.1, 0.2, 0.5 and 1.0) with an injection interval of 30 minutes achieving intended insulin dose of 12 units by Day 3 with a decreased local reaction in a T2 DM patient with insulin allergy.[3] Desensitisation protocol by R Barranco et al., included an initial insulin dose of 0.001 IU with a cumulative dose of 9 IU by Day 3 without any pre-treatment with antihistamine.[5] However, upon further increase of insulin doses to 15 IU tid, oral antihistamine was added for local urticarial reaction.[5] Most of the insulin desensitization protocol included oral antihistamine. All these patients who underwent insulin desensitization protocol as reported by Claudia et al., and R Barranco et al., experienced mild local reactions despite insulin initiation at a low dose of 0.001 IU.

In view of previous allergic and life-threatening reactions experienced by our patient, we modified the insulin desensitization protocol to start at a very low dose of analog insulin and frequent administration of very low doses of insulin, given as an intradermal injection to allow for a stable desensitization and avoiding any detrimental side-effects. An increase in 5- to 10-fold insulin concentration was given at subsequent doses at 30-minute intervals on day 1. No steroid coverage was given as there was no visible rash noted and no hemodynamic instability during the therapy. Dose titration continued if the allergic reaction was transient. Patient eventually developed tolerance to rapid-acting insulin lispro and intermediate-acting insulin NPH insulin after 72 hours of desensitization.

In comparison to previous reports, our modified desensitization protocol given at a very low dose of insulin and frequent incremental dose for a total of 12 hour duration was tolerable with no obvious adverse reactions seen in our patient (Table 1). The mechanism is unclear. The time required for successful desensitization with any protocol varies according to patient, technique used and the availability of alternative treatment.[6] No steroid was used as the insulin was administered at very low doses and at 30-min intervals to allow successful desensitization.

Table 1. Modified insulin desensitization therapy

Time (hr)	Insulin Doses (IU)			
	Day 1	Day 2	Day 3	Day 4
0730	0.0001	0.1	0.5	1
0800	0.0001	0.25	0.75	-
0830	0.005	0.5	1	2
0900	0.01	0.75	2	-
0930	0.03	1	-	3
1000	0.05	1	-	-
1030	0.1	-	-	4
1100	0.2	1	2	-
1130	0.3	-	-	-
1200	0.4	1	-	4
1230	0.5	-	-	-
1300	0.5	1	2	-
1400	0.5	1	-	-
1500	0.5	1	2	-
1600	0.5	1	-	-
1700	0.5	1	2	-
1800	0.5	1	-	4
1900	0.5	1	2	-

Continued with Metformin 1 g BD and Gliclazide (Diamicron MR) 90 mg daily

Desensitization protocol in T1 DM patients with insulin allergy is more complicated as they require continuous insulin administration either via intravenous or subcutaneous infusion during the desensitization period in view of the state of absolute insulin deficiency.

The practicality and simple method of our modified desensitization protocol will be beneficial to T2 DM patients with insulin allergy.

There is no reported risk factors that can predispose patient to insulin allergy. Due to the rarity of insulin allergy and its excipients, it may not be feasible to conduct a controlled study of an insulin desensitization protocol.

CONCLUSION

Allergic reaction to insulin excipients which leads to systemic reactions such as anaphylaxis is rare. A modified desensitisation therapy proved to be successful in the management of allergy to insulin excipient in T2 DM patient.

Ethical consideration

All means have been exhausted to obtain patient consent to no avail. All patient identifiers have been removed.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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CASE REPORT

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Aldosterone-Producing Adrenocortical Carcinoma with Co-Secretion of Cortisol and Estradiol: A Case Report*

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Abstract

Aldosterone-producing adrenocortical carcinoma comprises less than 7% of all functioning adrenocortical carcinomas. We report a rare case of adrenocortical carcinoma with a clinical picture of primary aldosteronism and subclinical Cushing's syndrome and feminization. Complete surgical resection normalized blood pressures and aldosterone, cortisol and estradiol levels. Long-term monitoring is recommended with imaging and hormonal evaluation used as tumor markers for recurrence.

Key words: adrenal cancer, adrenocortical carcinoma, hyperaldosteronism, hypertension

INTRODUCTION

Adrenocortical carcinoma is a rare malignancy with an incidence of approximately one to two per million population per year.[1] Sixty two percent of adrenocortical carcinomas present as functioning tumors with the most common presentation being Cushing's syndrome or a combination of hypercortisolism and virilization.[2] Aldosterone-producing adrenocortical carcinoma is even more uncommon, comprising only ≤7% of all functioning adrenocortical carcinomas.[3] A complete hormonal evaluation is needed prior to surgery and is necessary to establish tumor markers for monitoring of tumor recurrence. Management involves complete surgical resection of the tumor followed by chemotherapy depending on the clinical staging. Lifelong monitoring for tumor recurrence is recommended. This report presents a rare case of aldosterone-producing adrenocortical carcinoma with cosecretion of cortisol and estradiol with a clinical picture of primary aldosteronism and subclinical Cushing's syndrome and feminization. A review of literature related to the diagnosis and management of adrenocortical carcinoma is also discussed.

CASE

An 18-year-old male presented with intermittent bilateral leg weakness and uncontrolled hypertension. He is a known hypertensive maintained on 5 antihypertensive medications. History started 3 years prior to admission when the patient was noted to have BP elevations, highest was at 140/90 mmHg, with no associated symptoms. Consultation with a pediatrician was done and he was prescribed with Amlodipine 5 mg OD and Metoprolol 50 mg OD which he only took for less than a month. No work-up was performed. Two years prior to admission, after undergoing high intensity volleyball training for 3 straight hours, the patient experienced weakness of both lower extremities which progressed to inability to move his lower extremities after a day. He consulted after 5 days and was admitted for hypokalemia (serum potassium 2.7 mmol/L) and hypertension (BP 180/100 mmHg). Serum potassium was corrected and he was discharged improved with the following medications: Amlodipine 10 mg OD and Metoprolol 50 mg OD. The patient was again not compliant with his medications and continued to experience intermittent body weakness until, 1 year prior to admission, the patient experienced loose bowel movement and was admitted and diagnosed to have amoebiasis. During this admission, the patient was again noted to have hypokalemia (serum potassium 2.7 mmol/L) and hypertension. Potassium correction and BP control were done. Further work-up showed mirror image dextrocardia and left atrial and ventricular enlargement on 2D echocardiogram and situs inversus with normal kidneys on ultrasound. The patient was discharged improved with the following medications: Losartan 50 mg OD and Potassium Chloride tablet TID and was told to follow up with a cardiologist. On follow-up, the patient was still noted to have BP elevations hence the following medications were subsequently added: Spironolactone 100 mg OD, Verapamil 180 mg OD, Clonidine 150 mcg OD, and Terazosin 5 mg OD. He was then referred to an endocrinologist for further work-up.

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Table 1. Co-secretion of hormones

	Result	Normal value
Plasma aldosterone	47.66 ng/dL	4.20 – 20.15 ng/dL
Plasma renin activity	0.04 ng/ml/hr	0.30 – 1.90 ng/ml/hr
Aldosterone-renin ratio	1,195	<20
24-hr urine free cortisol	131.20 ug/24 hrs	20 – 90 ug/24 hrs
Serum cortisol (1 mg dexamethasone suppression test)	2.8 ug/dL	<1.8 ug/dL
Basal ACTH	0.25 pg/ml	10 – 90 pg/ml
Estradiol	60.00 pg/ml	11 – 44 pg/ml

He has no headache, increased sweating, palpitations, weight changes, easy bruisability, moon facies, excessively oily nor acne-prone skin, hair loss over the axillary and pubic areas, decreased hair growth, nipple discharge, breast tenderness, decreased libido, or impotence. He is obese with gynecomastia and minimally scattered violaceous striae over the abdomen.

Given a young patient with uncontrolled hypertension on more than 3 anti-hypertensive medications, intermittent bilateral leg weakness and history of hypokalemia, the initial impression then was hypertension most probably due to primary aldosteronism. Thyroid function tests, creatinine, blood sugar, lipid profile, complete blood count, and ultrasound of the kidneys were all normal. A 2D echocardiogram showed mirror-image dextrocardia, left atrial and ventricular enlargement with normal ejection fraction. Laboratory tests showed an elevated plasma aldosterone concentration (PAC) of 47.66 ng/dL (normal value 4.20-20.15), suppressed plasma renin activity (PRA) of 0.04 ng/ml/hr (normal value 0.30-1.90), elevated aldosterone/renin ratio (ARR) (1,191.5), elevated 24 hour urine metanephrine (6.8 mg/24 hours, normal <1.0) and normal plasma free metanephrine (5.650 pg/ml, normal <90.00) (Table 1). Since the patient had undetectable renin, PAC >20 ng/dL and spontaneous hypokalemia, there was no need for confirmatory testing.[4] CT scan with adrenal protocol showed a well-defined, enhancing hypodense focus measuring 4.7 x 4.1 x 4.8 cm in the left suprarenal region, indenting on segment 6 of the right liver lobe (Figure 1). It has an average HU of 26 in the unenhanced phase, 52 HU in the adrenal/venous phase, and 35 HU in the delayed phase with an absolute washout of 65.4% suggestive of a lipid-poor tumor. The 24-hour urine free cortisol was elevated at 131.20 ug/24 hours (normal value: 20.00-90.00), nonsupressible cortisol after 1 mg dexamethasone (2.8 ug/dL, normal value < 1.8), normal basal cortisol (10.00 ug/dL), decreased basal ACTH (0.25 pg/ml, normal value 10-90), elevated estradiol (60.00 pg/ml, normal value 11-44) and normal DHEA-S (176.10 ug/dL, normal value 45.10-385). Since the patient was young (<age 35) with spontaneous hypokalemia, marked aldosterone excess, and unilateral adrenal mass, adrenal venous sampling was not performed before proceeding with adrenalectomy.[4]

Laparoscopic adrenalectomy was done with steroid coverage. The specimen weighed 62 grams and measured 7.0 x 6.4 x 4.3 cm (Figure 2A). Serial sections of the specimen showed a well-defined mass measuring 6.0 cm in its widest diameter. It has pink-tan to yellow soft cut surface with hemorrhagic areas (Figure 2B). Histopathologic diagnosis was malignant adrenal neoplasm (adrenocortical carcinoma versus pheochromocytoma) based on the Modified Weiss criteria.

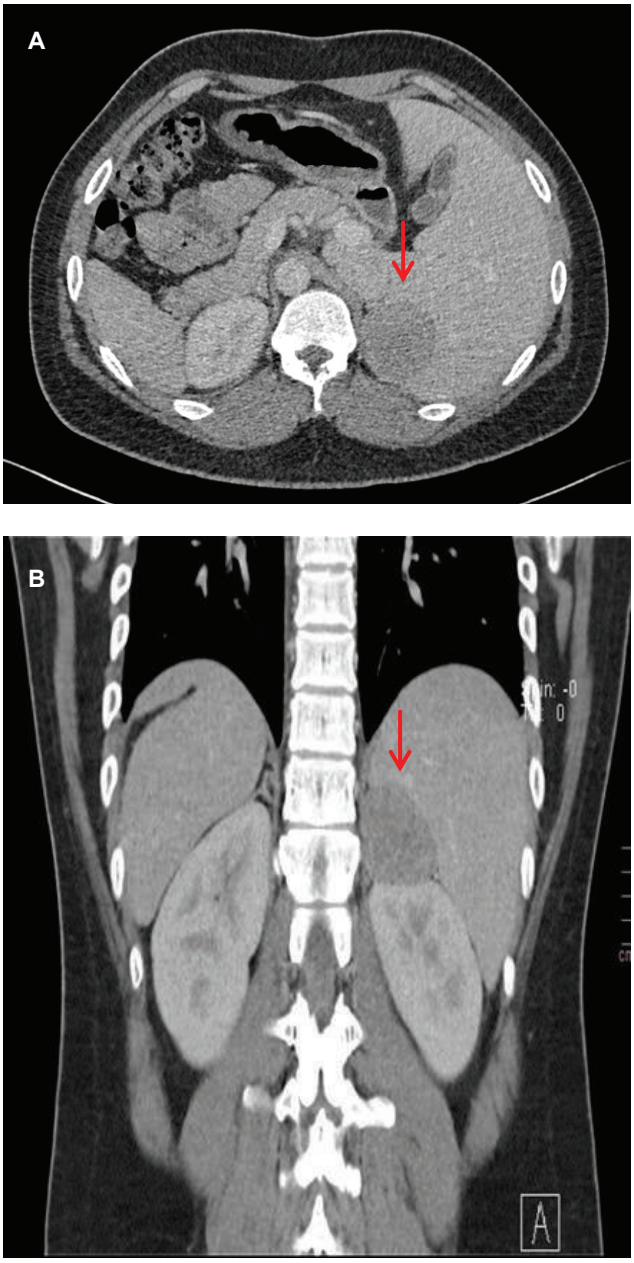

Figure 1. Computed tomography scans taken during the adrenal/venous phase (60 seconds after contrast injection). A well-defined, enhancing hypodense focus measuring 4.7 x 4.1 x 4.8 cm is seen in the left suprarenal region. **(A)** Axial view **(B)** Coronal view.

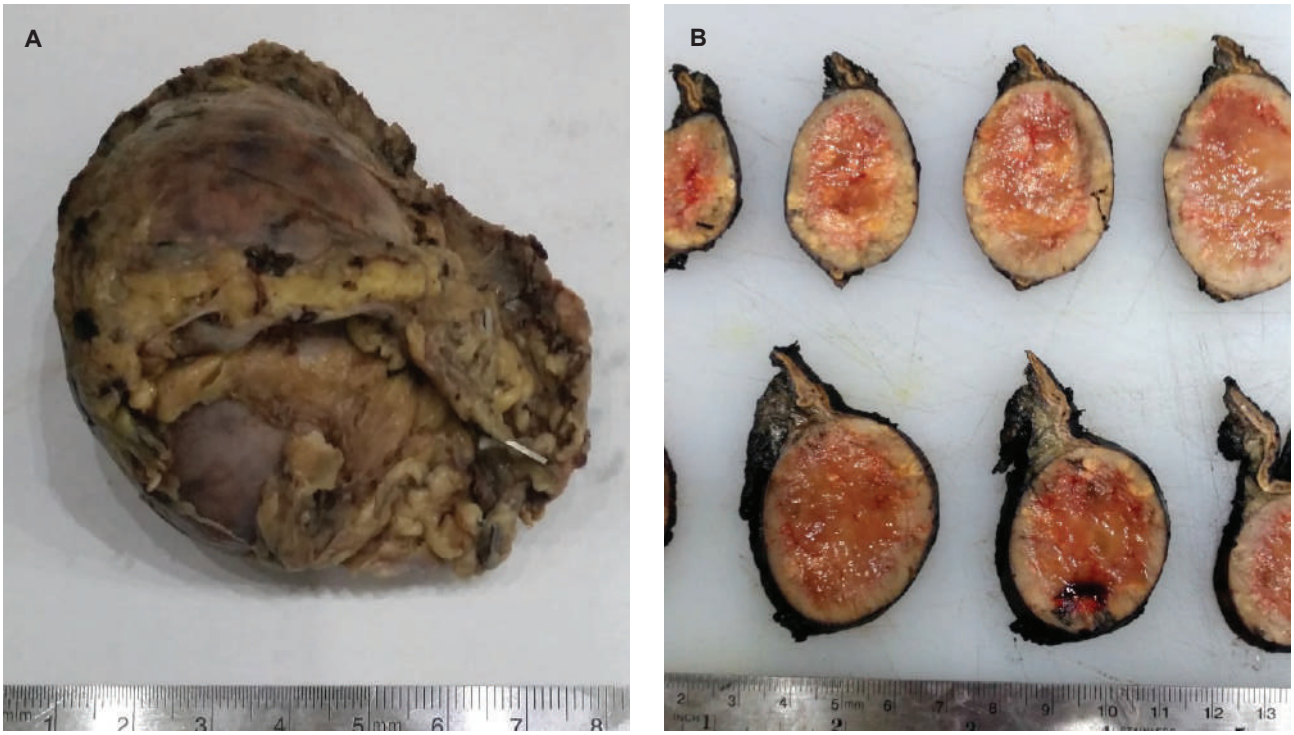

Figure 2. Gross appearance of the left adrenalectomy specimen. **(A)** The specimen weighed 62 grams and measured 7.0 x 6.4 x 4.3 cm, brown tan to gray and partially covered with fibrofatty tags. **(B)** Serial sections of the specimen showed a well-defined mass measuring 6.0 cm in its widest diameter with pink-tan to yellow soft cut surface and hemorrhagic areas.

Immunohistomorphology supported the diagnosis of adrenocortical caricnoma. The Ki67 index, a marker of proliferative activity, was 5-10%. No further treatment such as chemotherapy was done after complete surgical resection. His blood pressure decreased and aldosterone, cortisol and estradiol levels returned to normal. He was told to follow up regularly for monitoring of tumor recurrence.

DISCUSSION

Adrenocortical carcinoma is a rare malignancy with an incidence of 1 to 2 per million population per year.[1] The most common presentation of adrenocortical carcinoma is Cushing's syndrome or a combination of hypercortisolism and virilization. Only less than 40% would present as nonfunctioning tumors.[3] Aldosterone-producing adrenocortical carcinoma is even more uncommon presenting as uncontrolled hypertension and severe hypokalemia. The patient initially presented with uncontrolled hypertension and intermittent bilateral leg weakness due to hypokalemia. A high plasma aldosterone concentration and suppressed plasma renin activity confirmed the diagnosis of primary aldosteronism. Aldosterone-producing adenomas and bilateral idiopathic hyperplasia are the most common causes of primary aldosteronism. Only less than 1% are due to aldosterone-producing adrenocortical carcinomas.

Further evaluation showed a left adrenal mass with enhancement features suggestive of a lipid-poor tumor. The characteristics of the tumor on adrenal CT scan will help distinguish a benign from a malignant lesion. Adrenal tumors with irregular margins more than 4 cm, with more than 10 HU and less than 50% washout point to a probable malignant lesion. An adrenal mass that measures less than 10 HU on unenhanced CT, has the density of fat, and is most likely a benign adenoma. However, up to 30% of benign adenomas are considered lipid-poor and may be indistinguishable from non-adenomas.[5] The patient's adrenal mass had 26 HU and 65.4% washout, which were compatible with a lipid-poor tumor and therefore warranted further evaluation.

Complete hormonal work up is necessary in patients with suspected adrenocortical carcinoma even if clinical symptoms are absent not only for preoperative preparation but also because these can be used as markers for tumor recurrence. Autonomous hormone secretion can be expected in 80% of patients with adrenocortical carcinoma. There is a high likelihood that a large adrenal mass is not an adrenocortical cancer if autonomous steroid secretion is absent.[6] The pattern of hormone secretion may also point to the malignant potential of the lesion such as estradiol in males and virilization in females.[7] The patient had no feminizing symptoms such as decreased libido and erectile dysfunction but had mild gynecomastia on physical examination, which can be explained by his elevated estradiol levels. It is possible that the elevated estradiol level was due to aromatization of testosterone to estradiol in adipose tissue in an obese patient, however, normalization of estradiol after adrenalectomy confirmed that the tumor was secreting estradiol.

Although the patient had no signs and symptoms of hypercortisolism, hormonal evaluation showed elevated 24-hour urinary free cortisol, nonsuppressible cortisol after dexamethasone and decreased serum ACTH, consistent with subclinical Cushing's syndrome. This can be associated with the risk of postoperative adrenal insufficiency. Due to the variable hypercortisolemia and the rapid development of adrenocortical carcinoma, clinical features of Cushing's syndrome are often incomplete or even missing (atypical or subclinical Cushing's syndrome).[8] Preoperative preparation therefore entails glucocorticoid coverage in patients with Cushing's or subclinical Cushing's syndrome. Preparation is also needed for patients with tumors secreting metanephrines, therefore it is important to exclude a pheochromocytoma prior to surgery. The patient's 24-hour urine metanephrines were elevated but his plasma metanephrines were normal which made pheochromocytoma unlikely.

The histopathologic diagnosis of adrenocortical carcinoma is challenging as no single marker indicates malignancy. The Weiss criteria, with modification proposed by Aubert, is the most widely used diagnostic score. This includes high nuclear grade, >5 mitoses per 50 high-power fields, atypical mitotic figures, <25% of tumor cells are clear cells, diffuse architecture (>33% of tumor), necrosis, venous, sinusoidal and capsular invasion.[9] The presence of three or more criteria highly correlates with subsequent malignant behavior.

The patient's tumor showed a high nuclear grade, frequent and atypical mitotic figures, diffuse architecture and areas suspicious for capsular invasion and therefore fulfilled the Modified Weiss criteria for malignant adrenocortical neoplasm (Figure 3). The provisional histopathologic diagnosis was malignant adrenal neoplasm (adrenocortical carcinoma versus pheochromocytoma). Immunohistochemistry stains were requested to differentiate between the two tumors. The immunohistochemistry stained positive for inhibin which confirmed the adrenocortical origin of the tumor. S100, a marker for neuronal origin, and chromogranin, a marker for neuroendocrine differentiation were negative, which ruled out pheochromocytoma. The Ki67 index which is a marker for proliferative activity can be used to determine the aggressiveness of the tumor. It is the most powerful prognostic marker in both localized and advanced adrenocortical carcinoma to guide treatment decisions[6]. A Ki67 index more than 10% indicates high-risk adrenocortical carcinoma and would require more aggressive treatment after surgery such as adjuvant therapy with mitotane.[8] The patient's tumor had a Ki67 index of 5-10% which is classified as low-risk adrenocortical carcinoma.

All patients suspected of having adrenocortical carcinoma should have a thoracic CT scan prior to surgery for proper staging.[8] The TNM classification is used in the assessment of disease stage. Stages I and II are described as localized tumors with a size of 5 cm or smaller and larger than 5 cm, respectively. Stage III includes locally invasive tumors whereas stage IV consists of tumors with distant metastases. The 5-year disease-specific survival rates are 82% for stage I, 61% for stage II, 50% for stage III, and 13% for stage IV disease.[6] Complete surgical resection of the tumor is the cornerstone of treatment in all patients having localized and locally-advanced disease. The resection status is a major predictor of prognosis and a margin-free complete resection provides the only means to achieve longterm survival.[6] Adrenalectomy was also reported to initially cure both hypokalemia and hypertension in most cases of aldosterone-producing adrenocortical carcinomas.[3] Open adrenalectomy is the standard surgical approach to patients with stages I to III adrenocortical carcinomas. Laparoscopic adrenalectomy may be done in patients with small tumors of less than 8 cm without preoperative evidence for invasiveness and suspected to be only potentially malignant.[8]

For patients with complete tumor resection, regular follow-up every 3 months with abdominal and thoracic CT scans and monitoring of initially elevated hormones are recommended. Interval follow-up may then be increased after 2 years and should be continued for at least 10 years thereafter.[7]

The patient underwent laparoscopic adrenalectomy with steroid coverage due to preoperative findings of hypercortisolism. He was classified as stage II based on the size of the tumor which measured 6 cm in its largest diameter. No further treatment such as adjuvant chemotherapy was done after complete surgical resection since his Ki67 of 5-10% was classified as low-risk. His blood pressure decreased, serum potassium, aldosterone, cortisol and estradiol levels returned to normal. However, he was still advised to follow up regularly for monitoring of tumor recurrence.

CONCLUSION

Aldosterone-producing adrenocortical carcinoma is a rare malignancy often presenting with uncontrolled hypertension and hypokalemia. In the work-up of suspected adrenal carcinoma, complete hormonal evaluation is necessary even if clinical symptoms are absent. Clinical features of hypercortisolism are often absent due to the variable hypercortisolemia and rapid development of adrenocortical carcinoma. It is important to exclude hypercortisolism and pheochromocytoma as these require preoperative preparation. The pattern of tumor secretion and tumor characteristics on CT scan may point to the malignant potential of the tumor. Complete surgical resection is the cornerstone of treatment. Ki67 index is the most powerful prognostic marker to guide treatment decisions. Long-term monitoring is recommended with imaging and hormonal evaluation used as tumor markers for recurrence.

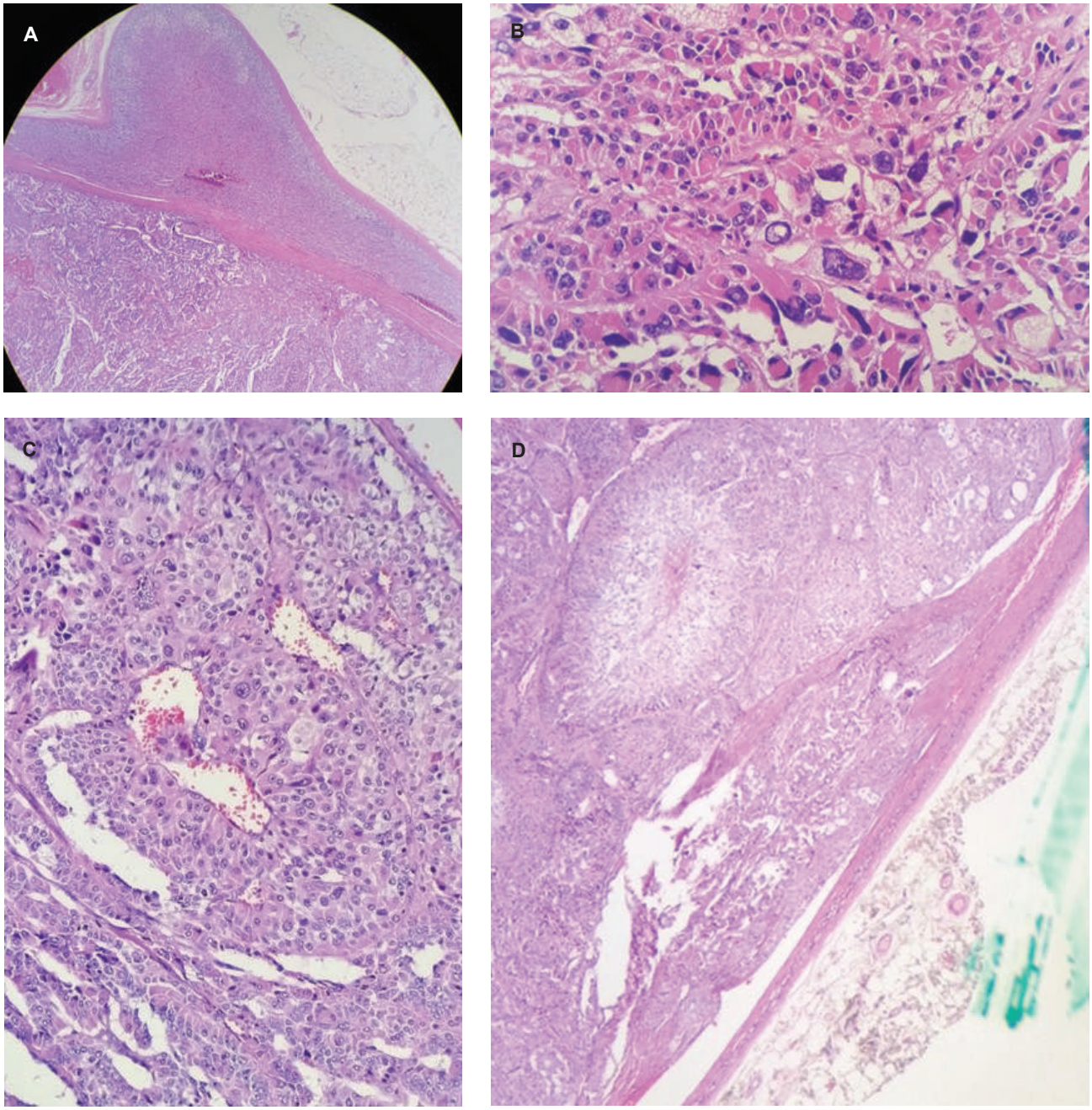

Figure 3. Histopathologic results of the left adrenal gland. **(A)** Uninvolved adrenal tissue and the encapsulated mass (H & E, 40x). The cells in the mass are arranged haphazardly compared to normal tissue. **(B)** Cells with marked pleomorphism, hyperchromatic nuclei and prominent nucleoli (H & E, 100x). **(C)** Areas with serpentine/ribbon-like arrangement of tumor cells with vascular channels within the tumor (H & E, 100x). **(D)** Areas suspicious for capsular invasion (H & E, 40x).

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Metastatic Bone Disease Secondary to Bronchial Adenocarcinoma in a Patient with Paget's Disease of the Bone*

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Abstract

A 69-year-old female complained of intermittent left hip pain for the past 3 years. Biochemical tests revealed normal serum calcium and phosphorus with markedly raised alkaline phosphatase. MRI of the hip revealed extensive marrow signal abnormalities at the left pelvic bone, while CT of the thorax revealed a spiculated lung nodule at the left lower lung lobe. In order to diagnose either primary, metastatic bone tumour or Paget's disease of the bone (PDB), an open biopsy of the left iliac bone was performed. The histopathology of bone biopsy of the left iliac bone was consistent with PDB. A CT guided biopsy of the lung mass done later revealed adenocarcinoma of the lung. She had ^{18}F-FDG PET-CECT Scan for staging evaluation and result was suggestive of new bony metastases. Patient was started on IV Zoledronic acid for treatment of the PDB. In view of the stage 4 lung adenocarcinoma with bony metastases, patient was scheduled for palliative chemotherapy.

Key words: Paget's disease of the bone, bronchial adenocarcinoma, metastatic bone disease

INTRODUCTION

Paget's Disease of the bone (PDB) is a chronic bone disorder characterized by focal areas of excessive osteoclastic resorption accompanied by a secondary increase in osteoblastic activity, resulting in abnormal bone structure, fractures and deformity.[1] The disease is often asymptomatic and commonly seen in an aging population. PDB typically affects more than one bone in the body with frequently affected bones include the pelvis, vertebrae, skull, femur and tibia.[2,3] The majority of the patients do not seek medical treatment unless there is associated pain or other related symptoms. Moreover, there are rarely neurologic complications associated with compression of intraspinal nerve tissues.[2] The simultaneous occurrence of PDB of the bone and bony metastases from adenocarcinoma of the lung in the same patient is uncommon.

CASE

A 69-year-old female with history of type 2 diabetes, hypertension and dyslipidemia complained of intermittent left hip pain for 3 years with constitutional symptoms. She denied any headache, hearing loss, tinnitus, back pain, joint pain or failure symptoms. There was no history of fracture, trauma or heart failure. On examination, she was unable to ambulate due to her left hip pain. There was no bowing of tibia or femur. Apart from her left hip, her musculoskeletal examinations of other joints and neurological examination were unremarkable. Biochemical tests revealed normal serum calcium and phosphorus with markedly raised alkaline phosphatase (Table 1). The initial differential diagnoses were osteoarthritis, osteoporosis, secondary metastasis or metabolic bone diseases. Her X-ray of the hip revealed diffuse sclerotic left pelvic bone and Magnetic Resonance Imaging (MRI) of the hip revealed extensive marrow signal abnormalities at the left pelvic bone (Figure1). The radiological images above were reported as primary, metastatic bone disease or other metabolic bone disorders like PDB. As part of workup of bony lesion in adult to rule out possibility of secondary malignancy, contrast enhanced computed tomography of thorax, abdomen and pelvis (CECT-TAP) were performed which revealed a spiculated lung nodule at the left lower lung lobe, suggestive of lung malignancy (Figure 2).

In order to ascertain the lesion being a primary, metastatic bone tumour or PDB, an open biopsy of the left iliac bone was done. The histopathology result of bone biopsy of the left iliac bone was later reported as Paget's disease of the bone (Figure 3). A CT guided biopsy of the lung mass was done later which revealed adenocarcinoma of the lung (Figure 4). She had ^{18}F-FDG PET-CECT Scan for staging

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Table 1. Biochemical investigations

Parameters	Results	Normal Range
Corrected Calcium, mmol/L	2.37	2.10-2.55
Phosphate, mmol/L	1.31	0.74-1.52
Alkaline Phosphatase (ALP), U/L	410	40-150
Creatinine, mmol/L	63	53-10
Magnesium, mmol/L	0.84	0.66-1.07
25 hydroxyl Vitamin D, nmol/L	22	<25, severe deficiency
free Thyroxine 4(fT4), pmol/L	12.91	9-19.05
Thyroid Stimulating Hormone (TSH), mIU/L	1.35	0.35-4.94

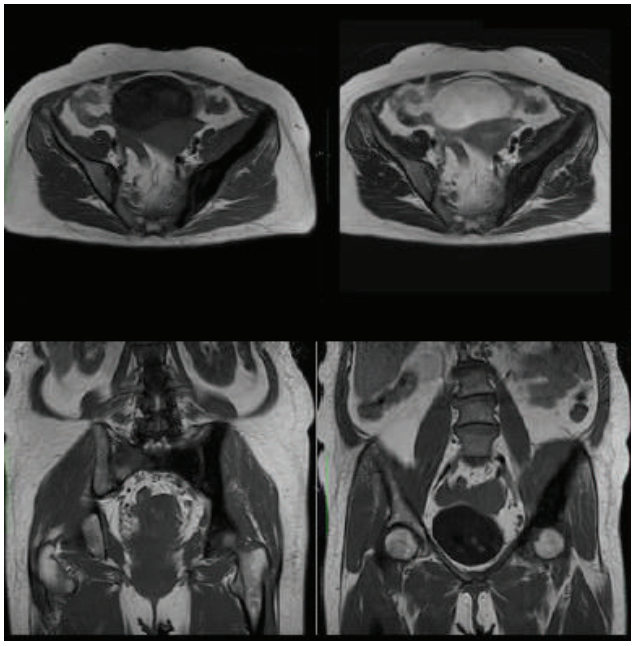

Figure 1. MRI of the hip revealed that there were extensive marrow signal abnormalities of left pubic bone with mild expansion seen in sacrum *predominantly left side seen at axial plane (above) and coronal plane (below)*. The findings were suggestive of primary or metastatic bone disease or other metabolic bone disorder like PDB.

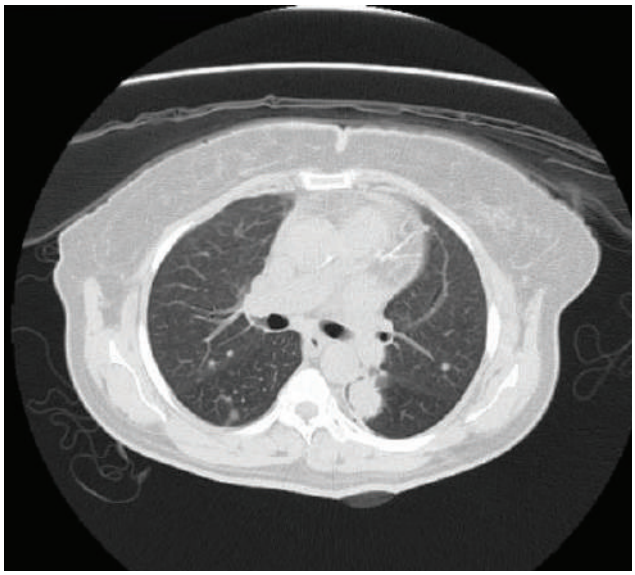

Figure 2. CE CT of thorax revealed that there was a spiculated lung nodule in the superior segment of left lower lobe, adjacent to the left oblique fissure, measuring 2.6 x 1.8 x 2.5 cm (AP x W x CC) associated with thickening of the adjacent left oblique fissure.

evaluation and showed intense tracer uptake in the left lower lobe of the lung with multiple mediastinal lymph nodes as well as right sacral bone, right ilium and bodies of L3-L5 suggestive of new bony metastases. There was also diffuse sclerosis of the left hemi pelvis (ilium, ischium and pubic bone) with minimal metabolic activity in keeping with PDB (Figure 5A and B). The final diagnosis was metastatic bone disease secondary to adenocarcinoma of the lung with underlying PDB. Dual energy X-ray absorptiometry (DEXA) scan was unable to be interpreted due to osteoblastic changes at the lumbar spine and hip. Her echocardiogram did not show any systolic or diastolic dysfunction.

Patient was initiated on high dose Vitamin D and subsequently IV Zoledronic acid for the treatment of the PDB. In view of the stage 4 lung adenocarcinoma with bony metastases, patient was scheduled for palliative systemic chemotherapy.

DISCUSSION

PDB is a chronic, progressive bone disease of unknown etiology with unevenly increased osteoclastic and osteoblastic skeletal remodelling. It is commonly diagnosed in northern Europe, North America, Australia, and New Zealand, but is rare in the Asia, including Malaysia.[4,5] About 3.7% of individuals of Anglo-Saxon origin older than the age of 55 are afflicted with PDB.[6-9] It rarely manifest itself clinically before age 40, and the frequency of the condition increases with advancing age. The disease can be divided into three phases of increasing clinical and radiographic severity: 1) initial resorptive/osteolytic phase, 2) mid-phase, mixed osteoblastic/osteoclastic hyperplasia and 3) late sclerotic phase.[10]

The diagnosis of the disease is based as a whole on clinical presentation, radiological findings and biochemical markers of bone turnover. Since PDB is a chronic progressive disease with minimal symptoms, there is a high possibility that the PDB was pre-existing and there were new bony metastases due to lung adenocarcinoma. Markedly elevated serum alkaline phosphatase (ALP) is a constant feature while calcium and phosphate levels are typically within normal limits. However, about 15% patients present with normal serum ALP level and isoenzymes of ALP.[11] On the other hand, metastatic bony disease can cause disruption of the normal homeostasis of bone which results in skeletal complications such as bone

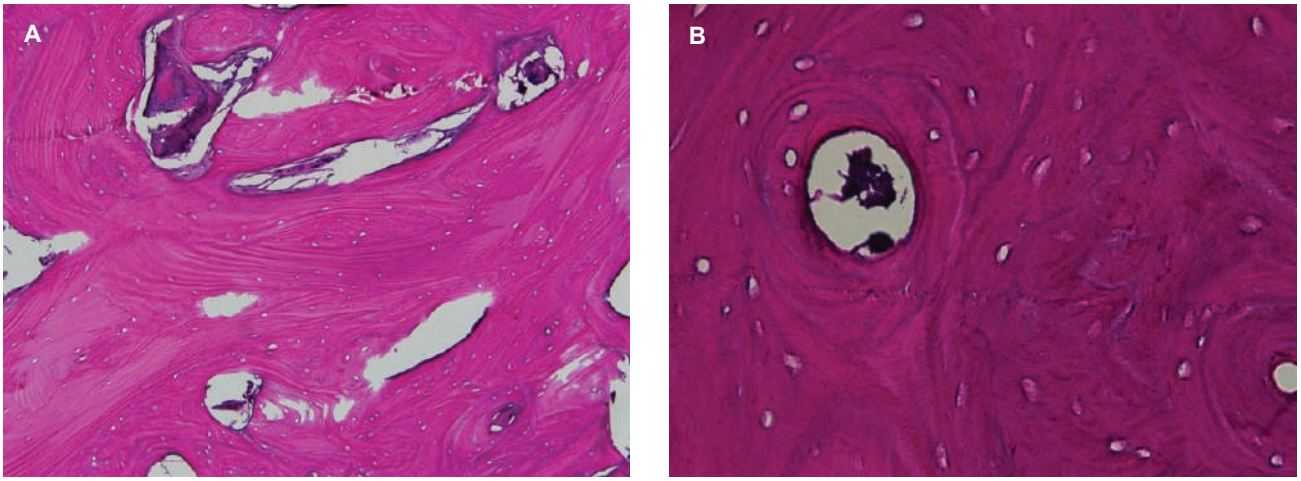

Figure 3. Histopathologic examination of the left iliac bone showed **(A)** thickening and disorganized trabecular pattern (H & E, 40x). **(B)** Cement lines along the coarsened and enlarged trabeculae are characteristically seen. The marrow was calcified and replacement of the marrow space by fibrous tissue was seen (H & E, 40x).

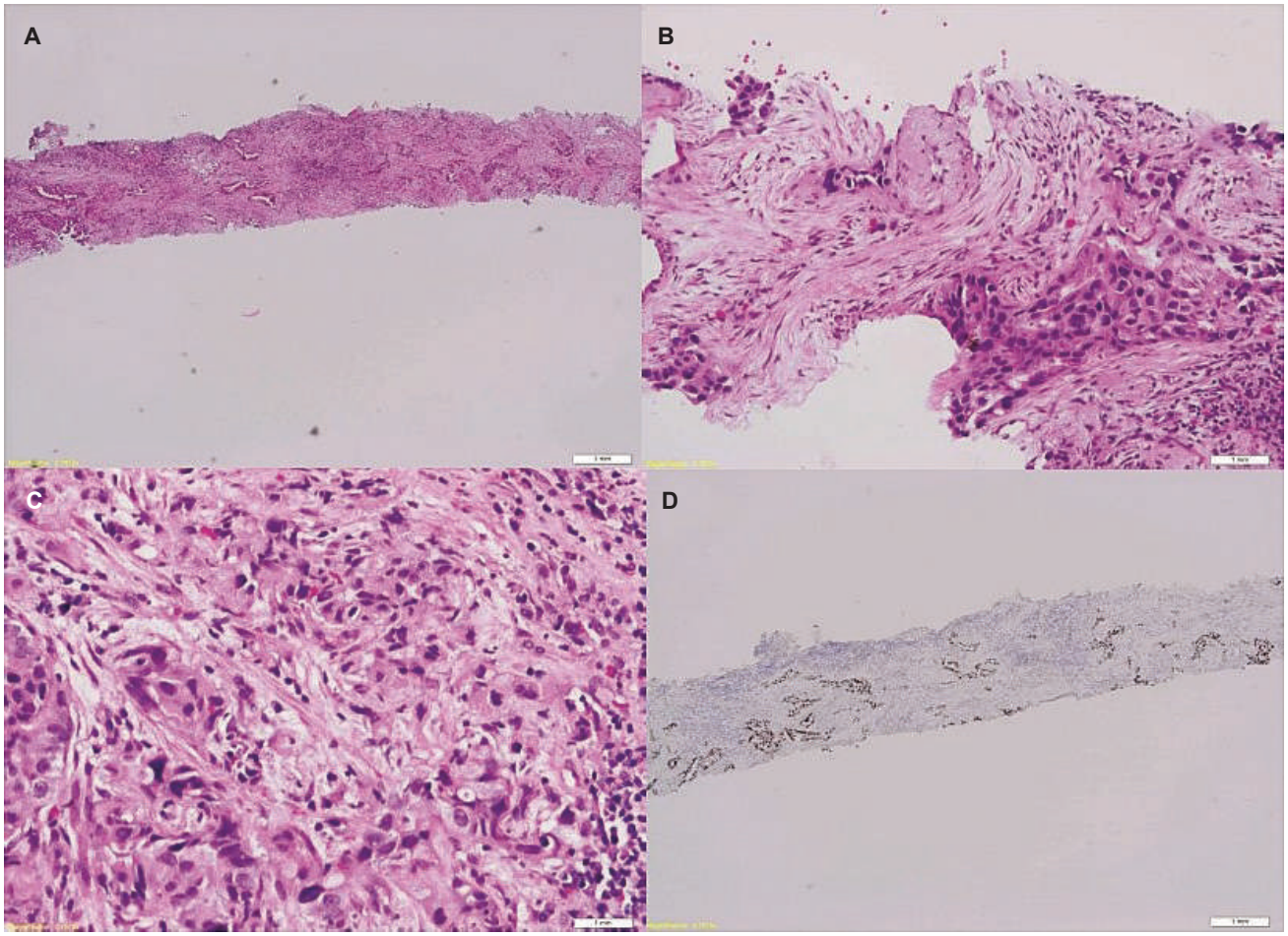

Figure 4. Lung biopsy showed moderately differentiated adenocarcinoma. **(A)**, **(B)** There were 2 fragments of fibrocollagenous tissue and alveolar tissue displaying infiltration by tumour cells in small cluster, glandular and single cell pattern (H & E, 10x, 20x) **(C)** The tumour cells exhibit moderate pleomorphism with hyperchromatic nuclei and moderate amount of eosinophilic cytoplasm (H & E, 40x) **(D)** Immunohistochemistry study shows the tumour cells are positive for transcription factor (TTF-1) (10x).

pain, fractures and paraneoplastic syndrome like hypercalcemia.[12] Serum ALP level, as mentioned above, can also be elevated in metastatic bone disease as the degree of ALP elevation is a general measure of metabolic activity. In PDB, the increased ALP not only correlates well with the changes on bone resorption but also the extent of skeletal involvement assessed from either radiographs or scintigraph[13] and the probability of

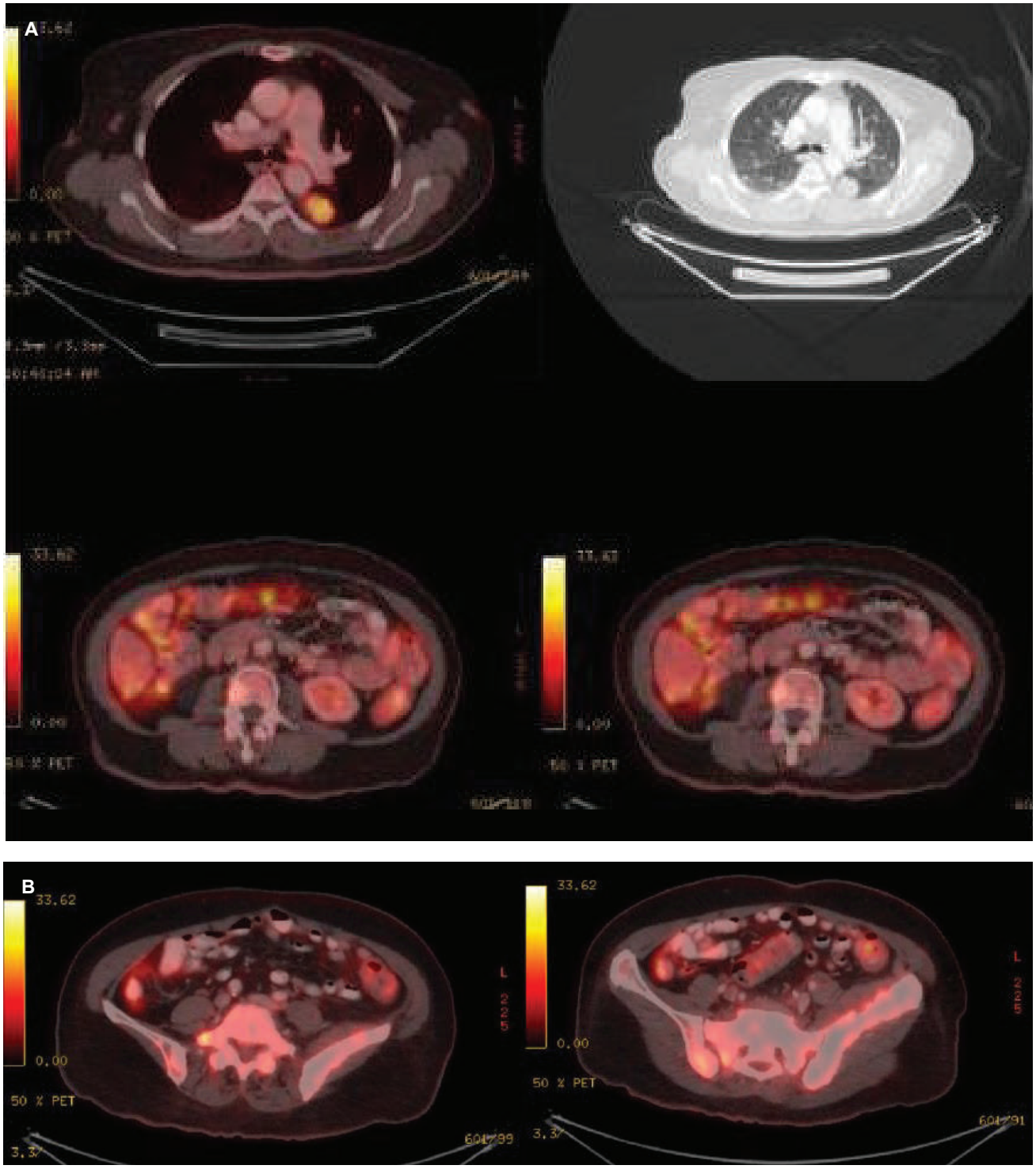

Figure 5. (A) ^{18}F-FDG PET/CT revealed that there was a hypermetabolic lung mass (SUV max 7.3) measuring 2.7x2.1x3.7cm at left lower lobe of the lung corresponded to the hypodense lesion at CT scan. There was a new hypermetabolic activity in patchy areas of lucency and sclerosis of the right side of sacral bone, right ilium, bodies of L3-L5 and right lamina of L5. **(B)** ^{18}F-FDG PET/CT revealed that there was diffuse sclerosis of the left hemi pelvis (ilium, ischium and pubic bone) with minimal metabolic activity in keeping with PDB.

achieving normal values with a potent bisphosphonate.[14] Serum amino-terminal propeptide of type 1 collagen (P1NP) as a measure of bone formation and resorption markers such as serum Beta C-terminal propeptide of type 1 collagen (bCTx) or urine N-terminal propeptide of type 1 collagen (NTx) provide accurate estimates of baseline bone metabolic activity and the response to treatment in patients with PDB.[14] The use of bone turnover markers including the bone formation and resorption markers has been investigated for diagnostic and prognostic purposes in advanced cancer patients.[12]

A single 5-mg dose of IV Zoledronate is the recommended choice of treatment in PDB. In two clinical

trials, Zoledronate comparing with risedronate showed Zoledronate provided a more rapid onset of action, and superior effects on quality of life, including pain relief.[15,16] A follow-up study that compared the duration of remissions with these two treatments showed that Zoledronate produced more frequent, more complete, and more sustained responses to therapy. It allowed normalization of bone turnover markers and improvements in quality of life for many years in most patients after only a single infusion.[16] However, potent bisphosphonates can produce symptomatic hypocalcemia in the presence of marked vitamin D deficiency. In those at risk of vitamin D deficiency, supplementation before treatment is advisable prior to treatment which was applied in our case.[9,17]

Patients with PDB presenting with bony metastases is rarely reported. Among the previously published cases that reported coexistence of PDB and metastatic bone disease, the primary sites of malignancy were the breast, lung, and prostate.[18-21] In our patient, the final diagnosis of metastatic bone disease secondary to adenocarcinoma of the lung was found after PDB was diagnosed by bone biopsy. As illustrated in the case, three modalities, including radiography, bone biopsy and ^{18}F-FDG PET/CT were utilized in the diagnostic process. The radiographic and bone biopsy findings and the elevation of the ALP level were compatible with PDB.

Bone biopsy is a minimally invasive procedure performed to evaluate bone abnormalities by sampling and detecting abnormal bone tissue. It is used in diagnosing any of the primary bone malignancy, secondary metastatic bone disease and metabolic bone disorders. The bone biopsy can be performed using fine needle aspiration technique, core biopsy technique or open biopsy technique wherein the region is removed for analysis. In the past, the histology of PDB had focused on iliac crest bone or vertebrae. Hyperosteoclastosis and poor definition of the boundary between cortical and medullary bone are the main histological findings in PDB.[22] Additionally, pagetic bone is also characterized by multinucleated osteoclasts with more than 12 nuclei per cell were frequently found at the trabecular surface. A typical appearance of deep resorption lacunae with the so-called swallowtail pattern also observed in the iliac crest biopsies.[23]

A previous report revealed no statistical correlation between ^{18}F-FDG uptake and the serum ALP level in patients with PDB.[24] Majority of patients with PDB revealed no abnormal ^{18}F-FDG uptake that suggested absence of relationship between increased osteoblastic or osteoclastic activity with the increased use of glucose.[24] Therefore, there is a potential to utilise different grade of ^{18}F-FDG uptake to discriminate between benign PDB and metastatic bone disase.[24] However, low-grade uptake may be seen in patients with more active disease indicated by higher ALP. Rarely, PDB could be a possible cause of false-positive scans in elderly patients who are being assessed for metastatic disease. Previous case reports of increased tracer uptake in Paget's disease mimicking metastasis in a case of malignant mesothelioma and rectal cancer have been reported.[25,26]

CONCLUSION

This case highlighted the possible coexistence of PDB and bony metastasis in a patient. Both diseases require careful evaluation to permit appropriate therapies to be instituted albeit for both conditions. Therefore, in cases which are of a diagnostic challenge, a bone biopsy may be essential to establish the diagnosis.

Ethical Consideration
Patient consent form was obtained before submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
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CASE REPORT

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'Houdini's Pituitary:' A Case Report of Regression of Pituitary Mass to Empty Sella in a 58-Year-Old Man with Autoimmune Hypophysitis

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Abstract

A 58-year-old male presented with persistent severe headache, lethargy, decline libido and no neurological deficits. Besides quadruple anterior pituitary hormonal deficiencies, magnetic resonance imaging (MRI) demonstrated an enlarged ring-enhanced non-homogenous pituitary. Following hormonal replacement, these symptoms improved but empty sella evolved. The challenges of diagnosis and management were discussed. Awareness of the unclear etiology and uncertain clinical course of autoimmune hypophysitis in a man in this age group is essential for prompt and appropriate management.

Key words: autoimmune hypophysitis, empty sella, hypopituitarism, older male, pituitary enlargement

INTRODUCTION

We described our experience in managing an uncommon case of autoimmune hypophysitis (AH) in a 58-year-old man. The initial clinical picture of quadruple anterior pituitary hormonal deficits and pituitary enlargement suggested the patient had macroadenoma but did not completely correlate with the presenting symptoms and the rate of evolvement to empty sella. The presence of AH in a man of this age group with a pituitary mass evolving to an empty sella within a short duration of seven months is rare. The etiology in this patient was a suspected autoimmune mechanism when we considered the unusual clinical course and the coincidental rate of regression of the enlarged pituitary to an almost empty sella.

CASE

A 58-year-old man initially had a three-month history of persistent severe headache, lethargy and decline in sexual function with no visual and neurological deficit. There were no drenching night sweats, unexplained weight loss, fever, abdominal discomfort, swelling on the neck, axilla or groin, arthralgia and joint swelling, myalgia or myositis, shortness of breath or cough. His past medical history was unremarkable with no history of autoimmune disorders or endocrinopathy. The baseline early morning serum cortisol level was low (<22 nmol/L) (N: 68-469) with a normal serum adrenocortical hormone (ACTH) level of 5.0 pg/mL (N: 0-46.0). Despite the subnormal serum luteinizing hormone (LH) 0.9 IU/L (N: 2.0-12.0) and the follicle stimulating hormone (FSH) of 1.9 IU/L (N: 1.5-14.0) at the lower limit of normal, the corresponding serum testosterone level of 1.71 nmol/L (N: 9.9-52.4) was also low. In addition, the low level of serum TSH (0.86 uIU/L) (N: 032-5.0) response was inappropriate to the low serum free thyroxine (T4) level of 9.26 pmol/L (N: 9.10-23.80). There was also a low growth hormone (GH) level of <0.15 mIU/L (N: 0.16-16.0) with normal prolactin level of 2.04 ug/L (N: 1.61-18.77) at presentation. Formal perimetry showed no visual field deficit. There was no diabetes insipidus. Anti-thyroid peroxidase (TPO) antibodies level was not raised at 20.4 IU/mL (N: 0-35). The full blood picture did not show any histiocytes. Chest X-ray also showed no mediastinal enlargement, pulmonary infiltrates or hilar lymphadenopathy in both the lung fields. However, serum angiotensin-converting enzyme was not sent as there was no suggestion of sarcoidosis from our clinical assessment. Moreover, this assay was not available in our institution, and the patient could not afford the additional cost of sending to another laboratory with the facilities.

Initial magnetic resonance imaging (MRI) demonstrated a 20 mm by 14 mm by 10 mm non-homogenous mass occupying the pituitary fossa. This enlarged pituitary mass (white arrow in A) is associated with suprasellar extension (Figure 1). There is a T1 hyperintense rim around the wall of the mass, with some more amorphous hyperintensities at a dependent location within the lesion core. These T1 hyperintensities could represent either methemoglobin or proteinaceous content. Polypoidal T1 hypointensity within the sphenoid sinus anteriorly (white

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arrowhead in A), which enhanced post-gadolinium (not shown), is attributed to reactive inflammation. No appreciable enhancement of this mass was detected, nor was there evidence for a thickened pituitary infundibulum or hypothalamus. This initial MRI features of the enlarged pituitary, no thickening of pituitary infundibulum or hypothalamus, the negative clinical screening test for autoantibodies, sarcoidosis, tuberculosis, lymphoproliferative disorders and other granulomatous lesions suggested a macroadenoma.

Correction of the hormonal deficit was the priority as our patient did not have compression of the optic nerve leading to visual field deficit. A physiological dose of hydrocortisone (10 mg am and 5 mg at noon) and oral levothyroxine of 75 mcg daily were commenced. Intramuscular testosterone 250 mg every three weeks was also initiated. His symptoms improved with the hormonal replacement therapy, which correlated with the improvement in his repeated hormonal profile. After the hormonal treatments for more than six months, the free T4 level improved to 16.72 pmol/L with only a minimal decline in the serum TSH level (0.27 uIU/L) and an improvement in serum testosterone of 49.8 nmol/L. His early morning serum cortisol level remained at <0.22 nmol/L. During this interval period, he denied any symptoms, such as syncope and severe headache, nor there was a new hormonal deficit to suggest pituitary apoplexy.

An MRI of the pituitary was repeated seven months following clinical improvement with hormone replacement therapy. Despite the absence of visual field deficit, reassessment of the size of pituitary mass is important for the determination of the subsequent treatment course. This follow-up MRI showed a drastic regression of the pituitary mass (Figure 2). While the T1 hyperintense "bright spot" of the posterior pituitary is appreciated (white arrowhead in A), much of the anterior pituitary appears to be flattened against the seller floor (white arrow in A). The optic chiasm prolapsed directly and inferiorly into the sella from its normal suprasellar location (black arrow in B), possibly reflecting traction due to post-inflammatory fibrotic process. Predominantly cerebrospinal fluid-filled pituitary fossa and the resolution of the inflammatory changes within the sphenoid sinus is also noted. A third MRI six months later revealed similar features of an empty sella. Formal perimetry assessments on both follow-up assessments did not show any visual field deficit.

DISCUSSION

The gender, the age of our patient at diagnosis and regressing pituitary mass to an empty sella without any neurological deficit or worsening of hormonal status is unusual.[1] We diagnosed AH clinically with the exclusion of other important causes of enlarged pituitary: lymphoma and granulomatous hypophysitis. Our patient was assessed and screened clinically with clinical history, physical examination and relevant biochemical, endocrinological, hematological and radiological investigations for the above problems. In addition, the clinical course of improved symptoms and well-being with a physiological dose of hydrocortisone as well as the initial inflammation with subsequent fibrosis in the empty sella (Figures 1 and 2), suggest an autoimmune inflammatory etiology in the pituitary. Moreover, the features of pituitary regression in the serial MRIs (Figures 1 and 2) appeared to be similar to the changes of AH induced in mice leading to pituitary atrophy and secondary empty sella.[2] In contrast, pituitary enlargement secondary to lymphoma or sarcoidosis have other clinical features and will require definitive chemotherapy or high dose corticosteroids respectively.

AH is a rare autoimmune inflammation of the pituitary gland. Majority, 90%, of AH are women (woman: man 6: 1-8: 1) with 90% premenopausal.[1,3] There is a preponderance of women in late pregnancy and first six months of postpartum. The average age at diagnosis is 35 years for women and 45 for men.[1] Sporadic cases have also been reported in children, men, and the elderly.[4] No family or ethnic predisposition has been described. This rate of regression to empty sella in AH (three to seven months) has been reported in postpartum, young women and a younger man but not in a man of this age group.

The symptoms and hormonal deficits in our patient were consistent with adenohypophysitis, the most common manifestation of AH. In addition, the affected pattern of corticotrophs, gonadotrophs, somatotrophs, and thyrotrophs were also like most of the previously reported cases.[5] Other manifestations not found in our patient, for example, involving the infundibular stem, the posterior lobe of the pituitary gland (infundibuloneurohypophysitis) or the whole pituitary (panhypophysitis) are less common. In addition, adenohypophysitis preceded both infundibuloneurohypophysitis and panhypophysitis has also been reported.[3]

The presenting clinical features in our patient, his hormonal profile of the anterior pituitary and the secondary target organs suggested a primary pituitary dysfunction. Despite the low early morning serum cortisol level (<22 nmol/L), there was no paradoxical increase in the serum ACTH level which remained at 5.0 pg/mL. Similarly, the low level of serum free T4 (9.26 pmol/L), serum testosterone (1.71 nmol/L nmol/L) were not associated with a raised serum TSH level (0.86 uIU/L), serum LH (0.9 IU/L) and FSH (1.9 IU/L) respectively. This suggests secondary hypocortisolism (cortisol <22 mmol/L; ACTH 5.0 pg/mL), secondary hypogonadism (LH 0.9 IU/L, FSH 1.9 IU/L, serum testosterone 1.71 nmol/L), and secondary hypothyroidism (TSH 0.86 uIU/L, serum free T4 9.26 pmol/L) at baseline. A normal serum prolactin level (2.04 ug/L) ruled out a stalk effect of the pituitary gland. Taken together with the low serum GH level

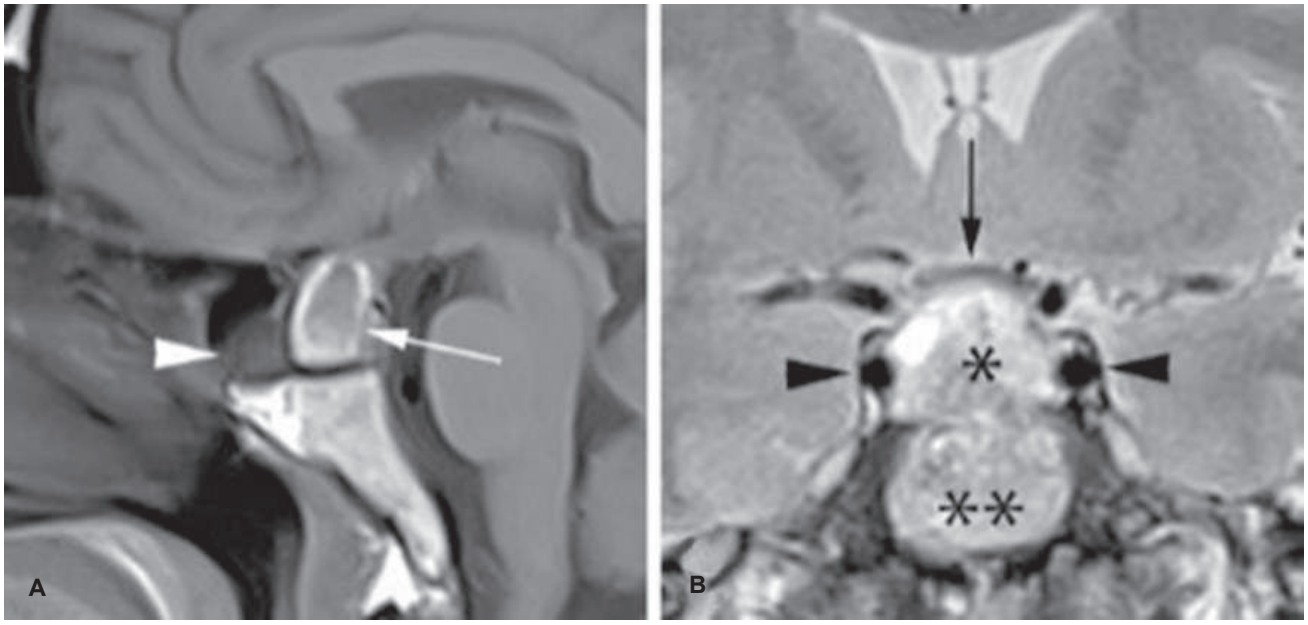

Figure 1. First pituitary MRI, T1-weighted midsagittal image without contrast **(A)** and T2-weighted coronal image **(B).** Heterogeneous pituitary mass but predominantly high signal at T2-weighted sequence *(single asterisk in B)*. Its suprasellar component causes compression & mild upward displacement of the optic chiasm *(black arrow in B)*. Double asterisks indicate the basisphenoid.

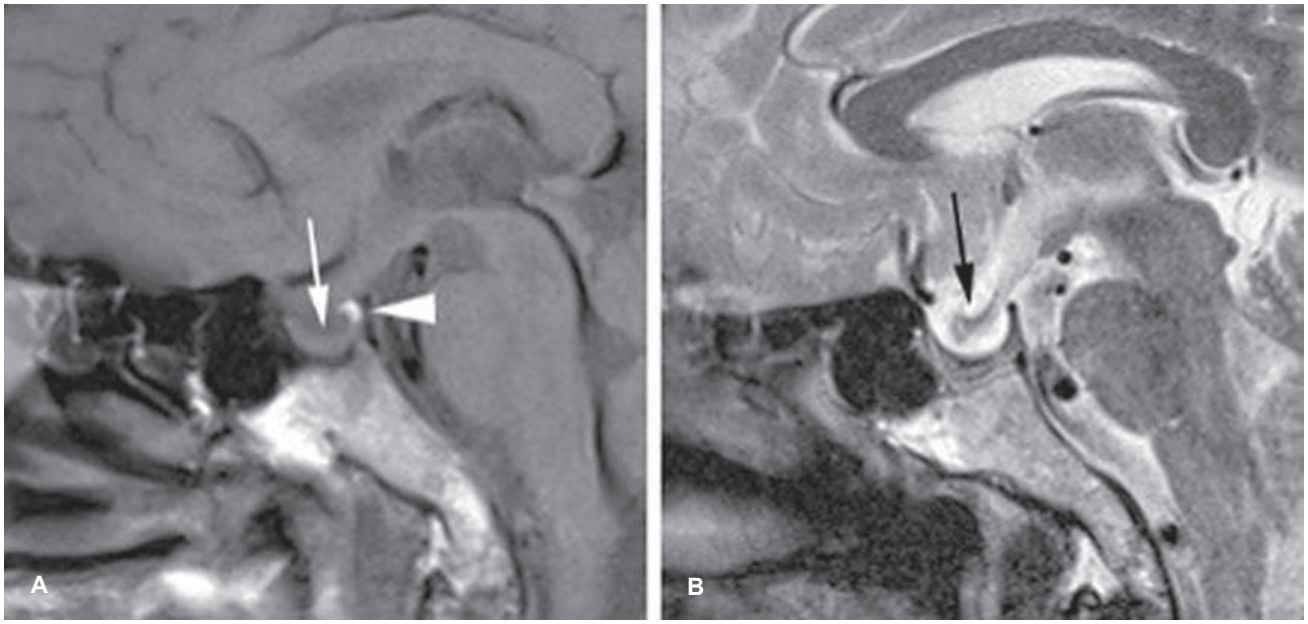

Figure 2. Follow up MRI in the midsaggital plane, T1-weighted **(A)** and T2-weighted images **(B)**. The T1 hyperintense posterior pituitary *(white arrowhead in A)*, with much of the anterior pituitary, flattened against the seller floor *(white arrow in A)*. The optic chiasm is prolapsed inferiorly into the sella *(black arrow in B)*.

(0.15 mIU/L) this indicates an underlying primary dysfunction of the pituitary gland. Further, no improvement in the pituitary hormone responses over the follow-up periods suggested lack of recovery in the pituitary-primary organs hormonal axes.

The first MRI of this patient had findings suggestive of adenohypophysitis with no innfundibuloneurohypophysitis (Figure 1). Although MRI of the pituitary gland is the imaging technique of choice for the characterization of the lesions, identifying AH is still challenging.[6] In 75-90% of cases of AH, a pituitary mass was observed as in Figure 1, 70% showed ring-like enhancement after administration of contrast.[7] In infundibuloneurohypophysitis, thickening of the pituitary stalk, with a diameter of more than 3.5 mm in the medial eminence of the hypothalamus is characteristic.[7] Marked enhancement of the stem after administration of gadolinium, which can extend to the lower end of the hypothalamus with a loss of hyperintensity of the neurohypophysis in the T1 sequence are also common characteristics. However, a hypointense posterior pituitary signal on T1 can also be observed in

Table 1. Differences between AH and pituitary adenoma[3,4,6-8]

	AH	Pituitary adenoma
Clinical features	• Mass effect eg headache	• Asymptomatic or mass effect
	• Varying degree of hypopituitarism	• Varying degree of hypopituitarism
	• Predilection for young female during pregnancy or postpartum. Less common in other age group and male	• No age or sex predilection
	• Other autoimmune diseases may be present	• No association with autoimmune diseases
Radiological features	• Characteristically diffusely thickened pituitary stalk >3.5 mm (absent in our patient)	• Pituitary stalk normal size
	• Symmetrical enlargement	• Asymmetrical enlargement
	• High post-gadolinium enhancement	• Low post-gadolinium enhancement
	• Preserved posterior pituitary 'bright spot'	• Lost posterior 'bright spot'
	• Intact sellar floor	• Sellar floor may be eroded
	• May regress to 'empty sella' with fibrosis	• Cystic lesion may be present

10% of normal subjects.[8] In our patient, the serial hyperintense pituitary MRI images suggested a normal posterior pituitary and consistent with the absence of diabetes insipidus. Nevertheless, the absence of thickened pituitary stalk, the T1 hyperintense rim encased mass without contrast, and a radiological regression of the anterior pituitary to empty sella is unusual. In addition, even though the pituitary regressed to empty sella, there is no deterioration of the adenohypophysis hormonal pattern deficit in our patient.

Our patient did not present with any history of clinical autoimmune disorders, and the TSH and TPO antibodies were negative in this patient. Thus, the use of antibodies to facilitate the diagnosis of AH was unhelpful for this patient. TSH and TPO antibodies were sent because the presence of associated autoimmune diseases was reported in 20-50% AH, consisting mainly Hashimoto thyroiditis followed by Graves' disease.[9] Autoimmune adrenalitis was reported in 5-7% of cases, pernicious anemia and diabetes mellitus type 1 in 2%. Less frequently, association with autoimmune polyglandular syndrome type 2, vitiligo, mumps, lymphocytic disease, celiac disease, systemic lupus erythematosus and rheumatoid arthritis were also reported.

Antihypophyseal antibodies (against A-enolase or specific neuronal enolase) was not sent as these assays were not available in the local laboratories. These antibodies may support the diagnosis in 24% of the cases[10,11] but its sensitivity does not exceed 36%.[12] However, these antibodies are nonspecific and detected in other endocrinopathies such as Cushing's disease, pituitary adenomas, Sheehan's syndrome, type 1 diabetes mellitus, Hashimoto's thyroiditis and Graves' disease. Therefore, antihypophyseal antibodies are only useful together with a thorough clinical assessment of the patient. As almost 80% of those patients with pituitary antibodies also have antibodies to thyroid gland or hormones,[12] thyroid antibodies may be surrogate markers in the absence of antihypophyseal antibodies assay. In our patient, thyroid antibodies screening was negative.

Although we did not have any histopathological specimen to confirm the diagnosis, our approach did not compromise the management of the patients. In the past, only two-thirds of patients with AH have biopsy confirmation.[3] Histopathological specimen from the biopsy specimen confirmed the nature of the lymphoplasmacytic infiltrate.[13-15] Biopsy also rules out other diseases that may have a similar clinical presentation. However, diseases such as tuberculosis, sarcoidosis and immunoglobulin deposits (IgG4) have other presentations which can be diagnosed with other safe investigative modalities.[11] In our patient, the absence of symptoms and signs along with the negative blood investigations and normal chest x-ray rule out the above conditions. Considering the potential risks of unnecessary invasive procedure of the pituitary, presumptive diagnosis combining context and clinical features can facilitate effective treatment. Confirmation of pituitary biopsy is not always necessary.[16] A case series suggested at the one, five and ten-year follow-up, there was no significant difference between the medically and surgically managed cohorts in term of ongoing symptomatology or need for pituitary hormone replacement.[17] Therefore, it is important to differentiate between AH and pituitary adenoma to avoid putting the patient at risk for unnecessary surgery (Table 1).

AH has a variable course, with no definitive treatment. Our patient receiving a physiological dose of hydrocortisone. High dose corticosteroids have been used to suppress the inflammation in AH,[3,18,19] and high doses of prednisolone were reported to be effective in reducing pituitary growth in 62.5% of the cases.[3,20] Pulse methylprednisolone was most effective when the disease is less than six months.[21] Nevertheless, the number of AH is still too small for randomized controlled trials as well as characterization of the clinical features that respond to corticosteroid. Other authors have suggested immunosuppressive treatments such as methotrexate and azathioprine.[9,18,19,21] Since our patient had drastic regression of the pituitary size, other immunosuppressive treatment was not indicated.

The prognosis of AH is variable, depending on the degree of inflammatory infiltration, duration, residual fibrosis and response to treatment.[1] In our patient, the clinical features, persistent yet stable pituitary hormonal deficit, was discordant with the regression of pituitary mass. Due to the uncertain clinical course, close, continuous active

surveillance to monitor the long-term progression of the disease in our patient is required.

CONCLUSION

Although AH is extremely rare in a man in the late fifties, it must be considered in any sudden loss of anterior pituitary hormonal functions, and MRI findings of ring-enhanced varying hypointense mass. Since a biopsy for definitive diagnosis involved risks, a presumptive diagnosis of AH may be made based on clinical, laboratory, and radiologic information and a high index of suspicion. Exclusion of pituitary macroadenoma, lymphoma and granulomatous hypophysitis is also important. Prompt diagnosis will facilitate prompt treatment and rapid hormonal replacement by a multidisciplinary medical team to minimize the morbidity. Although there is documentation of variable rate of regression of pituitary mass to an empty sella in AH of younger premenopausal women, this rate of regression in a man of this age group has not been reported. Since the course of the disease for this patient is uncertain, close, continuous active surveillance along with prompt and appropriate management is essential.

Ethical Consideration

Patient consent was obtained before submission of the manuscript.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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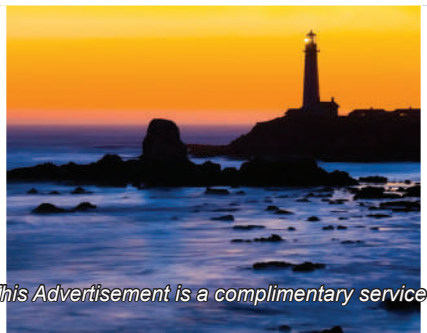

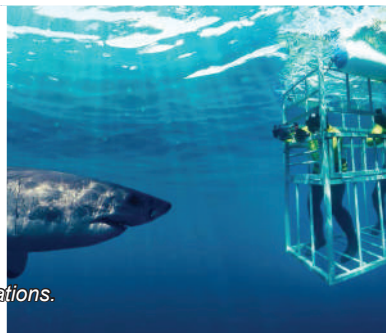

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Updated December 2017

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B. Who Should Use the Recommendations?

These recommendations are intended primarily for use by authors who might submit their work for publication to ICMJE member journals. Many non-ICMJE journals voluntarily use these recommendations (see www.icmje.org/journals.html). The ICMJE encourages that use but has no authority to monitor or enforce it. In all cases, authors should use these recommendations along with individual journals' instructions to authors. Authors should also consult guidelines for the reporting of specific study types (e.g., the CONSORT guidelines for the reporting of randomized trials); see http://equator-network.org.

Journals that follow these recommendations are encouraged to incorporate them into their instructions to authors and to make explicit in those instructions that they follow ICMJE recommendations. Journals that wish to be identified on the ICMJE website as following these recommendations should notify the ICMJE secretariat via e-mail at icmje@acponline.org. Journals that in the past have requested such identification but who no longer follow ICMJE recommendations should use the same means to request removal from this list.

The ICMJE encourages wide dissemination of these recommendations and reproduction of this document in its entirety for educational, not-for-profit purposes without regard for copyright, but all uses of the recommendations and document should direct readers to www.icmje.org for the official, most recent version, as the ICMJE updates the recommendations periodically when new issues arise.

C. History of the Recommendations

The ICMJE has produced multiple editions of this document, previously known as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URMs). The URM was first published in 1978 as a way of standardizing manuscript format and preparation across journals. Over the years, issues in publishing that went well beyond manuscript preparation arose, resulting in the development of separate statements, up-dates to the document, and its renaming as "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" to reflect its broader scope. Previous versions of the document may be found in the "Archives" section of www.icmje.org.

II. Roles and Responsibilities of Authors, Contributors, Reviewers, Editors, Publishers, and Owners

A. Defining the Role of Authors and Contributors

1. Why Authorship Matters

Authorship confers credit and has important academic, social, and financial implications. Authorship also implies responsibility and accountability for published work. The following recommendations are intended to ensure that contributors who have made substantive intellectual contributions to a paper are given credit as authors, but also that contributors credited as authors understand their role in taking responsibility and being accountable for what is published.

Because authorship does not communicate what contributions qualified an individual to be an author, some journals now request and publish information about the contributions of each person named as having participated in a submitted study, at least for original research. Editors are strongly encouraged to develop and implement a contributorship policy. Such policies remove much of the ambiguity surrounding contributions, but leave unresolved the question of the quantity and quality of contribution that qualify an individual for authorship. The ICMJE has thus developed criteria for authorship that can be used by all journals, including those that distinguish authors from other contributors.

2. Who Is an Author?

The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged—see Section II.A.3 below. These authorship criteria are intended to reserve the status of authorship for those who deserve credit and can take responsibility for the work. The criteria are not intended for use as a means to disqualify colleagues from authorship who otherwise meet authorship criteria by denying them the opportunity to meet criterion #s 2 or 3. Therefore, all individuals who meet the first criterion should have the opportunity to participate in the review, drafting, and final approval of the manuscript.

The individuals who conduct the work are responsible for identifying who meets these criteria and ideally should do so when planning the work, making modifications as appropriate as the work progresses. It is the collective responsibility of the authors, not the journal to which the work is submitted, to determine that all people named as authors meet all four criteria; it is not the role of journal editors to determine who qualifies or does not qualify for authorship or to arbitrate authorship conflicts. If agreement cannot be reached about who qualifies for authorship, the institution(s) where the work was performed, not the journal editor, should be asked to investigate. If authors request removal or addition of an author after manuscript submission or publication, journal editors should seek an explanation and signed statement of agreement for the requested change from all listed authors and from the author to be removed or added.

The corresponding author is the one individual who takes primary responsibility for communication with the journal during the manuscript submission, peer review,

and publication process, and typically ensures that all the journal's administrative requirements, such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and gathering conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer-review process to respond to editorial queries in a timely way, and should be available after publication to respond to critiques of the work and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication. Although the corresponding author has primary responsibility for correspondence with the journal, the ICMJE recommends that editors send copies of all correspondence to all listed authors.

When a large multi-author group has conducted the work, the group ideally should decide who will be an author before the work is started and confirm who is an author before submitting the manuscript for publication. All members of the group named as authors should meet all four criteria for authorship, including approval of the final manuscript, and they should be able to take public responsibility for the work and should have full confidence in the accuracy and integrity of the work of other group authors. They will also be expected as individuals to complete conflict-of-interest disclosure forms.

Some large multi-author groups designate authorship by a group name, with or without the names of individuals. When submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists, and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript, and MEDLINE lists as authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.

3. Non-Author Contributors

Contributors who meet fewer than all 4 of the above criteria for authorship should not be listed as authors, but they should be acknowledged. Examples of activities that alone (without other contributions) do not qualify a contributor for authorship are acquisition of funding; general supervision of a research group or general administrative support; and writing assistance, technical editing, language editing, and proofreading. Those whose contributions do not justify authorship may be acknowledged individually or together as a group under a single heading (e.g., "Clinical Investigators" or "Participating Investigators"), and their contributions should be specified (e.g., "served as scientific advisors," "critically reviewed the study proposal," "collected data," "provided and cared for study patients", "participated in writing or technical editing of the manuscript").

Because acknowledgment may imply endorsement by acknowledged individuals of a study's data and conclusions, editors are advised to require that the corresponding author obtain written permission to be acknowledged from all acknowledged individuals.

B. Author Responsibilities—Conflicts of Interest

Public trust in the scientific process and the credibility of published articles depend in part on how transparently conflicts of interest are handled during the planning, implementation, writing, peer review, editing, and publication of scientific work.

A conflict of interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain). Perceptions of conflict of interest are as important as actual conflicts of interest.

Financial relationships (such as employment, consultancies, stock ownership or options, honoraria, patents, and paid expert testimony) are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, and science itself. However, conflicts can occur for other reasons, such as personal relationships or rivalries, academic competition, and intellectual beliefs. Authors should avoid entering in to agreements with study sponsors, both for-profit and nonprofit, that interfere with authors' access to all of the study's data or that interfere with their ability to analyze and interpret the data and to prepare and publish manuscripts independently when and where they choose.

1. Participants

All participants in the peer-review and publication process—not only authors but also peer reviewers, editors, and editorial board members of journals—must consider their conflicts of interest when fulfilling their roles in the process of article review and publication and must disclose all relationships that could be viewed as potential conflicts of interest.

a. Authors

When authors submit a manuscript of any type or format they are responsible for disclosing all financial and personal relationships that might bias or be seen to bias their work. The ICMJE has developed a Form for Disclosure of Conflicts of Interest to facilitate and standardize authors' disclosures. ICMJE member journals require that authors use this form, and ICMJE encourages other journals to adopt it.

b. Peer Reviewers

Reviewers should be asked at the time they are asked to critique a manuscript if they have conflicts of interest that could complicate their review. Reviewers must disclose to editors any conflicts of interest that could bias their opinions of the manuscript, and should recuse themselves from reviewing specific manuscripts if the potential for bias exists. Reviewers must not use knowledge of the work they're reviewing before its publication to further their own interests.

c. Editors and Journal Staff

Editors who make final decisions about manuscripts should recuse themselves from editorial decisions if they have conflicts of interest or relationships that pose potential conflicts related to articles under consideration. Other editorial staff members who participate in editorial decisions must provide editors with a current description of their financial interests or other conflicts (as they might relate to editorial judgments) and recuse themselves from any decisions in which a conflict of interest exists. Editorial staff must not use information gained through working with manuscripts for private gain. Editors should publish regular disclosure statements about potential conflicts of interests related to their own commitments and those of their journal staff. Guest editors should follow these same procedures.

2. Reporting Conflicts of Interest

Articles should be published with statements or supporting documents, such as the ICMJE conflict of interest form, declaring:

– Authors' conflicts of interest; and

– Sources of support for the work, including sponsor names along with explanations of the role of those sources if any in study design; collection, analysis, and interpretation of data; writing of the report; the decision to submit the report for publication; or a statement declaring that the supporting source had no such involvement; and

– Whether the authors had access to the study data, with an explanation of the nature and extent of access, including whether access is ongoing.

To support the above statements, editors may request that authors of a study sponsored by a funder with a proprietary or financial interest in the outcome sign a statement, such as "I had full access to all of the data in this study and I take complete responsibility for the integrity of the data and the accuracy of the data analysis."

C. Responsibilities in the Submission and Peer-Review Process

1. Authors

Authors should abide by all principles of authorship and declaration of conflicts of interest detailed in section IIA and B of this document.

a. Predatory or Pseudo-Journals

A growing number of entities are advertising themselves as "scholarly medical journals" yet do not function as such. These journals ("predatory"or "pseudo-journals") accept and publish almost all submissions and charge article processing (or publication) fees, often informing authors about this after a paper's acceptance for publication. They often claim to perform peer review but do not and may purposefully use names similar to well established journals. They may state that they are members of ICMJE but are not (see www.icmje.org for current members of the ICMJE) and that they follow the recommendations of organizations such as the ICMJE, COPE and WAME. Researchers must be aware of the existence of such entities and avoid submitting research to them for publication. Authors have a responsibility to evaluate the integrity, history, practices and reputation of the journals to which they submit manuscripts. Guidance from various organizations is available to help identify the characteristics of reputable peer-reviewed journals (http://www.wame.org/identifying-predatory-or-pseudo-journals and http://www.wame.org/about/principlesof-transparency-and-best-practice). Seeking the assistance of scientific mentors, senior colleagues and others with many years of scholarly publishing experience may also be helpful.

2. Journals

a. Confidentiality

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Editors therefore must not share information about manuscripts, including whether they have been received and are under review, their content and status in the review process, criticism by reviewers, and their ultimate fate, to anyone other than the authors and reviewers. Requests from third parties to use manuscripts and reviews for legal proceedings should be politely refused, and editors should do their best not to provide such confidential material should it be subpoenaed.

Editors must also make clear that reviewers should keep manuscripts, associated material, and the information they contain strictly confidential. Reviewers and editorial staff members must not publicly discuss the authors' work, and reviewers must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy paper copies of manuscripts and delete electronic copies after submitting their reviews.

When a manuscript is rejected, it is best practice for journals to delete copies of it from their editorial systems unless retention is required by local regulations. Journals that retain copies of rejected manuscripts should disclose this practice in their Information for Authors.

When a manuscript is published, journals should keep copies of the original submission, reviews, revisions, and correspondence for at least three years and possibly in perpetuity, depending on local regulations, to help answer future questions about the work should they arise.

Editors should not publish or publicize peer reviewers' comments without permission of the reviewer and author. If journal policy is to blind authors to reviewer identity and comments are not signed, that identity must not be revealed to the author or anyone else without the reviewers' expressed written permission.

Confidentiality may have to be breached if dishonesty or fraud is alleged, but editors should notify authors or reviewers if they intend to do so and confidentiality must otherwise be honored.

b. Timeliness

Editors should do all they can to ensure timely processing of manuscripts with the resources available to them. If editors intend to publish a manuscript, they should attempt to do so in a timely manner and any planned delays should be negotiated with the authors. If a journal has no intention of proceeding with a manuscript, editors should endeavor to reject the manuscript as soon as possible to allow authors to submit to a different journal.

c. Peer Review

Peer review is the critical assessment of manuscripts submitted to journals by experts who are usually not part of the editorial staff. Because unbiased, independent, critical assessment is an intrinsic part of all scholarly work, including scientific research, peer review is an important extension of the scientific process.

The actual value of peer review is widely debated, but the process facilitates a fair hearing for a manuscript among members of the scientific community. More practically, it helps editors decide which manuscripts are suitable for their journals. Peer review often helps authors and editors improve the quality of reporting.

It is the responsibility of the journal to ensure that systems are in place for selection of appropriate reviewers. It is the responsibility of the editor to ensure that reviewers have access to all materials that may be relevant to the evaluation of the manuscript, including supplementary material for e-only publication, and to ensure that reviewer comments are properly assessed and interpreted in the context of their declared conflicts of interest.

A peer-reviewed journal is under no obligation to send submitted manuscripts for review, and under no obligation to follow reviewer recommendations, favorable or negative. The editor of a journal is ultimately responsible for the selection of all its content, and editorial decisions may be informed by issues unrelated to the quality of a manuscript, such as suitability for the journal. An editor can reject any article at any time before publication, including after acceptance if concerns arise about the integrity of the work.

Journals may differ in the number and kinds of manuscripts they send for review, the number and types of reviewers they seek for each manuscript, whether the review process is open or blinded, and other aspects of the review process. For this reason and as a service to authors, journals should publish a description of their peer-review process.

Journals should notify reviewers of the ultimate decision to accept or reject a paper, and should acknowledge the contribution of peer reviewers to their journal. Editors are encouraged to share reviewers' comments with co-reviewers of the same paper, so reviewers can learn from each other in the review process.

As part of peer review, editors are encouraged to review research protocols, plans for statistical analysis if separate from the protocol, and/or contracts associated with project-specific studies. Editors should encourage authors to make such documents publicly available at the time of or after publication, before accepting such studies for publication. Some journals may require public posting of these documents as a condition of acceptance for publication.

Journal requirements for independent data analysis and for public data availability are in flux at the time of this revision, reflecting evolving views of the importance of data availability for pre- and post-publication peer review. Some journal editors currently request a statistical analysis of trial data by an independent biostatistician before accepting studies for publication. Others ask authors to say whether the study data are available to third parties to view and/or use/reanalyze, while still others encourage or require authors to share their data with others for review or reanalysis. Each journal should establish and publish their specific requirements for data analysis and post in a place that potential authors can easily access.

Some people believe that true scientific peer review begins only on the date a paper is published. In that spirit, medical journals should have a mechanism for readers to submit comments, questions, or criticisms about published articles, and authors have a responsibility to respond appropriately and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication (see Section III).

ICMJE believes investigators have a duty to maintain the primary data and analytic procedures underpinning the published results for at least 10 years. The ICMJE encourages the preservation of these data in a data repository to ensure their longer-term availability.

d. Integrity

Editorial decisions should be based on the relevance of a manuscript to the journal and on the manuscript's originality, quality, and contribution to evidence about important questions. Those decisions should not be influenced

by commercial interests, personal relationships or agendas, or findings that are negative or that credibly challenge accepted wisdom. In addition, authors should submit for publication or otherwise make publicly available, and editors should not exclude from consideration for publication, studies with findings that are not statistically significant or that have inconclusive findings. Such studies may provide evidence that, combined with that from other studies through meta-analysis, might still help answer important questions, and a public record of such negative or inconclusive findings may prevent unwarranted replication of effort or otherwise be valuable for other researchers considering similar work.

Journals should clearly state their appeals process and should have a system for responding to appeals and complaints.

3. Peer Reviewers

Manuscripts submitted to journals are privileged communications that are authors' private, confidential property, and authors may be harmed by premature disclosure of any or all of a manuscript's details.

Reviewers therefore should keep manuscripts and the information they contain strictly confidential. Reviewers must not publicly discuss authors' work and must not appropriate authors' ideas before the manuscript is published. Reviewers must not retain the manuscript for their personal use and should destroy copies of manuscripts after submitting their reviews.

Reviewers are expected to respond promptly to requests to review and to submit reviews within the time agreed. Reviewers' comments should be constructive, honest, and polite.

Reviewers should declare their conflicts of interest and recuse themselves from the peer-review process if a conflict exists.

D. Journal Owners and Editorial Freedom

1. Journal Owners

Owners and editors of medical journals share a common purpose, but they have different responsibilities, and sometimes those differences lead to conflicts.

It is the responsibility of medical journal owners to appoint and dismiss editors. Owners should provide editors at the time of their appointment with a contract that clearly states their rights and duties, authority, the general terms of their appointment, and mechanisms for resolving conflict. The editor's performance may be assessed using mutually agreed-upon measures, including but not necessarily limited to readership, manuscript submissions and handling times, and various journal metrics.

Owners should only dismiss editors for substantial reasons, such as scientific misconduct, disagreement with the long-term editorial direction of the journal, inadequate performance by agreed-upon performance metrics, or inappropriate behavior that is incompatible with a position of trust.

Appointments and dismissals should be based on evaluations by a panel of independent experts, rather than by a small number of executives of the owning organization. This is especially necessary in the case of dismissals because of the high value society places on freedom of speech within science and because it is often the responsibility of editors to challenge the status quo in ways that may conflict with the interests of the journal's owners.

A medical journal should explicitly state its governance and relationship to a journal owner (e.g., a sponsoring society).

2. Editorial Freedom

The ICMJE adopts the World Association of Medical Editors' definition of editorial freedom, which holds that editors-in-chief have full authority over the entire editorial content of their journal and the timing of publication of that content. Journal owners should not interfere in the evaluation, selection, scheduling, or editing of individual articles either directly or by creating an environment that strongly influences decisions. Editors should base editorial decisions on the validity of the work and its importance to the journal's readers, not on the commercial implications for the journal, and editors should be free to express critical but responsible views about all aspects of medicine without fear of retribution, even if these views conflict with the commercial goals of the publisher.

Editors-in-chief should also have the final say in decisions about which advertisements or sponsored content, including supplements, the journal will and will not carry, and they should have final say in use of the journal brand and in overall policy regarding commercial use of journal content.

Journals are encouraged to establish an independent editorial advisory board to help the editor establish and maintain editorial policy. Editors should seek input as needed from a broad array of advisers, such as reviewers, editorial staff, an editorial board, and readers, to support editorial decisions and potentially controversial expressions of opinion, and owners should ensure that appropriate insurance is obtained in the event of legal action against the editors, and should ensure that legal advice is available when necessary. If legal problems arise, the editor should inform their legal adviser and their owner and/or publisher as soon as possible. Editors should defend the confidentiality of authors and peer-reviewers (names and reviewer comments) in accordance with ICMJE policy (see Section II C.2.a). Editors should take all reasonable steps to check the facts in journal commentary, including that in news sections and social media postings, and should ensure that staff working for the journal adhere to best journalistic practices including contemporaneous note-taking and seeking a response from all parties when possible before

publication. Such practices in support of truth and public interest may be particularly relevant in defense against legal allegations of libel.

To secure editorial freedom in practice, the editor should have direct access to the highest level of ownership, not to a delegated manager or administrative officer.

Editors and editors' organizations are obliged to support the concept of editorial freedom and to draw major transgressions of such freedom to the attention of the international medical, academic, and lay communities.

E. Protection of Research Participants

All investigators should ensure that the planning conduct and reporting of human research are in accordance with the Helsinki Declaration as revised in 2013 (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). All authors should seek approval to conduct research from an independent local, regional, or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional, or national review body explicitly approved the doubtful aspects of the study. Approval by a responsible review body does not preclude editors from forming their own judgment whether the conduct of the research was appropriate.

Patients have a right to privacy that should not be violated without informed consent. Identifying information, including names, initials, or hospital numbers, should not be published in written descriptions, photographs, or pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives written informed consent for publication. Informed consent for this purpose requires that an identifiable patient be shown the manuscript to be published. Authors should disclose to these patients whether any potential identifiable material might be available via the Internet as well as in print after publication. Patient consent should be written and archived with the journal, the authors, or both, as dictated by local regulations or laws. Applicable laws vary from locale to locale, and journals should establish their own policies with legal guidance. Since a journal that archives the consent will be aware of patient identity, some journals may decide that patient confidentiality is better guarded by having the author archive the consent and instead providing the journal with a written statement that attests that they have received and archived written patient consent.

Nonessential identifying details should be omitted. Informed consent should be obtained if there is any doubt that anonymity can be maintained. For example, masking the eye region in photographs of patients is inadequate protection of anonymity. If identifying characteristics are de-identified, authors should provide assurance, and editors should so note, that such changes do not distort scientific meaning.

The requirement for informed consent should be included in the journal's instructions for authors. When informed consent has been obtained, it should be indicated in the published article.

When reporting experiments on animals, authors should indicate whether institutional and national standards for the care and use of laboratory animals were followed. Further guidance on animal research ethics is available from the International Association of Veterinary Editors' Consensus Author Guidelines on Animal Ethics and Welfare (http://veteditors.org/ethicsconsensusguidelines.html).

III. Publishing and Editorial Issues Related to Publication in Medical Journals

A. Corrections, Retractions, Republications, and Version Control

Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. Matters of debate are best handled as letters to the editor, as print or electronic correspondence, or as posts in a journal-sponsored online forum. Updates of previous publications (e.g., an updated systematic review or clinical guideline) are considered a new publication rather than a version of a previously published article.

If a correction is needed, journals should follow these minimum standards:

- The journal should publish a correction notice as soon as possible detailing changes from and citing the original publication; the correction should be on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing.
- The journal should also post a new article version with details of the changes from the original version and the date(s) on which the changes were made.
- The journal should archive all prior versions of the article. This archive can be either directly accessible to readers or can be made available to the reader on request.
- Previous electronic versions should prominently note that there are more recent versions of the article.
- The citation should be to the most recent version.

Pervasive errors can result from a coding problem or a miscalculation and may result in extensive inaccuracies throughout an article. If such errors do not change the direction or significance of the results, interpretations, and conclusions of the article, a correction should be published that follows the minimum standards noted above.

Errors serious enough to invalidate a paper's results and conclusions may require retraction. However, retraction with republication (also referred to as "replacement") can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations,

and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then retraction with republication of the changed paper, with an explanation, allows full correction of the scientific literature. In such cases, it is helpful to show the extent of the changes in supplementary material or in an appendix, for complete transparency.

B. Scientific Misconduct, Expressions of Concern, and Retraction

Scientific misconduct includes but is not necessarily limited to data fabrication; data falsification, including deceptive manipulation of images; and plagiarism. Some people consider failure to publish the results of clinical trials and other human studies a form of scientific misconduct. While each of these practices is problematic, they are not equivalent. Each situation requires individual assessment by relevant stakeholders. When scientific misconduct is alleged, or concerns are otherwise raised about the conduct or integrity of work described in submitted or published papers, the editor should initiate appropriate procedures detailed by such committees as the Committee on Publication Ethics (COPE) (publicationethics.org/resources/flowcharts) and may choose to publish an expression of concern pending the outcomes of those procedures. If the procedures involve an investigation at the authors' institution, the editor should seek to discover the outcome of that investigation; notify readers of the outcome if appropriate; and if the investigation proves scientific misconduct, publish a retraction of the article. There may be circumstances in which no misconduct is proven, but an exchange of letters to the editor could be published to highlight matters of debate to readers.

Expressions of concern and retractions should not simply be a letter to the editor. Rather, they should be prominently labelled, appear on an electronic or numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing, and include in their heading the title of the original article. Online, the retraction and original article should be linked in both directions and the retracted article should be clearly labelled as retracted in all its forms (abstract, full text, PDF). Ideally, the authors of the retraction should be the same as those of the article, but if they are unwilling or unable the editor may under certain circumstances accept retractions by other responsible persons, or the editor may be the sole author of the retraction or expression of concern. The text of the retraction should explain why the article is being retracted and include a complete citation reference to that article. Retracted articles should remain in the public domain and be clearly labelled as retracted.

The validity of previous work by the author of a fraudulent paper cannot be assumed. Editors may ask the author's institution to assure them of the validity of other work published in their journals, or they may retract it. If this is not done, editors may choose to publish an announcement expressing concern that the validity of previously published work is uncertain.

The integrity of research may also be compromised by inappropriate methodology that could lead to retraction.

See COPE flowcharts for further guidance on retractions and expressions of concern. See Section IV.g.i. for guidance about avoiding referencing retracted articles.

C. Copyright

Journals should make clear the type of copyright under which work will be published, and if the journal retains copyright, should detail the journal's position on the transfer of copyright for all types of content, including audio, video, protocols, and data sets. Medical journals may ask authors to transfer copyright to the journal. Some journals require transfer of a publication license. Some journals do not require transfer of copyright and rely on such vehicles as Creative Commons licenses. The copyright status of articles in a given journal can vary: Some content cannot be copyrighted (e.g., articles written by employees of some governments in the course of their work). Editors may waive copyright on other content, and some content may be protected under other agreements.

D. Overlapping Publications

1. Duplicate Submission

Authors should not submit the same manuscript, in the same or different languages, simultaneously to more than one journal. The rationale for this standard is the potential for disagreement when two (or more) journals claim the right to publish a manuscript that has been submitted simultaneously to more than one journal, and the possibility that two or more journals will unknowingly and unnecessarily undertake the work of peer review, edit the same manuscript, and publish the same article.

2. Duplicate and Prior Publication

Duplicate publication is publication of a paper that overlaps substantially with one already published, without clear, visible reference to the previous publication. Prior publication may include release of information in the public domain.

Readers of medical journals deserve to be able to trust that what they are reading is original unless there is a clear statement that the author and editor are intentionally republishing an article (which might be considered for historic or landmark papers, for example). The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources. Duplicate publication of original research is particularly problematic because it can result in inadvertent double-counting of data or inappropriate weighting of the results of a single study, which distorts the available evidence.

When authors submit a manuscript reporting work that has already been reported in large part in a published article or is contained in or closely related to another paper

that has been submitted or accepted for publication elsewhere, the letter of submission should clearly say so and the authors should provide copies of the related material to help the editor decide how to handle the submission. See also Section IV.B.

This recommendation does not prevent a journal from considering a complete report that follows publication of a preliminary report, such as a letter to the editor, a preprint, or an abstract or poster displayed at a scientific meeting. It also does not prevent journals from considering a paper that has been presented at a scientific meeting but was not published in full, or that is being considered for publication in proceedings or similar format. Press reports of scheduled meetings are not usually regarded as breaches of this rule, but they may be if additional data tables or figures enrich such reports. Authors should also consider how dissemination of their findings outside of scientific presentations at meetings may diminish the priority journal editors assign to their work.

In the event of a public health emergency (as defined by public health officials), information with immediate implications for public health should be disseminated without concern that this will preclude subsequent consideration for publication in a journal.

Sharing with public media, government agencies, or manufacturers the scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. Such reporting may be warranted when the paper or letter describes major therapeutic advances; reportable diseases; or public health hazards, such as serious adverse effects of drugs, vaccines, other biological products, medical devices. This reporting, whether in print or online, should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance when possible.

The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the criteria noted in Section III.L. if results are limited to a brief (500 word) structured abstract or tables (to include participants enrolled, key outcomes, and adverse events). The ICMJE encourages authors to include a statement with the registration that indicates that the results have not yet been published in a peer-reviewed journal, and to update the results registry with the full journal citation when the results are published.

Editors of different journals may together decide to simultaneously or jointly publish an article if they believe that doing so would be in the best interest of public health. However, the National Library of Medicine (NLM) indexes all such simultaneously published joint publications separately, so editors should include a statement making the simultaneous publication clear to readers.

Authors who attempt duplicate publication without such notification should expect at least prompt rejection of the submitted manuscript. If the editor was not aware of the violations and the article has already been published, then the article might warrant retraction with or without the author's explanation or approval.

See COPE flowcharts for further guidance on handling duplicate publication.

3. Acceptable Secondary Publication

Secondary publication of material published in other journals or online may be justifiable and beneficial, especially when intended to disseminate important information to the widest possible audience (e.g., guidelines produced by government agencies and professional organizations in the same or a different language). Secondary publication for various other reasons may also be justifiable provided the following conditions are met:

1. The authors have received approval from the editors of both journals (the editor concerned with secondary publication must have access to the primary version).
2. The priority of the primary publication is respected by a publication interval negotiated by both editors with the authors.
3. The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient.
4. The secondary version faithfully reflects the data and interpretations of the primary version.
5. The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first reported in the [journal title, with full reference]"—and the secondary version cites the primary reference.
6. The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication. Of note, the NLM does not consider translations to be "republications" and does not cite or index them when the original article was published in a journal that is indexed in MEDLINE.

When the same journal simultaneously publishes an article in multiple languages, the MEDLINE citation will note the multiple languages (e.g., Angelo M. Journal networking in nursing: a challenge to be shared. Rev Esc Enferm USP. 2011 Dec 45[6]:1281-2,1279-80,1283-4. Article in English, Portuguese, and Spanish. No abstract available. PMID 22241182).

4. Manuscripts Based on the Same Database

If editors receive manuscripts from separate research groups or from the same group analyzing the same data set (e.g., from a public database, or systematic reviews or meta-analyses of the same evidence), the manuscripts should be considered independently because they may differ in their analytic methods, conclusions, or both. If the data interpretation and conclusions are similar, it may be

reasonable although not mandatory for editors to give preference to the manuscript submitted first. Editors might consider publishing more than one manuscript that overlap in this way because different analytical approaches may be complementary and equally valid, but manuscripts based upon the same dataset should add substantially to each other to warrant consideration for publication as separate papers, with appropriate citation of previous publications from the same dataset to allow for transparency.

Secondary analyses of clinical trial data should cite any primary publication, clearly state that it contains secondary analyses/results, and use the same identifying trial registration number as the primary trial and unique, persistent dataset identifier.

Sometimes for large trials it is planned from the beginning to produce numerous separate publications regarding separate research questions but using the same original participant sample. In this case authors may use the original single trial registration number, if all the outcome parameters were defined in the original registration. If the authors registered several substudies as separate entries in, for example, clinicaltrials.gov, then the unique trial identifier should be given for the study in question, The main issue is transparency, so no matter what model is used it should be obvious for the reader.

E. Correspondence

Medical journals should provide readers with a mechanism for submitting comments, questions, or criticisms about published articles, usually but not necessarily always through a correspondence section or online forum. The authors of articles discussed in correspondence or an online forum have a responsibility to respond to substantial criticisms of their work using those same mechanisms and should be asked by editors to respond. Authors of correspondence should be asked to declare any competing or conflicting interests.

Correspondence may be edited for length, grammatical correctness, and journal style. Alternatively, editors may choose to make available to readers unedited correspondence, for example, via an online commenting system. Such commenting is not indexed in Medline unless it is subsequently published on a numbered electronic or print page. However the journal handles correspondence, it should make known its practice. In all instances, editors must make an effort to screen discourteous, inaccurate, or libellous comments.

Responsible debate, critique, and disagreement are important features of science, and journal editors should encourage such discourse ideally within their own journals about the material they have published. Editors, however, have the prerogative to reject correspondence that is irrelevant, uninteresting, or lacking cogency, but they also have a responsibility to allow a range of opinions to be expressed and to promote debate.

In the interests of fairness and to keep correspondence within manageable proportions, journals may want to set time limits for responding to published material and for debate on a given topic.

F. Fees

Journals should be transparent about their types of revenue streams. Any fees or charges that are required for manuscript processing and/or publishing materials in the journal shall be clearly stated in a place that is easy for potential authors to find prior to submitting their manuscripts for review or explained to authors before they begin preparing their manuscript for submission (http://publicationethics.org/files/u7140/Principles_of_Transparency_and_Best_Practice_in_Scholarly_Publishing.pdf).

G. Supplements, Theme Issues, and Special Series

Supplements are collections of papers that deal with related issues or topics, are published as a separate issue of the journal or as part of a regular issue, and may be funded by sources other than the journal's publisher. Because funding sources can bias the content of supplements through the choice of topics and viewpoints, journals should adopt the following principles, which also apply to theme issues or special series that have external funding and/or guest editors:

1. The journal editor must be given and must take full responsibility for the policies, practices, and content of supplements, including complete control of the decision to select authors, peer reviewers, and content for the supplement. Editing by the funding organization should not be permitted.

2. The journal editor has the right to appoint one or more external editors of the supplement and must take responsibility for the work of those editors.

3. The journal editor must retain the authority to send supplement manuscripts for external peer review and to reject manuscripts submitted for the supplement with or without external review. These conditions should be made known to authors and any external editors of the supplement before beginning editorial work on it.

4. The source of the idea for the supplement, sources of funding for the supplement's research and publication, and products of the funding source related to content considered in the supplement should be clearly stated in the introductory material.

5. Advertising in supplements should follow the same policies as those of the primary journal.

6. Journal editors must enable readers to distinguish readily between ordinary editorial pages and supplement pages.

7. Journal and supplement editors must not accept personal favors or direct remuneration from sponsors of supplements.

8. Secondary publication in supplements (republication of papers published elsewhere) should be clearly identified by the citation of the original paper and by the title.

9. The same principles of authorship and disclosure of potential conflicts of interest discussed elsewhere in this document should be applied to supplements.

H. Sponsorship or Partnership

Various entities may seek interactions with journals or editors in the form of sponsorships, partnerships, meetings, or other types of activities. To preserve editorial independence, these interactions should be governed by the same principles outlined above for Supplements, Theme Issues, and Special Series (Section III.G).

I. Electronic Publishing

Most medical journals are now published in electronic as well as print versions, and some are published only in electronic form. Principles of print and electronic publishing are identical, and the recommendations of this document apply equally to both. However, electronic publishing provides opportunities for versioning and raises issues about link stability and content preservation that are addressed here.

Recommendations for corrections and versioning are detailed in Section III.A.

Electronic publishing allows linking to sites and resources beyond journals over which journal editors have no editorial control. For this reason, and because links to external sites could be perceived as implying endorsement of those sites, journals should be cautious about external linking. When a journal does link to an external site, it should state that it does not endorse or take responsibility or liability for any content, advertising, products, or other materials on the linked sites, and does not take responsibility for the sites' availability.

Permanent preservation of journal articles on a journal's website, or in an independent archive or a credible repository, is essential for the historical record. Removing an article from a journal's website in its entirety is almost never justified as copies of the article may have been downloaded even if its online posting was brief. Such archives should be freely accessible or accessible to archive members. Deposition in multiple archives is encouraged. However, if necessary for legal reasons (e.g., libel action), the URL for the removed article must contain a detailed reason for the removal, and the article must be retained in the journal's internal archive.

Permanent preservation of a journal's total content is the responsibility of the journal publisher, who in the event of journal termination should be certain the journal files are transferred to a responsible third party who can make the content available.

Journal websites should post the date that nonarticle web pages, such as those listing journal staff, editorial board members, and instructions for authors, were last updated.

J. Advertising

Most medical journals carry advertising, which generates income for their publishers, but journals should not be dominated by advertisements, and advertising must not be allowed to influence editorial decisions.

Journals should have formal, explicit, written policies for advertising in both print and electronic versions. Best practice prohibits selling advertisements intended to be juxtaposed with editorial content on the same product. Advertisements should be clearly identifiable as advertisements. Editors should have full and final authority for approving print and online advertisements and for enforcing advertising policy.

Journals should not carry advertisements for products proven to be seriously harmful to health. Editors should ensure that existing regulatory or industry standards for advertisements specific to their country are enforced, or develop their own standards. The interests of organizations or agencies should not control classified and other nondisplay advertising, except where required by law. Editors should consider all criticisms of advertisements for publication.

K. Journals and the Media

Journals' interactions with media should balance competing priorities. The general public has a legitimate interest in all journal content and is entitled to important information within a reasonable amount of time, and editors have a responsibility to facilitate that. However media reports of scientific research before it has been peer-reviewed and fully vetted may lead to dissemination of inaccurate or premature conclusions, and doctors in practice need to have research reports available in full detail before they can advise patients about the reports' conclusions.

An embargo system has been established in some countries and by some journals to assist this balance, and to prevent publication of stories in the general media before publication of the original research in the journal. For the media, the embargo creates a "level playing field," which most reporters and writers appreciate since it minimizes the pressure on them to publish stories before competitors when they have not had time to prepare carefully. Consistency in the timing of public release of biomedical information is also important in minimizing economic chaos, since some articles contain information that has potential to influence financial markets. The ICMJE acknowledges criticisms of embargo systems as being self-serving of journals' interests and an impediment to rapid dissemination of scientific information, but believe the benefits of the systems outweigh their harms.

The following principles apply equally to print and electronic publishing and may be useful to editors as they seek to establish policies on interactions with the media:

- Editors can foster the orderly transmission of medical information from researchers, through peer-reviewed journals, to the public. This can be accomplished by an agreement with authors that they will not publicize their work while their manuscript is under consideration or awaiting publication and an agreement with the media that

they will not release stories before publication of the original research in the journal, in return for which the journal will cooperate with them in preparing accurate stories by issuing, for example, a press release.

- Editors need to keep in mind that an embargo system works on the honor system—no formal enforcement or policing mechanism exists. The decision of a significant number of media outlets or biomedical journals not to respect the embargo system would lead to its rapid dissolution.
- Notwithstanding authors' belief in their work, very little medical research has such clear and urgently important clinical implications for the public's health that the news must be released before full publication in a journal. When such exceptional circumstances occur, the appropriate authorities responsible for public health should decide whether to disseminate information to physicians and the media in advance and should be responsible for this decision. If the author and the appropriate authorities wish to have a manuscript considered by a particular journal, the editor should be consulted before any public release. If editors acknowledge the need for immediate release, they should waive their policies limiting prepublication publicity.
- Policies designed to limit prepublication publicity should not apply to accounts in the media of presentations at scientific meetings or to the abstracts from these meetings (see Duplicate Publication). Researchers who present their work at a scientific meeting should feel free to discuss their presentations with reporters but should be discouraged from offering more detail about their study than was presented in the talk, or should consider how giving such detail might diminish the priority journal editors assign to their work (see Duplicate Publication).
- When an article is close to being published, editors or journal staff should help the media prepare accurate reports by providing news releases, answering questions, supplying advance copies of the article, or referring reporters to appropriate experts. This assistance should be contingent on the media's cooperation in timing the release of a story to coincide with publication of the article.

L. Clinical Trials

i. Registration

The ICMJE's clinical trial registration policy is detailed in a series of editorials (see Updates and Editorials [www.icmje.org/news-and-editorials/] and FAQs [http://www.icmje.org/about-icmje/faqs/]).

Briefly, the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance [icmje.org/journals.html] should recognize that the listing implies enforcement by the journal of ICMJE's trial registration policy.

The ICMJE defines a clinical trial as any research project that prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the relationship between a health-related intervention and a health outcome. Health-related interventions are those used to modify a biomedical or health-related outcome; examples include drugs, surgical procedures, devices, behavioral treatments, educational programs, dietary interventions, quality improvement interventions, and process-of-care changes. Health outcomes are any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE does not define the timing of first participant enrollment, but best practice dictates registration by the time of first participant consent.

The ICMJE accepts publicly accessible registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/network/primary/en/index.html) or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP. The ICMJE endorses these registries because they meet several criteria. They are accessible to the public at no charge, open to all prospective registrants, managed by a not-for-profit organization, have a mechanism to ensure the validity of the registration data, and are electronically searchable. An acceptable registry must include the minimum 20-item trial registration dataset (http://prsinfo.clinicaltrials.gov/trainTrainer/WHO-ICMJE-ClinTrialsgov-Cross-Ref.pdf or www.who.int/ictrp/network/trds/en/index.html) at the time of registration and before enrollment of the first participant. The ICMJE considers inadequate trial registrations missing any of the 20 data fields those that have fields that contain uninformative information, or registrations that are not made publicly accessible such as phase I trials submitted to the EU-CTR. Although not a required item, the ICMJE encourages authors to include a statement that indicates that the results have not yet been published in a peer-reviewed journal, and to update the registration with the full journal citation when the results are published.

The purpose of clinical trial registration is to prevent selective publication and selective reporting of research outcomes, to prevent unnecessary duplication of research effort, to help patients and the public know what trials are planned or ongoing into which they might want to enroll, and to help give ethics review boards considering approval of new studies a view of similar work and data relevant to the research they are considering. Retrospective registration, for example at the time of manuscript submission, meets none of these purposes. Those purposes apply also to research with alternative designs, for example observational studies. For that reason, the ICMJE encourages registration of research with non-trial designs, but because the exposure

or intervention in non-trial research is not dictated by the researchers, the ICMJE does not require it.

Secondary data analyses of primary (parent) clinical trials should not be registered as separate clinical trials, but instead should reference the trial registration number of the primary trial.

The ICMJE expects authors to ensure that they have met the requirements of their funding and regulatory agencies regarding aggregate clinical trial results reporting in clinical trial registries, and encourages registry results reporting even when not required. It is the authors', and not the journal editors', responsibility to explain any discrepancies between results reported in registries and journal publications. The ICMJE will not consider as prior publication the posting of trial results in any registry that meets the above criteria if results are limited to a brief (500 word) structured abstract or tables (to include trial participants enrolled, baseline characteristics, primary and secondary outcomes, and adverse events).

The ICMJE recommends that journals publish the trial registration number at the end of the abstract. The ICMJE also recommends that, whenever a registration number is available, authors list this number the first time they use a trial acronym to refer either to the trial they are reporting or to other trials that they mention in the manuscript.

Editors may consider whether the circumstances involved in a failure to appropriately register a clinical trial were likely to have been intended to or resulted in biased reporting. Because of the importance of prospective trial registration, if an exception to this policy is made, trials must be registered and the authors should indicate in the publication when registration was completed and why it was delayed. Editors should publish a statement indicating why an exception was allowed. The ICMJE emphasizes that such exceptions should be rare, and that authors failing to prospectively register a trial risk its inadmissibililty to our journals.

ii. Data Sharing

The ICMJE's data sharing statement policy is detailed in an editorial (see Updates and Editorials [www.icmje.org/update.html]).

1. As of 1 July 2018 manuscripts submitted to ICMJE journals that report the results of clinical trials must contain a data sharing statement as described below.

2. Clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration. The ICMJE's policy regarding trial registration is explained at www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. If the data sharing plan changes after registration this should be reflected in the statement submitted and published with the manuscript, and updated in the registry record.

Data sharing statements must indicate the following: whether individual deidentified participant data (including data dictionaries) will be shared; what data in particular will be shared; whether additional, related documents will be available (e.g., study protocol, statistical analysis plan, etc.); when the data will become available and for how long; by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Illustrative examples of data sharing statements that would meet these requirements are provided in the **Table**.

Authors of secondary analyses using shared data must attest that their use was in accordance with the terms (if any) agreed to upon their receipt. They must also reference the source of the data using its unique, persistent identifier to provide appropriate credit to those who generated it and allow searching for the studies it has supported. Authors of secondary analyses must explain completely how theirs differ from previous analyses. In addition, those who generate and then share clinical trial data sets deserve substantial credit for their efforts. Those using data collected by others should seek collaboration with those who collected the data. As collaboration will not always be possible, practical, or desired, the efforts of those who generated the data must be recognized.

IV. Manuscript Preparation and Submission

A. Preparing a Manuscript for Submission to a Medical Journal

1. General Principles

The text of articles reporting original research is usually divided into Introduction, Methods, Results, and Discussion sections. This so-called "IMRAD" structure is not an arbitrary publication format but a reflection of the process of scientific discovery. Articles often need subheadings within these sections to further organize their content. Other types of articles, such as meta-analyses, may require different formats, while case reports, narrative reviews, and editorials may have less structured or unstructured formats.

Electronic formats have created opportunities for adding details or sections, layering information, cross-linking, or extracting portions of articles in electronic versions. Supplementary electronic-only material should be submitted and sent for peer review simultaneously with the primary manuscript.

2. Reporting Guidelines

Reporting guidelines have been developed for different study designs; examples include CONSORT (www.consort-statement.org) for randomized trials, STROBE for observational studies (http://strobe-statement.org/), PRISMA for systematic reviews and meta-analyses (http://prisma-statement.org/), and STARD for studies of diagnostic accuracy (www.stard-statement.org/). Journals are encouraged to ask authors to follow these guidelines because they

Table. **Examples of Data Sharing Statements That Fulfill These ICMJE Requirements***

	Example 1	Example 2	Example 3	Example 4
Will individual participant data be available (including data dictionaries)?	Yes	Yes	Yes	No
What data in particular will be shared?	All of the individual participant data collected during the trial, after deidentification.	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices).	Not available
What other documents will be available?	Study Protocol, Statistical Analysis Plan, Informed Consent Form, Clinical Study Report, Analytic Code	Study Protocol, Statistical Analysis Plan, Analytic Code	Study Protocol	Not available
When will data be available (start and end dates)?	Immediately following publication. No end date.	Beginning 3 months and ending 5 years following article publication.	Beginning 9 months and ending 36 months following article publication.	Not applicable
With whom?	Anyone who wishes to access the data.	Researchers who provide a methodologically sound proposal.	Investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.	Not applicable
For what types of analyses?	Any purpose.	To achieve aims in the approved proposal.	For individual participant data meta-analysis.	Not applicable
By what mechanism will data be made available?	Data are available indefinitely at (*Link to be included)*.	Proposals should be directed to xxx@yyy. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at a third party website (*Link to be included).*	Proposals may be submitted up to 36 months following article publication. After 36 months the data will be available in our University's data warehouse but without investigator support other than deposited metadata. Information regarding submitting proposals and accessing data may be found at (*Link to be provided*).	Not applicable

* These examples are meant to illustrate a range of, but not all, data sharing options.

help authors describe the study in enough detail for it to be evaluated by editors, reviewers, readers, and other researchers evaluating the medical literature. Authors of review manuscripts are encouraged to describe the methods used for locating, selecting, extracting, and synthesizing data; this is mandatory for systematic reviews. Good sources for reporting guidelines are the EQUATOR Network (www.equator-network.org/home/) and the NLM's Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

3. Manuscript Sections

The following are general requirements for reporting within sections of all study designs and manuscript formats.

a. Title Page

General information about an article and its authors is presented on a manuscript title page and usually includes the article title, author information, any disclaimers, sources of support, word count, and sometimes the number of tables and figures.

Article title. The title provides a distilled description of the complete article and should include information that, along with the abstract, will make electronic retrieval of the article sensitive and specific. Reporting guidelines recommend and some journals require that information about the study design be a part of the title (particularly important for randomized trials and systematic reviews and meta-analyses). Some journals require a short title, usually no more than 40 characters (including letters and spaces) on the title page or as a separate entry in an electronic submission system. Electronic submission systems may restrict the number of characters in the title.

Author information. Each author's highest academic degrees should be listed, although some journals do not

publish these. The name of the department(s) and institution(s) or organizations where the work should be attributed should be specified. Most electronic submission systems require that authors provide full contact information, including land mail and e-mail addresses, but the title page should list the corresponding authors' telephone and fax numbers and e-mail address. ICMJE encourages the listing of authors' Open Researcher and Contributor Identification (ORCID).

Disclaimers. An example of a disclaimer is an author's statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

Source(s) of support. These include grants, equipment, drugs, and/or other support that facilitated conduct of the work described in the article or the writing of the article itself.

Word count. A word count for the paper's text, excluding its abstract, acknowledgments, tables, figure legends, and references, allows editors and reviewers to assess whether the information contained in the paper warrants the paper's length, and whether the submitted manuscript fits within the journal's formats and word limits. A separate word count for the abstract is useful for the same reason.

Number of figures and tables. Some submission systems require specification of the number of figures and tables before uploading the relevant files. These numbers allow editorial staff and reviewers to confirm that all figures and tables were actually included with the manuscript and, because tables and figures occupy space, to assess if the information provided by the figures and tables warrants the paper's length and if the manuscript fits within the journal's space limits.

Conflict of interest declaration. Conflict of interest information for each author needs to be part of the manuscript; each journal should develop standards with regard to the form the information should take and where it will be posted. The ICMJE has developed a uniform conflict of interest disclosure form for use by ICMJE member journals (www.icmje.org/coi_disclosure.pdf), and the ICMJE encourages other journals to adopt it. Despite availability of the form, editors may require conflict of interest declarations on the manuscript title page to save the work of collecting forms from each author prior to making an editorial decision or to save reviewers and readers the work of reading each author's form.

b. Abstract

Original research, systematic reviews, and meta-analyses require structured abstracts. The abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. It should emphasize new and important aspects of the study or observations, note important limitations, and not overinterpret findings. Clinical trial abstracts should include items that the CONSORT group has identified as essential (www.consort-statement.org/resources/downloads/extensions/consort-extension-for-abstracts-2008pdf/). Funding sources should be listed separately after the abstract to facilitate proper display and indexing for search retrieval by MEDLINE.

Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to ensure that they accurately reflect the content of the article. Unfortunately, information in abstracts often differs from that in the text. Authors and editors should work in the process of revision and review to ensure that information is consistent in both places. The format required for structured abstracts differs from journal to journal, and some journals use more than one format; authors need to prepare their abstracts in the format specified by the journal they have chosen.

The ICMJE recommends that journals publish the clinical trial registration number at the end of the abstract. The ICMJE also recommends that, when a registration number is available, authors list that number the first time they use a trial acronym to refer to the trial they are reporting or to other trials that they mention in the manuscript. If the data have been deposited in a public repository and/or are being used in a secondary analysis, authors should state at the end of the abstract the unique, persistent data set identifier; repository name; and number.

c. Introduction

Provide a context or background for the study (that is, the nature of the problem and its significance). State the specific purpose or research objective of, or hypothesis tested by, the study or observation. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

d. Methods

The guiding principle of the Methods section should be clarity about how and why a study was done in a particular way. The Methods section should aim to be sufficiently detailed such that others with access to the data would be able to reproduce the results. In general, the section should include only information that was available at the time the plan or protocol for the study was being written; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.

The Methods section should include a statement indicating that the research was approved by an independent local, regional or national review body (e.g., ethics committee, institutional review board). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the local, regional or national review body explicitly approved the doubtful aspects of the study. See Section II.E.

i. Selection and Description of Participants

Clearly describe the selection of observational or experimental participants (healthy individuals or patients, including controls), including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age, sex, or ethnicity is not always known at the time of study design, researchers should aim for inclusion of representative populations into all study types and at a minimum provide descriptive data for these and other relevant demographic variables. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

ii. Technical Information

Specify the study's main and secondary objectives—usually identified as primary and secondary outcomes. Identify methods, equipment (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. Identify appropriate scientific names and gene names.

iii. Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

e. Results

Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (e.g., percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

f. Discussion

It is useful to begin the discussion by briefly summarizing the main findings, and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study, and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section.

Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the

manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly.

g. References

i. General Considerations

Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. On the other hand, extensive lists of references to original work on a topic can use excessive space. Fewer references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and since electronic literature searching allows readers to retrieve published literature efficiently.

Do not use conference abstracts as references: they can be cited in the text, in parentheses, but not as page footnotes. References to papers accepted but not yet published should be designated as "in press" or "forthcoming." Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

Published articles should reference the unique, persistent identifiers of the datasets employed.

Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication.

Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed, or print copies from original sources. Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions. Authors can identify retracted articles in MEDLINE by searching PubMed for "Retracted publication [pt]", where the term "pt" in square brackets stands for publication type, or by going directly to the PubMed's list of retracted publications (www.ncbi.nlm.nih.gov/pubmed?term=retracted+publication+[pt]).

References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by Arabic numerals in parentheses.

References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure. The titles of journals should be abbreviated according to the style used for MEDLINE (www.ncbi.nlm.nih.gov/nlmcatalog/journals). Journals vary on whether they ask authors to cite electronic references within parentheses in the text or in numbered references following the text. Authors should consult with the journal to which they plan to submit their work.

ii. Style and Format

References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals: Sample References (www.nlm.nih.gov/bsd/uniform_requirements.html) webpage and detailed in the NLM's Citing Medicine, 2nd edition (www.ncbi.nlm.nih.gov/books/NBK7256/). These resources are regularly updated as new media develop, and currently include guidance for print documents; unpublished material; audio and visual media; material on CD-ROM, DVD, or disk; and material on the Internet.

h. Tables

Tables capture information concisely and display it efficiently; they also provide information at any desired level of detail and precision. Including data in tables rather than text frequently makes it possible to reduce the length of the text.

Prepare tables according to the specific journal's requirements; to avoid errors it is best if tables can be directly imported into the journal's publication software. Number tables consecutively in the order of their first citation in the text and supply a title for each. Titles in tables should be short but self-explanatory, containing information that allows readers to understand the table's content without having to go back to the text. Be sure that each table is cited in the text.

Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use symbols to explain information if needed. Symbols may vary from journal to journal (alphabet letter or such symbols as *, †, ‡, §), so check each journal's instructions for authors for required practice. Identify statistical measures of variations, such as standard deviation and standard error of the mean.

If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

Additional tables containing backup data too extensive to publish in print may be appropriate for publication in the electronic version of the journal, deposited with an archival service, or made available to readers directly by the authors. An appropriate statement should be added to the text to inform readers that this additional information is available and where it is located. Submit such tables for consideration with the paper so that they will be available to the peer reviewers.

i. Illustrations (Figures)

Digital images of manuscript illustrations should be submitted in a suitable format for print publication. Most submission systems have detailed instructions on the quality of images and check them after manuscript upload. For print submissions, figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints.

For radiological and other clinical and diagnostic images, as well as pictures of pathology specimens or photomicrographs, send high-resolution photographic image files. Before-and-after images should be taken with the same intensity, direction, and color of light. Since blots are used as primary evidence in many scientific articles, editors may require deposition of the original photographs of blots on the journal's website.

Although some journals redraw figures, many do not. Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication. Figures should be made as self-explanatory as possible, since many will be used directly in slide presentations. Titles and detailed explanations belong in the legends—not on the illustrations themselves.

Photomicrographs should have internal scale markers. Symbols, arrows, or letters used in photomicrographs should contrast with the background. Explain the internal scale and identify the method of staining in photomicrographs.

Figures should be numbered consecutively according to the order in which they have been cited in the text. If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce it. Permission is required irrespective of authorship or publisher except for documents in the public domain.

In the manuscript, legends for illustrations should be on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend.

j. Units of Measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.

Temperatures should be in degrees Celsius. Blood pressures should be in millimeters of mercury, unless other units are specifically required by the journal.

Journals vary in the units they use for reporting hematologic, clinical chemistry, and other measurements. Authors must consult the Information for Authors of the particular journal and should report laboratory information in both local and International System of Units (SI).

Editors may request that authors add alternative or non-SI units, since SI units are not universally used. Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

k. Abbreviations and Symbols

Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

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Manuscripts should be accompanied by a cover letter or a completed journal submission form, which should include the following information:

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A statement of financial or other relationships that might lead to a conflict of interest, if that information is not included in the manuscript itself or in an authors' form. See also Section II.B.

A statement on authorship. Journals that do not use contribution declarations for all authors may require that the submission letter includes a statement that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work if that information is not provided in another form See also Section II.A.

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bodies) regarding the conduct of the research or if corrective action has been recommended. The letter or form should give any additional information that may be helpful to the editor, such as the type or format of article in the particular journal that the manuscript represents. If the manuscript has been submitted previously to another journal, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Editors encourage authors to submit these previous communications. Doing so may expedite the review process and encourages transparency and sharing of expertise.

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JAFES welcomes manuscripts on all aspects of endocrinology and metabolism in the form of original articles, review articles, case reports, feature articles (clinical practice guidelines, clinical case seminars, book reviews, et cetera), editorials, letters to the Editor, brief communications and special announcements. See Inset Box for descriptions and specific requirements per article type.

COVER LETTER UPDATE

A cover letter must accompany each manuscript which should cite the title of the manuscript, the list of authors (complete names and affiliations and their specific role/s in writing the manuscript), with one (1) author clearly designated as correspondent, providing his/her complete postal/mailing address, telephone number, e-mail address and fax number.

*All authors are required to obtain an ORCID iD. To register, kindly follow this link: https://orcid.org/register.

The **JAFES cover letter template** must be used.

AUTHOR FORM UPDATE

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1. CONSORT (2010) Checklist for Reporting Clinical Trials
2. CARE (2013) Checklist for Reporting Case Reports
3. COREQ (2007) Checklist for Reporting Qualitative Research
4. PRISMA (2009) Checklist for Reporting Systematic Reviews and Meta-Analyses
5. STROBE (2007) Checklist for Reporting Observational Studies
6. STARD (2015) Checklist for Reporting Diagnostic Accuracy Studies
7. CHEERS (2013) Checklist for Reporting Economic Evaluation of Health Interventions
8. SQUIRE (2015) Checklist for Quality Improvement Reporting in Healthcare
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In order to ensure scientific objectivity and independence, the JAFES requires all authors to make a full disclosure of areas of potential conflict of interest. Such disclosure will indicate whether the person and/or his/her immediate family has any financial relationship with pharmaceutical companies, medical equipment manufacturers, biomedical device manufacturers, or any companies with significant involvement in the field of health care.

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ETHICS REVIEW APPROVAL UPDATE

For Original Articles, authors are required to submit a scanned soft copy of the Ethics Review Approval of their research. For manuscripts reporting data from studies involving animals, authors are required to submit a scanned copy of the Institutional Animal Care and Use Committee approval.

INFORMED CONSENT UPDATE

For Case Reports, Images in Endocrinology and Clinical Case Seminars, authors are required to submit scanned soft copy of signed informed consent for publication from the involved subject/s ("Patient Consent Form").

GENERAL GUIDELINES

1. The manuscript should be encoded using Microsoft Word, double-spaced throughout with 1¼ cm (½ inch) paragraph indentation, with 3-cm margins (1¼ inch) all around on A4 size paper. The preferred font style and size is Times New Roman 12.
2. The manuscript should be arranged in sequence as follows: (1) Title Page, (2) Abstract, (3) Text, (4) References, (5) Tables, and (6) Figures & Illustrations.
3. References should pertain directly to the work being reported.
4. All the sheets of the manuscript should be labelled with the family name of the main author (all in capital letters) and page number (in Arabic Numerals) printed on the upper right corner.
5. All manuscripts not complying with the above shall be promptly returned for correction and resubmission.

Title Page

1. The title should be as concise as possible.
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3. The highest educational attainment or title of the authors should be included as an attachment whenever appropriate
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5. If the paper has been presented in a scientific forum or convention, a note should be provided indicating the name, location and date of its presentation.

Abstract

For original articles, the abstract should contain no more than 200 words with a structured format consisting of the objective/s, methodology, results and conclusion. For feature articles, case reports, interhospital grand rounds, and brief communications, the abstract should be from 50 to 75 words and need not be structured.

Keywords

At least 3 keywords but no more than 6, preferably using terms from the Medical Subject Headings (MeSH) list of Index Medicus, should be listed horizontally under the abstract for cross-indexing of the article.

Text

1. Generally, the text should be organized consecutively as follows: Introduction, Methodology, Results and Discussion, and Conclusion (IMRAD format).
2. All references, tables, figures and illustrations should be cited in the text, in numerical order.
3. All abbreviations should be spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses. The same abbreviation may then be used subsequently instead of the long names.
4. All measurements and weights should preferably be in System International (SI) units.
5. If appropriate, information should be provided on institutional review board/ethics committee approval.
6. Acknowledgements to individuals/groups of persons, or institution/s should be included at the end of the text just before the references. Grants and subsidies from government or private institutions should also be acknowledged.

References

1. References in the text should be identified by Arabic Numerals in superscript on the same line as the preceding sentence.
2. References should be typed double-spaced on a separate sheet. They should be numbered consecutively in the order by which they are mentioned in the text. They should not be alphabetized.
3. All references should provide inclusive page numbers.
4. Journal abbreviations should conform to those used in PubMed.
5. A maximum of six authors per article can be cited; beyond that, name the first three and add "et al."
6. The style/punctuation approved by JAFES conforms to that recommended by the International Committee of Medical Journal Editors (ICMJE) available at http://www.icmje.org. Follow the format of the examples shown below:

Journal Article

Padua FR, Paspe MG. Antinuclear antibody in the rheumatic and non-rheumatic diseases among Filipinos. Acta Med Philippina. 1990; 26(2):81-85.

One to Six Authors (Commentary, Online)

Krause RM. The origin of plagues: old and new. Science. 1992;257:1073-1078.

Barry JM. The site of origin of the 1918 influenza pandemic and its public health implications. [Commentary]. JTranslational Med. January 20, 2004;2(3):1-4. http://www.translational-medicine.com/content/2/1/3. Accessed November 18, 2005.

Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the US. JAMA. 2001;286(10):1195-1200.

More than Six Authors

McGlynn EA, M.Asch S, Adams J, et al. The quality of health care delivered to adults in the United States.N Engl J Med. June 26, 2003;348(26):2635-2645.

Authors Representing a Group

Moher D, Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285(15):1987-1991.

Book

Byrne, DW. Publishing your medical research paper: What they don't teach in medical school. Baltimore: Williams & Wilkins, 1998.

World Wide Web

The key and critical objectives of JAMA. http://jama.ama-assn.org/misc/aboutjama.dtl. Accessed April 4, 2007.

Tables

1. Cite all tables consecutively in the text and number them accordingly.
2. Create tables preferably using Microsoft Excel with one table per worksheet.
3. Tables should not be saved as image files.
4. The content of tables should include a table number (Arabic) and title in capital letters above the table, and explanatory notes and legends as well as definitions of abbreviations used below.
5. Font should be Arial Narrow size 8.
6. Each table must be self-explanatory, being a supplement rather than a duplicate of information in the text.
5. Up to a maximum of five (5) tables are allowed.

Figures and Graphs

1. Figures or graphs should be identified by Arabic Numeral/s with titles and explanations underneath.
2. The numbers should correspond to the order in which the figures/graphs occur in the text. It is recommended that figures/graphs also be submitted as image files (preferably as .jpeg or .gif files) of high resolution.
3. Provide a title and brief caption for each figure or graph. Caption should not be longer than 15-20 words.
4. All identifying data of the subject/s or patient/s under study such as name or case numbers, should be removed.
5. Up to a maximum of five (5) figures and graphs are allowed.

Illustrations and Photographs

1. Where appropriate, all illustrations/photographic images should be at least 800 x 600 dpi and submitted as image files (preferably as .jpeg or .gif files).
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1. Upon receipt of the manuscript, the Editor shall review the submission, check if it has met aforementioned criteria and consult with members of the Editorial Board to decide whether it shall be considered for publication or not.
2. Within one (1) week of submission, authors shall be notified through e-mail that their manuscript either (a) has been sent to referees for peer-review or (b) has been declined without review.
3. The JAFES implements a strict double blind peer review policy. For manuscripts that are reviewed, authors can expect an initial decision within forty five (45) days after submission. There may be instances when decisions can take longer than 45 days, in such cases, the editorial assistant shall inform the authors. The editorial decision for such manuscripts shall be one of the following: (a) acceptance without further revision, (b) acceptance with minor revisions, or (c) major manuscript revision and resubmission.
4. Accepted manuscripts are subject to editorial modifications to bring them in conformity with the style of the journal.

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ARTICLE TYPES

Original articles
The abstract should contain no more than 200 words with a structured format consisting of the objective/s, methodology, results and conclusion. A manuscript for original articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Reviews
Review articles provide information on the "state of the art." JAFES encourages that reviews not only summarize current understanding of a particular topic but also describe significant gaps in the research, and current debates. The abstract should be from 50 to 75 words and should not be structured. A manuscript for reviews should not exceed 15 typewritten pages (including tables, figures, illustrations and references) or 4000 words.

Case Reports
The abstract should be from 50 to 75 words and should not be structured. A manuscript for case reports should not exceed 10 typewritten pages (including tables, figures, illustrations and references) or 3000 words.

Feature articles
JAFES may feature articles, either as part of an issue theme, such as Summary Clinical Practice Guidelines on endocrinology from each AFES country society, or a special topic on endocrinology by an international expert or authority. The abstract should be from 50 to 75 words and should not be structured. A manuscript for feature articles should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

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JAFES encourages submission of special articles that summarize and document the proceedings of endocrinology grand rounds, which includes presentation of medical problems of a particular patient, evaluation and work-up, treatment and clinical course, discussion of key diagnostic and management points, and commentaries by specialty experts. JAFES recognizes the importance of this type of article as an educational tool for physicians and health practitioners. The abstract should be from 50 to 75 words and should not be structured. A manuscript for grand rounds should not exceed 25 typewritten pages (including tables, figures, illustrations and references) or 6000 words.

Brief Communications
Brief Communications are short reports intended to either extend or expound on previously published research OR present new and significant findings which may have a major impact in current practice. If the former, authors must acknowledge and cite the research which they are building upon. The abstract should be from 50 to 75 words and should not be structured. A manuscript for brief communications should not exceed 5 typewritten pages (including tables, figures, illustrations and references) or 1500 words.

Editorials
Articles that represent the scientific opinion and views of an author. Every issue of JAFES includes an Editorial by the Editor-in-Chief and may include one or two additional editorials from experts from the scientific community commenting on a particular field or issue on endocrinology. No abstract or keywords necessary.

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Keywords	☐ Provide 3-5 keywords (listed in MeSH)
Content	☐ Provide text/content in IMRAD format (Introduction, Methodology, Results and Discussion, Conclusion) ☐ Make sure all abbreviations are spelled out once (the first time they are mentioned in the text) followed by the abbreviation enclosed in parentheses; the same abbreviation may then be used subsequently ☐ Make sure all measurements and weights are in SI units ☐ If appropriate, provide information on institutional review board/ethics review committee approval ☐ Acknowledgements to individuals/groups of persons, or institution/s should be included at the end of the text just before the references; grants and subsidies from government or private institutions should also be acknowledged
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SPECIFIC CONTRIBUTIONS OF THE AUTHORS (CHECK ALL THAT APPLY)

Complete Name	Conception and design of the work	Data analysis and interpretation	writing the article	Critical revision of the article for important intellectual content	Data Collection	Provision of materials, patients, resources	Statistical analysis	Obtain funding	Literature search	Accountability for all aspects of the work	Others

For others, kindly specify the task below

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Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. It contains programming that allows appropriate data display. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in six parts.

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This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party -- that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

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4. Intellectual Property.

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Entity: government agency, foundation, commercial sponsor, academic institution, etc.
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wish to announce the dates for the

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JANUARY 18, 2019 (Friday)
WRITTEN EXAMINATION

JANUARY 20, 2019 (Sunday)
ORAL EXAMINATION

DEADLINE FOR APPLICATIONS:
AUGUST 3, 2018 (Friday)

For further details, please contact:

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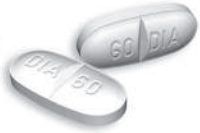

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COMPOSITION: Diamicron MR 60 mg, modified release tablet containing 60 mg of gliclazide, contains lactose as an excipient. INDICATION: Non-insulin-dependent diabetes (type 2) in adults, in association with dietary measures and with exercise, when these measures alone are not sufficient. DOSAGE AND ADMINISTRATION: One half to 2 tablets per day i.e. from 30 to 120 mg taken orally as a single intake at breakfast time, including in elderly patients and those with mild to moderate renal insufficiency with careful patient monitoring. One tablet of Diamicron MR 60 mg is equivalent to 2 tablets of Diamicron MR 30 mg. The breakability of Diamicron MR 60 mg enables flexibility of dosing to be achieved. In patients at risk of hypoglycemia, daily starting dose of 30 mg is recommended. Combination with other antidiabetics: Diamicron MR 60 mg can be given in combination with biguanides, alpha glucosidase inhibitors or insulin (under close medical supervision). CONTRAINDICATIONS: Hypersensitivity to gliclazide or to any of the excipients, other sulfonylurea or sulphonamides; type 1 diabetes; diabetic pre-coma and coma, diabetic ketoacidosis; severe renal or hepatic insufficiency (in these cases the use of insulin is recommended); treatment with miconazole (see interactions section); lactation (see fertility, pregnancy and lactation section). WARNINGS: Hypoglycemia may occur with all sulfonylurea drugs, in cases of accidental overdose, when calorie or glucose intake is deficient, following prolonged or strenuous exercise, and in patients with severe hepatic or renal impairment. Hospitalization and glucose administration for several days may be necessary. Patient should be informed of the importance of following dietary advice, of taking regular exercise, and of regular monitoring of blood glucose levels. To be prescribed only in patients with regular food intake. Use with caution in patients with G6PD-deficiency. Excipient: contains lactose. INTERACTIONS: Risk of hypoglycemia - contraindicated: miconazole; not recommended: phenylbutazone; alcohol; use with caution: other antidiabetic agents, beta-blockers, fluconazole, ACE inhibitors (captopril, enalapril), H2-receptor antagonists, MAOIs, sulfonamides, clarithromycin, NSAIDs. Risk of hyperglycemia - not recommended: danazol; use with caution: chlorpromazine at high doses; glucocorticoids; ritodrine; salbutamol; terbutaline; Saint John's Wort (hypericum perforatum) preparations. Risk of dysglycemia - use with caution: fluoroquinolones. Potentiation of anticoagulant therapy (e.g. warfarin), adjustment of the anticoagulant may be necessary. PREGNANCY AND BREASTFEEDING: Pregnancy: Change to insulin before a pregnancy is attempted, or as soon as pregnancy is discovered. Lactation: Contraindicated. DRIVING & USE OF MACHINES: Possible symptoms of hypoglycemia to be taken into account especially at the beginning of the treatment. UNDESIRABLE EFFECTS: Hypoglycemia, abdominal pain, nausea, vomiting, dyspepsia, diarrhea, constipation. Rare: changes in hematology generally reversible (anemia, leukopenia, thrombocytopenia, granulocytopenia). Raised hepatic enzymes levels (AST, ALT, alkaline phosphatase), hepatitis (isolated reports). If cholestatic jaundice: discontinuation of treatment. Transient visual disturbances at start of treatment. More rarely: rash, pruritus, urticaria, angioedema, erythema, maculopapular rashes, bullous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and exceptionally, drug rash with eosinophilia and systemic symptoms (DRESS). As for other sulfonylureas: observed cases of erythrocytopenia, agranulocytosis, hemolytic anemia, pancytopenia, allergic vasculitis, hyponatremia, elevated liver enzymes, impairment of liver function (cholestasis, jaundice) and hepatitis which led to life-threatening liver failure in isolated cases. OVERDOSE: Possible severe hypoglycemia requiring urgent IV glucose, immediate hospitalization and monitoring. PROPERTIES: Diamicron MR 60 mg is a sulfonylurea reducing blood glucose levels by stimulating insulin secretion from beta cells in the islets of Langerhans, thereby restoring the first peak of insulin secretion and increasing the second phase of insulin secretion in response to a meal or intake of glucose. Independent hemovascular properties. PRESENTATION: Box of 60 tablets of Diamicron MR 60 mg in blister.

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