JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
REVIEW ARTICLE

Review of insulin-associated hypoglycemia and its impact on the management of diabetes in Southeast Asian countries

Su-Yen Goh[1]*, Zanariah Hussein[2], Achmad Rudijanto[3]

[1]Department of Endocrinology, Singapore General Hospital, Singapore, [2]Department of Medicine, Hospital Putrajaya, Putrajaya, Malaysia, and [3]Faculty of Medicine, Brawijaya University, Brawijaya, Indonesia

Keywords
Clinical, Hypoglycemia, Insulin

***Correspondence**
Su-Yen Goh
Tel.: +65-6321-4654
Fax: +65-6227-3576
E-mail address:
goh.su.yen@singhealth.com.sg

J Diabetes Investig 2017; 8: 635–645

doi: 10.1111/jdi.12647

ABSTRACT

Although the incidence of diabetes is rising in Southeast Asia, there is limited information regarding the incidence and manifestation of insulin-associated hypoglycemia. The aim of the present review was to discuss what is currently known regarding insulin-associated hypoglycemia in Southeast Asia, including its known incidence and impact in the region, and how the Southeast Asian population with diabetes differs from other populations. We found a paucity of data regarding the incidence of hypoglycemia in Southeast Asia, which has contributed to the adoption of Western guidelines. This might not be appropriate, as Southeast Asians have a range of etiological, educational and cultural differences from Western populations with diabetes that might place them at greater risk of hypoglycemia if not managed optimally. For example, Southeast Asians with type 2 diabetes tend to be younger, with lower body mass indexes than their Western counterparts, and the management of type 2 diabetes with premixed insulin preparations is more common in Southeast Asia. Both of these factors might result in higher rates of hypoglycemia. In addition, Southeast Asians are often poorly educated about hypoglycemia and its management, including during Ramadan fasting. We conclude there is a need for more information about Southeast Asian populations with diabetes to assist with the construction of more appropriate national and regional guidelines for the management of hypoglycemia, more closely aligned to patient demographics, behaviors and treatment practices. Such bespoke guidelines might result in a greater degree of implementation and adherence within clinical practice in Southeast Asian nations.

INTRODUCTION

The present article seeks to explore what is currently known about the problem of insulin-associated hypoglycemia in the populations with diabetes of members (Indonesia, Malaysia, the Philippines and Singapore) of the Association of South East Asian Nations (ASEAN), with a view to establishing guidelines for its avoidance and management. This is an important undertaking because the prevalence of type 2 diabetes is high and rising in these nations, and there are some potentially important cultural and etiological differences between ASEAN populations and those of the predominantly Caucasian nations for which some of the standard global guidelines have been developed. To assess what is known about insulin-associated hypoglycemia in these Southeast Asian countries and related issues of local significance, published scientific articles of potential relevance were identified by a PubMed search using search terms including 'hypoglyc(a)emia/hypoglyc(a)emic,' 'insulin/cost/quality of life' and countries/nationalities; for example, (Hypoglycaemia OR Hypoglycemia) AND insulin AND (Indonesia or Indonesian). The search results assessed were limited to recent publications (2000–2016), and the countries included were Indonesia, Malaysia, the Philippines and Singapore. The present review provides a narrative account of the subject based on the relatively few articles identified, supplemented where necessary by information from international studies.

Received 6 May 2016; revised 13 January 2017; accepted 21 February 2017

PREVALENCE OF DIABETES IN THE SOUTHEAST ASIA REGION

There is limited information regarding actual rates of diabetes in Southeast Asia, owing to a lack in many countries of regular population surveys that utilize appropriate methodology; that is,

utilization of household interviews and measurements of fasting blood glucose in those not previously diagnosed as diabetic at the time of survey. While Malaysia carries out a national health and morbidity survey[1], and has reported the prevalence of diabetes in adults at 17.5% in 2015[2], this information is lacking for other countries and relies on estimates. In Indonesia, Malaysia, the Philippines and Singapore, the estimated prevalence of diabetes (based on oral glucose tolerance tests) in adults was 6.2, 16.6, 6.1 and 12.8%, respectively[3], and since the 1980s there has been a large increase (1.5- to 5.2-fold) in the prevalence of diabetes[4]. The highest increases in this prevalence are in urban areas[4], with Southeast Asia seeing some of the highest rates of global urbanization[5]. Although rates of diabetes are increasing globally, there is a mismatch between the projected estimated increases in prevalence (1.5-fold) and spending (1.2-fold) from 2015–40, due to the fact that 75% of the global population with diabetes lives in low-to-middle-income countries, which contribute just 19% to global diabetes-related health expenditure[3]. However, in the Southeast Asian nations, diabetes-related health costs are predicted to escalate much higher than the global average of 8% total health expenditure. In 2010, Indonesia, the Philippines, Singapore and Malaysia spent, respectively, 7.0, 11.0, 15.0 and 16.0% of their total national health expenditure on diabetes, and by 2030 it is predicted that costs in these countries will rise 1.7- to 1.8-fold[3]. A contributor to this health expenditure is the prevalence and type of therapeutic treatment offered to patients in Southeast Asia. For example, a high proportion of patients with type 2 diabetes in Indonesia, the Philippines, Singapore and Malaysia take at least one oral antidiabetic drug (OAD) (57.2–85.0%), with a smaller proportion of patients taking insulin (3.0–19.3%) alone or in combination with OADs (8.0–19.4%; Table 1)[2,6–9]. Comparing these limited data with data from the USA, the use of OADs appears more common in Asia, with insulin used less frequently in some countries (particularly in combination with OADs) than in the USA.

INSULIN-ASSOCIATED HYPOGLYCEMIA

Insulin therapy is the primary therapeutic intervention for patients with type 1 diabetes, and in many countries this is also true for patients with type 2 diabetes who become inadequately controlled with lifestyle changes and OADs[10,11]. The goal of insulin therapy is to regain glycemic control, which is generally assessed by success in achieving target glycated hemoglobin (HbA_{1c}) concentration. However, successful management also requires monitoring of hypoglycemia, the most common side-effect of insulin and many other glucose-lowering therapies. In pursuit of glycemic targets, while minimizing patient risk of hypoglycemia, insulin is dosed according to self-monitoring of blood glucose (SMBG) levels, and is measured more frequently when patients are closer to glycemic target, at greater risk of hypoglycemia or symptomatic for low blood glucose[12]. Rates of hypoglycemia differ across the different treatment options for the first insulin prescribed, with higher rates of hypoglycemia associated with bolus and premixed insulins compared with basal insulin[13]. Intensified basal–bolus regimens inevitably result in higher rates of hypoglycemia compared with basal-only insulin regimens[14], and premixed insulins have been associated with a greater incidence of hypoglycemia than basal–bolus regimens[15,16]. The experience of hypoglycemia can be at best unpleasant and at worst life-threatening for the patient, hence the fear of repeated episodes can lead patients and their carers to become overly cautious in their treatment of diabetes – potentially to the detriment of the patient's long-term prognosis. Hypoglycemia is therefore an important consideration when constructing individualized glycemic targets[17,18]. Despite high awareness among patients and physicians that hypoglycemia is a significant barrier to the effective treatment of diabetes, it is feared that there is vast underreporting of hypoglycemia rates[19]. This might therefore mask the scale of the problem, and potential differences between insulin products and regimens.

INCIDENCE OF HYPOGLYCEMIA IN SOUTHEAST ASIA

There is a paucity of information regarding the incidence of hypoglycemia in Southeast Asia, particularly for patient-reported data from clinical practice. In contrast, there are a number of European and North American observational studies and surveys in patients with type 1 diabetes[20–23] and type 2 diabetes[20–25] reporting rates of non-severe hypoglycemia, but their comparability with South Asian countries might be questionable. The scarcity of hypoglycemia data for Asians was partly addressed after the completion of the A_1chieve® study – a non-interventional, observational study of 66,726 insulin-experienced (started on insulin detemir, insulin aspart or

Table 1 | Diabetes treatment patterns of patients from Southeast Asia and the USA[2,6–9]

Treatment	Indonesia (type 2 diabetes)[8]	Malaysia (DM)[2]	Philippines (DM)[7]	Singapore (type 2 diabetes)[9]	USA (DM)[6]
OADs[†]	61.9%	79.1%	85.0%[§]	57.2%	50.3%
Insulin	17.3%	25.1%	15.0%	3.0%	17.8%
OAD and insulin	19.4%	NA	8.0%	9.0%	13.0%
Other[‡]	0.3%	0.5%	NA	NA	NA

[†]Oral antidiabetic drugs (OADs) used without injectables. [‡]Traditional or complementary medicine. [§]Using at least one oral drug of which 97% were OADs. DM, diabetes mellitus; NA, not available; OAD, oral antidiabetic drug.

biphasic insulin aspart) and insulin-naïve patients with type 2 diabetes, in 28 countries across four continents[26]. A$_1$chieve® showed that initiation of, or switch to, insulin therapy using modern insulin analog products decreased the rates of hypoglycemia in patients with type 2 diabetes[27–29]. However, although A$_1$chieve® might provide reassurance about the clinical efficacy/safety profiles of particular insulin analogs, gaps remain in the reporting of hypoglycemia rates for patients with type 1 diabetes in each of the countries within the ASEAN region (e.g., data for Malaysia and Singapore are lacking), and for all diabetes patients taking other insulin regimens, such as basal and premix. Apart from A$_1$chieve®, there are few publications reporting the rates of hypoglycemia for exclusively Southeast Asian populations, with many studies reporting rates from multinational populations where Asian and Western populations are mixed[30–32]. With a lack of comprehensive data regarding rates of hypoglycemia from Southeast Asian countries, it is difficult to quantify the potential impact of hypoglycemia in this region. However, there is a wealth of information from Western countries, which can be discussed alongside the available data detailing the impact of hypoglycemia in Southeast Asia. Collectively, the evidence shows that the impact of hypoglycemia is wide and far reaching, affecting the morbid burden of patients, treatment adherence and thereby diabetic complications. These in turn have health economic implications.

IMPACT OF HYPOGLYCEMIA

Impact on patient health, well-being and treatment adherence

Before insulin is even initiated, patients and physicians have misconceptions about hypoglycemia, creating a fear of insulin therapy that can result in reduced adherence once insulin is initiated[33,34], and in some cases, refusal to initiate it[35]. A study in Malaysia reported that non-adherent patients felt their healthcare professional (HCP) had not properly explained the risks and benefits of insulin to them[36], and some patients perceived that advice from their HCP was biased towards the benefits, with the risks of insulin therapy only explained once patients had agreed to start treatment[37]. In addition, 54.3% of Malaysians with type 2 diabetes, using insulin, were worried about the risk of hypoglycemic events, and 61.3% of those not currently using insulin were worried about starting insulin treatment[38]. This 'fear factor' about hypoglycemia has a negative impact on the management of diabetes, metabolic control and health outcomes[39]. Episodes of hypoglycemia, when symptomatic, lead to unpleasant and distressing symptoms including pounding heart, trembling, hunger, sweating and difficulty in concentrating[40]. In severe cases, this can lead to confusion/disorientation, seizures and loss of consciousness requiring third-party assistance[41]. The trauma created by hypoglycemia translates into a tangible fear of hypoglycemia and, although this has not been quantified in Southeast Asia, one Singaporean study of patients with type 1 diabetes or type 2 diabetes taking insulin for at least 1 year has validated the use of a fear-of-hypoglycemia survey[42] in patients who had at least one episode of mild (56%), moderate (51%) or severe hypoglycemia (31%) in the month, 6 and 12 months before the survey. Although patient fear has not been quantified to date, it is clear that severe episodes of hypoglycemia can result in medical complications[43], associated with increased risk of falls, fall-related morbidity[34,44] and increased risk of mortality[45–47]. Such symptoms and consequences contribute to an overall decrease in patients' health-related quality of life[48–50], and studies such as A$_1$chieve® have shown that if rates of hypoglycemia can be improved upon, so can health-related quality of life[27,29,51–54].

The fear of hypoglycemia works as a limiting factor to the achievement of glycemic control, preventing HCPs from intensifying insulin therapy[20], particularly in older patients with comorbidities[55], thus placing them at an increased risk of complications such as cardiovascular disease[56]. For this reason, both the American Diabetes Association and the European Association for the Study of Diabetes guidelines advise that the target level of glycemic control is individualized based on a patient's risk of hypoglycemia, duration of disease, comorbidities and life expectancy[17,18]. This individualized approach to treatment translates to hypoglycemia being a common reason for patients with type 2 diabetes changing or switching insulin therapy[57], and severe cases of hypoglycemia can lead to termination of insulin therapy[58].

Health economic impact

Severe hypoglycemia accounts for significant medical expenditure as a result of hospitalization[59–61] and loss of productivity[62], with lower blood glucose/more severe hypoglycemia being associated with increased length of stay and increased risk of mortality[63]. Furthermore, economic costs increase in patients with micro-and macrovascular complications arising from poor glucose control[64], which is likely to occur in patients receiving less intensive glucose-lowering therapies and those with reduced adherence to medications due to fear of hypoglycemia. One potential driver of increased economic cost in patients at high risk of hypoglycemia is the more frequent use of SMBG[65], but as SMBG is poorly utilized by patients in Asian countries, such as Malaysia[66,67] (despite incorporation into type 2 diabetes treatment guidelines[68]), the economic costs of hypoglycemia in Southeast Asia are more likely to be impacted by its underutilization and the economic consequences derived from poorer glycemic control[69]. The economic impact of hypoglycemia also differs among different insulins as a result of differences in their kinetic profiles, and because different doses might be required to reach the same glycemic target. For example, a cost-effectiveness analysis in Singaporean patients with type 2 diabetes estimated that the costs of treating complications, including severe hypoglycemia, were $5,450 and $2,800 per patient for those using neutral protamine Hagedorn or insulin glargine over a 5-year period[70]. However, this cost-effectiveness analysis requires validation with local outcomes data, as the rates of severe hypoglycemia (1.30 and 0.57 per patient-year for neutral protamine Hagedorn insulin and insulin glargine) were extrapolated from a study of Western patients with type 1 diabetes[71].

In summary, there is a scarcity of information regarding the true incidence and impact of hypoglycemia in Southeast Asia and, as a result, diabetes guidelines have been based on information taken from global studies that have informed Western guidelines. However, the Southeast Asian population is characterized by demographic, etiological and cultural differences from Western populations, as well as treatment differences, and these might have different consequences on both the incidence and impact of hypoglycemia.

DEMOGRAPHIC AND ETIOLOGICAL ISSUES PERTAINING TO SOUTHEAST ASIAN PATIENTS

Southeast Asian patients often present with type 2 diabetes at a younger age and with lower body mass index than their Caucasian counterparts[72], and with a phenotype characterized by loss of prandial insulin secretory reserve[73,74]. These factors in turn result in some differences between Southeast Asian and Western nations in the use of insulin therapy[75,76], and all of these issues can impact the risk, manifestation and appropriate management of hypoglycemia. For example, predictive factors for hypoglycemia include previous hypoglycemia, >2 injections per day, body mass index <30 kg/m^2 and duration of insulin therapy >10 years/longer duration of therapy[14,43]. In contrast to the incidence of type 2 diabetes, type 1 diabetes is less common in Asia compared with other regions[77–79], hence the following discussion will predominantly focus on issues concerning type 2 diabetes.

Southeast Asians might be genetically predisposed to developing type 2 diabetes[80] as, despite having a greater adiposity than Western populations[81], there is a tendency for those with type 2 diabetes to be younger and have a lower body mass index compared with Western populations with type 2 diabetes[72]. This might also explain the finding that Asians have type 2 diabetes characterized primarily by β-cell dysfunction/reduced insulin secretion rather than insulin resistance[82,83], with greater post-prandial rises in glycemia[84].

The notion that type 2 diabetes presents differently in people of Asian descent is supported by studies conducted outside of Asia. For example, in an observational study in the UK, people with a South Asian ethnicity experienced a smaller improvement in HbA_{1c}, independent of treatment type or social deprivation[85]; a finding that might have been explained by the earlier onset of diabetes in Asian ethnicities, and the tendency for HbA_{1c} control to become more challenging with duration of diabetes[86].

CULTURAL ISSUES PERTAINING TO SOUTHEAST ASIAN PATIENTS

Educational differences in Southeast Asia

The available evidence suggests there are communication/educational issues that might impact the manifestation of hypoglycemia in Southeast Asian populations. A survey examining communication between patients and physicians found that patients with type 2 diabetes in Asia had a poorer understanding of the symptoms and causes of hypoglycemia compared with other regions. While 53% of Europeans did not understand that medication is a cause of hypoglycemia, this was 72% in Asia. Furthermore, 74% of surveyed Asians reported that it would be extremely useful to discuss hypoglycemia more frequently with their physician[87].

Ramadan

Ramadan is a period of fasting of approximately 29 days based on the lunar calendar, where food is not consumed during daylight hours, and is typically divided by a light pre-dawn meal and a post-sunset large meal. As patients with increased daily activity and/or irregular eating habits (decrease, delay or omission of meals) are at increased risk of hypoglycemia[88], such behaviors represent a particular concern in Southeast Asia because of the high proportion of Muslim patients who practice Ramadan[89]. In 2013, the total populations of Indonesia, Malaysia, the Philippines and Singapore were, respectively, 249, 30, 99 and 5 million people[90], but because of a lack of any recent census data in many Southeast Asian countries, the sizes of the Muslim populations are unknown. However, a study from the year 2000 by Pew Research Center's Forum on Religion & Public Life[91] placed the proportion of Muslims in Indonesia, Malaysia, the Philippines, and Singapore at 88.2, 60.4, 5.1 and 14.9%, respectively.

In Malaysia, 89.8% of patients with type 2 diabetes fast for at least 15 days during Ramadan[77], and this fasting places Asians at a greater risk of both hypo- and hyperglycemia, as shown by the Epidemiology of Diabetes and Ramadan study[77]. The Epidemiology of Diabetes and Ramadan study assessed the effect of fasting on treatment patterns of patients with diabetes during Ramadan from 13 different countries, including some from Southeast Asia. It showed that 42.8 and 78.7% of patients with type 1 diabetes or type 2 diabetes fasted for ≥15 days, and during Ramadan there was a significant increase in the incidence of severe hypoglycemia in patients with type 2 diabetes[77]. Furthermore, significant associations between change in insulin dose and severe hypoglycemia were found during Ramadan, with 27.7% of patients with type 2 diabetes either decreasing (24.7%) or stopping insulin (3.0%)[77]. These findings are concerning, and highlight that there might be a need to improve patient education and awareness of the risks of fasting with diabetes. Additionally, as specific guidelines have been developed for the Southeast Asian countries with the highest proportion of Muslims (Indonesia[92] and Malaysia[93]), there could also be a need to increase awareness and adherence to these guidelines amongst HCPs. Both the Indonesian and Malaysian guidelines for patients with type 2 diabetes advise that special education about hypoglycemia and SMBG should be provided 2–4 months before Ramadan, and that during Ramadan patients should take care to ensure adequate hydration (≥1,500 mL/day), appropriate levels of exercise, and to make adjustments to the timing and dose of insulin if there are changes in meal times[92,93]. Furthermore, recent international guidelines for the

management of diabetes during Ramadan state that patients 'need careful blood glucose monitoring and if necessary such treatment regimens may be adjusted, ' because patients treated with sulfonylureas and insulin are at the highest risk of hypoglycemia[94]. However, just 68 and 62% of patients with type 1 or type 2 diabetes from the Epidemiology of Diabetes and Ramadan study received advice from HCPs regarding fasting and diabetes[77]. Insulin use is a particular concern in pregnant women (with either type 1 or type 2 diabetes) during Ramadan in Southeast Asia, with one Malaysian study showing that 20.8% of pregnant women were unable to fast for more than 15 days without hypoglycemia or fetal demise[95]. It is therefore of no surprise that recommendations suggest that physicians consider offering patient education, more regular SMBG and dose adjustment to minimize the risk of hypoglycemia in the weeks preceding Ramadan[94].

INSULIN TREATMENT DIFFERENCES IN SOUTHEAST ASIA AND WESTERN PRACTICE

Differences in the manifestation of type 2 diabetes have inevitably led to some differences in approach to insulin treatment between Southeast Asian and Western populations. Although the proportions of Southeast Asians using insulin appears to be similar to the West/USA, with the exception of Singapore (Table 1), the type of insulin preferred in these continents might differ. For example, while the first insulin to be used in the regimen of Westerners is most often a basal insulin, Asian patients are more often started with a premix (Figure 1)[38,96–98], as this addresses postprandial glucose as well as fasting plasma glucose control[75,76]. Premixed insulins being more popular in Asia[75,76] might result in higher rates of hypoglycemia compared with Western populations using basal insulins[15,16,99]. As hypoglycemia is a greater concern during Ramadan fasting, a South Asian consensus guidelines has been developed for the use of insulin during Ramadan[100], with different insulin doses recommended during fasting and at mealtime to minimize hypoglycemia and postprandial hyperglycemia, respectively. Additionally, these consensus guidelines recommend use of insulin analogs during Ramadan to help reduce the risk of hypoglycemia in insulin-treated patients[100]. The guidelines recommend that those on premix use 30 U of 70:30 (bolus:basal) in the evening with dinner and 10 U at predawn/morning; alternatively, an inverted dual regimen (30:70 or 25:75 and 50:50 in the evening) can also be used[100]. For those using basal–bolus insulin, the consensus guidelines recommend using a full dose of bolus insulin in the evening and a half dose in the morning, whereas basal insulin should be converted to a regimen of half a dose in the morning (neutral protamine

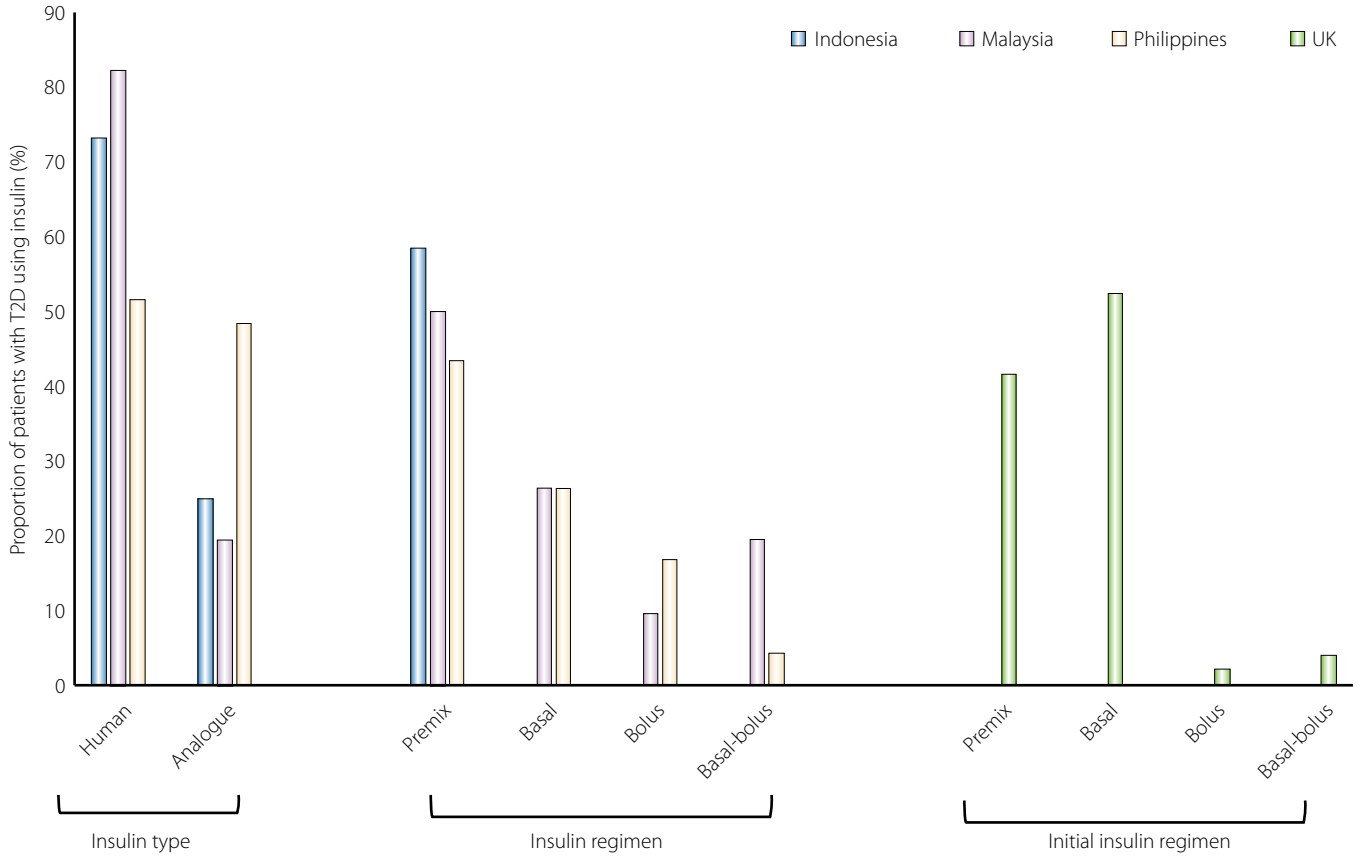

Figure 1 | Reported insulin use from DiabCare Indonesia[96], Malaysia[38] and the Philippines[97] studies, and in UK patients with type 2 diabetes[98].

Hagedorn insulin) or a full dose before bedtime, but given as a basal analog insulin[100]. Furthermore, Indonesian guidelines for the management of type 2 diabetes during Ramadan 2015 state that patients should change from premix insulin to basal plus or bolus to avoid hypoglycemia[92].

GUIDELINES

With so few studies of hypoglycemia in Southeast Asia, there is a lack of data on which bespoke guidelines can be constructed and therefore clinical practice guidelines have historically been based, and are heavily reliant, on data and guidelines from Western populations[10,101–104].

In a 2013 literature search for non-Western (including the ASEAN region) country diabetes guidelines, only the Philippines lacked national guidelines for type 1 and type 2 diabetes[10]. However, whilst Indonesia, Malaysia and Singapore had diabetes guidelines, a large proportion (30–55%) of non-Western guidelines are reliant on statements and definitions from the World Health Organization, International Diabetes Federation and American Diabetes Association[10]. For example, in Indonesia, Malaysia, the Philippines and Singapore, HbA_{1c} targets are similar to those in the West[11], with targets individualized to the patient, but a target of <6.0%[105] or <7.0% recommended for most patients[106–108].

Furthermore, as 70% of non-Western countries had guidelines that include recommendations for the management of hypoglycemia, a proportion of these would have based hypoglycemia guidelines on the Western population data referenced by the World Health Organization, International Diabetes Federation and American Diabetes Association – rather than data from their home nation and/or region[10]. Comparing the guidelines that are available for Indonesia, Malaysia, the Philippines and Singapore, with the exception of Ramadan, there is an absence of guidelines that address the concerns for HCPs in this region, namely the rise of diabetes, and the costs that will accompany an aging population that, on average, will have had diabetes longer than Western populations. As in the West, several of the guidelines recommend an individualized HbA_{1c} target, with frequent monitoring of blood glucose to minimize the risk of hypoglycemia in patients using insulin[11,17]. In addition, Indonesian and Singaporean guidelines emphasize the need to educate patients about hypoglycemia, and how insulin administration and glucose monitoring can help patients adjust their insulin dose, food intake and exercise levels to minimize the risk[106,107].

However, although some countries cover some of the needs of South Asian patients, there is the additional problem created by their poor implementation and adherence[109,110]. For example, in a recent report in Indonesia, despite a high awareness among GPs of the type 2 diabetes treatment guidelines, a large number neither adopted nor adhered to these guidelines in their treatment practice[111]. This was particularly prominent regarding adherence to screening guidelines for type 2 diabetes, with just 2% of GPs adhering to these, perhaps explaining the large deficit in diabetes awareness in Indonesia where two-thirds remain unaware of their condition[78]. In addition, non-adherence to dosing guidelines in Indonesia could go some way to explain why 68% of patients with type 2 diabetes in Indonesian hospitals have poor glycemic control[96].

FUTURE PERSPECTIVES/CONCLUSIONS

The main finding of this review is that, at present, there is a scarcity of data in the ASEAN and indeed Southeast Asian populations regarding the incidence and impacts of hypoglycemia. There are little to no data regarding the incidence of hypoglycemia in Southeast Asian patients with insulin-treated diabetes, especially in those managed according to real-world clinical practice. In addition, the present review has highlighted that there are several reasons to believe Southeast Asians might be of a different risk profile for hypoglycemia compared with Western populations because of physiological/etiological differences in the presentation of type 2 diabetes, gaps in patient knowledge of hypoglycemia, the high proportion of patients who practice Ramadan (exposing them to increased risk of hyper- and hypoglycemia), and a preference for human insulin and premix insulin regimens over regimens with lower associated rates of hypoglycemia, such as those based on modern insulin analogs. With no available data quantifying the impact of hypoglycemia in Southeast Asian populations, specifically based on the risks outlined above, it is difficult to envisage that there would not be considerable benefit in future studies focused on collecting real-world hypoglycemia data in this population.

Collecting data from South Asian populations will provide valuable information to assist in the construction of more appropriate national guidelines, which can then be more closely aligned to the national patient demographics, behaviors and treatment practices, and might result in a greater degree of implementation and adherence within clinical practice. This in turn could lead to improvements in the management of diabetes, and reduce the risk of hypoglycemia in insulin-treated patients.

As in the West, with healthcare improving in Asian countries, the demographic of patients with diabetes is shifting towards older age groups that have both impaired responses to hypoglycemia[112] and are at greater risk of severe hypoglycemia[113,114]. With Asian patients often developing type 2 diabetes at an earlier age than those in the West, and with so few (<30%) reaching glycemic targets (or even monitoring plasma glucose with SMBG)[69], Asians are at a unique risk of diabetes-related adverse events and complications, thus making it all the more important to effectively educate and manage patients, and develop more appropriate guidelines for this purpose.

One study that could help address the lack of data and aid development of new guidelines is the non-interventional International Operations Hypoglycemia Assessment Tool; this is a Novo Nordisk-sponsored study with the aim of assessing the incidence of hypoglycemia among patients with insulin-treated (premix, short-acting and long-acting) diabetes. Preliminary

results have been presented for some countries, and a full publication of the global study results was published in 2016[115].

ACKNOWLEDGMENTS

The authors are grateful for medical writing assistance from Sam Mason at Watermeadow Medical, UK, for drafting this review article, and Gabrielle Parker for help with submission. This assistance was funded by Novo Nordisk.

DISCLOSURE

Dr Su-Yen Goh is on the local advisory boards of the following companies, and has received speaker honoraria from the following companies: Novo Nordisk, Sanofi Aventis, AstraZeneca, Boehringer Ingelheim and Eli Lilly. Dr Zanariah Hussein is an advisory board member for AstraZeneca, Boehringer Ingelheim, Lilly, Sanofi-Aventis and Novo Nordisk; is currently participating in, and has participated in for the past 2 years, clinical trials with Novartis, Novo Nordisk and MSD; and receives research support from Medtronic. Professor Achmad Rudijanto has received research support from Novo Nordisk, and has received speaker fees from Novo Nordisk, Sanofi Aventis and AstraZeneca.

REFERENCES

1. National Health and Morbidity Survey 2011, Fact sheet [article online], 2011. Available from: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwiyjNSX_M7KAhWMXD4KHV7HCPMQFggcMAA&url=http%3A%2F%2Fwww.moh.gov.my%2Findex.php%2Ffile_manager%2Fdl_item%2F624746305a584e305833426b5a69394f51305176546b684e553138794d4445785830 5a4251315266553068465265 1756347526d&usg=AFQjCNGhQzew7gXGSDm7LInz8Vt-ktJ15w Accessed March 09, 2017.
2. Institute for Public Health. National Health and Morbidity Survey. Vol II: Non-Communicable Diseases, Risk Factors & Other Health Problems. 2015.
3. International Diabetes Federation. IDF Diabetes Atlas. Belgium: International Diabetes Federation, 2015.
4. Ramachandran A, Snehalatha C, Shetty AS, *et al.* Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 2012; 3: 110–117.
5. United Nations Department of Economic and Social Affairs. World population prospects: the 2007 revision population database [article online], 2007. Available from: http://www.un.org/esa/population/publications/wup2007/2007WUP_Highlights_web.pdf. Accessed March 09, 2017.
6. Centres for Disease Control. Age adjusted percentage of adults with diabetes using diabetes medication, by type of medication, United States, 1997–2011 [article online], 2011. Available from: http://www.cdc.gov/diabetes/statistics/meduse/fig 2.htm Accessed March 09, 2017.
7. Higuchi M. Costs, availability and affordability of diabetes care in the Philippines [article online], 2009. Available from: https://books.google.co.uk/books?id=w_YoM5HyTIsC&pg=PA29&lpg=PA29&dq=Foundation+for+Advanced+Studies+on+International+Development+2009+philippines&source=bl&ots=mKPrTvAHMg&sig=g69qsbjryQ7Ys2s-r1GT71bHjVM&hl=en&sa=X&ved=0ahUKEwjdx-ergc_KAhUBQiYKHTIwD-MQ6AEIJDAB#v=onepage&q=Foundation%20for%20Advanced%20Studies%20on%20International%20Development%202009%20philippines&f=false Accessed March 09, 2017.
8. Soewondo P, Ferrario A, Tahapary DL. Challenges in diabetes management in Indonesia: a literature review. *Global Health* 2013; 9: 1–17.
9. Shuyu Ng C, Toh MPHS, Ko Y, *et al.* Direct medical cost of type 2 diabetes in Singapore. *PLoS One* 2015; 10: e0122795.
10. Home P, Haddad J, Latif ZA, *et al.* Comparison of national/regional diabetes guidelines for the management of blood glucose control in non-Western countries. *Diabetes Ther* 2013; 4: 91–102.
11. Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2015; 38: 140–149.
12. Ong WM, Chua SS, Ng CJ. Barriers and facilitators to self-monitoring of blood glucose in people with type 2 diabetes using insulin: a qualitative study. *Patient Prefer Adherence* 2014; 8: 237–246.
13. Holman RR, Thorne KI, Farmer AJ, *et al.* Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. *N Engl J Med* 2007; 357: 1716–1730.
14. Giorda CB, Ozzello A, Gentile S, *et al.* Incidence and correlates of hypoglycemia in type 2 diabetes. The Hypos-1 Study. *J Diabetes Metab* 2014; 5: 1000344.
15. Aschner P, Sethi B, Gomez-Peralta F, *et al.* Insulin glargine compared with premixed insulin for management of insulin-naive type 2 diabetes patients uncontrolled on oral antidiabetic drugs: the open-label, randomized GALAPAGOS study. *J Diabetes Complications* 2015; 29: 838–845.
16. Giugliano D, Maiorino MI, Bellastella G, *et al.* Treatment regimens with insulin analogues and haemoglobin A1c target of <7% in type 2 diabetes: a systematic review. *Diabetes Res Clin Pract* 2011; 92: 1–10.
17. Inzucchi SE, Bergenstal RM, Buse JB, *et al.* Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35: 1364–1379.
18. Ismail-Beigi F, Moghissi E, Tiktin M, *et al.* Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann Intern Med* 2011; 154: 554–559.
19. Kenny C. When hypoglycemia is not obvious: diagnosing and treating under-recognized and undisclosed hypoglycemia. *Prim Care Diabetes* 2014; 8: 3–11.

20. Leiter LA, Boras D, Woo VC. Dosing irregularities and self-treated hypoglycemia in type 2 diabetes: results from the Canadian cohort of an international survey of patients and healthcare professionals. *Can J Diabetes* 2014; 38: 38–44.
21. Brod M, Wolden M, Christensen T, *et al.* Understanding the economic burden of nonsevere nocturnal hypoglycemic events: impact on work productivity, disease management, and resource utilization. *Value Health* 2013; 16: 1140–1149.
22. Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weitgasser R, *et al.* Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work-time loss, and wellbeing in insulin-treated patients with diabetes in seven European countries. *J Med Econ* 2013; 16: 1453–1461.
23. Ostenson CG, Geelhoed-Duijvestijn P, Lahtela J, *et al.* Self-reported non-severe hypoglycaemic events in Europe. *Diabet Med* 2014; 31: 92–101.
24. Luddeke HJ, Sreenan S, Aczel S, *et al.* PREDICTIVE - a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycaemia from the European cohort. *Diabetes Obes Metab* 2007; 9: 428–434.
25. Munro N, Barnett AH. Incidence, worry and discussion about dosing irregularities and self-treated hypoglycaemia amongst HCPs and patients with type 2 diabetes: results from the UK cohort of the Global Attitudes of Patient and Physicians (GAPP2) survey. *Int J Clin Pract* 2014; 68: 692–699.
26. Home P, Naggar NE, Khamseh M, *et al.* An observational non-interventional study of people with diabetes beginning or changed to insulin analogue therapy in non-Western countries: the A1chieve study. *Diabetes Res Clin Pract* 2011; 94: 352–363.
27. Soewondo P, Mohamed M, Jain AB, *et al.* Safety and effectiveness of insulin detemir in type 2 diabetes: results from the ASEAN cohort of the A1chieve study. *Diabetes Res Clin Pract* 2013; 100(Suppl 1): S10–S16.
28. Lim-Abrahan MA, Jain AB, Bebakar WM, *et al.* Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes: results from the ASEAN cohort of the A1chieve study. *Diabetes Res Clin Pract* 2013; 100(Suppl 1): S3–S9.
29. Bebakar W, Lim-Abrahan MA, Jain AB, *et al.* Safety and effectiveness of insulin aspart in type 2 diabetic patients: results from the ASEAN cohort of the A1chieve study. *Diabetes Res Clin Pract* 2013; 100(Suppl 1): S17–S23.
30. Kalra S, Plata-Que T, Kumar D, *et al.* Initiation with once-daily BIAsp 30 results in superior outcome compared to insulin glargine in Asians with type 2 diabetes inadequately controlled by oral anti-diabetic drugs. *Diabetes Res Clin Pract* 2010; 88: 282–288.
31. Strojek K, Bebakar WM, Khutsoane DT, *et al.* Once-daily initiation with biphasic insulin aspart 30 versus insulin glargine in patients with type 2 diabetes inadequately controlled with oral drugs: an open-label, multinational RCT. *Curr Med Res Opin* 2009; 25: 2887–2894.
32. Bebakar WM, Chow CC, Kadir KA, *et al.* Adding biphasic insulin aspart 30 once or twice daily is more efficacious than optimizing oral antidiabetic treatment in patients with type 2 diabetes. *Diabetes Obes Metab* 2007; 9: 724–732.
33. Nakar S, Yitzhaki G, Rosenberg R, *et al.* Transition to insulin in Type 2 diabetes: family physicians' misconception of patients' fears contributes to existing barriers. *J Diabetes Complications* 2007; 21: 220–226.
34. Seaquist ER, Anderson J, Childs B, *et al.* Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. *J Clin Endocrinol Metab* 2013; 98: 1845–1859.
35. Hassali M, Ching M-W, Yusoff Z, *et al.* 'Why I do not want to take insulin shots': findings from a qualitative study among diabetic patients in Malaysia. *J Public Health* 2014; 22: 3–11.
36. Karter AJ, Subramanian U, Saha C, *et al.* Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. *Diabetes Care* 2010; 33: 733–735.
37. Lee YK, Lee PY, Ng CJ. Tactics in counselling patients to start insulin. *Diabet Med* 2013; 30: 373–374.
38. Mafauzy MHZ, Chan SP. The status of diabetes control in Malaysia: results of Diabcare 2008. *Med J Malaysia* 2011; 66: 175–181.
39. Wild D, von Maltzahn R, Brohan E, *et al.* A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns* 2007; 68: 10–15.
40. Brod M, Christensen T, Thomsen TL, *et al.* The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value Health* 2011; 14: 665–671.
41. Workgroup on Hypoglycemia ADA. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care* 2005; 28: 1245–1249.
42. Lam AYR, Xin X, Tan WB, *et al.* Psychometric validation of the Fear of Hypoglycemia Survey-II in Singapore. *AACE Annual Meeting Abstract Archive* 2014; 90. Abstract 414.
43. Cariou B, Fontaine P, Eschwege E, *et al.* Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: results from the DIALOG study. *Diabetes Metab* 2015; 41: 116–125.
44. Berlie HD, Garwood CL. Diabetes medications related to an increased risk of falls and fall-related morbidity in the elderly. *Ann Pharmacother* 2010; 44: 712–717.
45. Bonds DE, Miller ME, Bergenstal RM, *et al.* The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010; 340: b4909.

46. Zoungas S, Patel A, Chalmers J, *et al.* Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010; 363: 1410–1418.
47. McCoy RG, Van Houten HK, Ziegenfuss JY, *et al.* Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012; 35: 1897–1901.
48. Barendse S, Singh H, Frier BM, *et al.* The impact of hypoglycaemia on quality of life and related patient-reported outcomes in Type 2 diabetes: a narrative review. *Diabet Med* 2012; 29: 293–302.
49. Amiel SA, Dixon T, Mann R, *et al.* Hypoglycaemia in Type 2 diabetes. *Diabet Med* 2008; 25: 245–254.
50. McCoy RG, Van Houten HK, Ziegenfuss JY, *et al.* Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. *Endocr Pract* 2013; 19: 792–799.
51. Shah S, Zilov A, Malek R, *et al.* Improvements in quality of life associated with insulin analogue therapies in people with type 2 diabetes: results from the A1chieve observational study. *Diabetes Res Clin Pract* 2011; 94: 364–370.
52. Hussein Z, Lim-Abrahan MA, Jain AB, *et al.* Switching from biphasic human insulin to biphasic insulin aspart 30 in type 2 diabetes: results from the ASEAN subgroup of the A(1)chieve study. *Diabetes Res Clin Pract* 2013; 100(Suppl 1): S24–S29.
53. Soewondo P, Lindarto D, Wibisono S, *et al.* Clinical safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes patients switched from biphasic human insulin 30: results from the Indonesian cohort of the A_1chieve study. *Diabetes Res Clin Pract* 2013; 100(Suppl 1): S41–S46.
54. Lim-Abrahan MA, Yu-Gan S, Jain AB, *et al.* Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes patients switched from biphasic human insulin 30: results from the Filipino cohort of the A1chieve study. *Diabetes Res Clin Pract* 2013; 100(Suppl 1): S35–S40.
55. American Diabetes Association. 6. Glycemic Targets. *Diabetes Care* 2015; 38: S33–S40.
56. Goto A, Arah OA, Goto M, *et al.* Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 2013; 347: f4533.
57. Randeree H, Liebl A, Hajjaji I, *et al.* Safety and effectiveness of bolus insulin aspart in people with type 2 diabetes: a1chieve sub-analysis. *Diabetes Ther* 2013; 4: 153–166.
58. Lee YK, Ng CJ, Lee PY, *et al.* What are the barriers faced by patients using insulin? A qualitative study of Malaysian health care professionals' views. *Patient Prefer Adherence* 2013; 7: 103–109.
59. Hammer M, Lammert M, Mejias SM, *et al.* Costs of managing severe hypoglycaemia in three European countries. *J Med Econ* 2009; 12: 281290.
60. Shrestha SS, Zhang P, Barker L, *et al.* Medical expenditures associated with diabetes acute complications in privately insured U.S. youth. *Diabetes Care* 2010; 33: 2617–2622.
61. Frier BM. The economic costs of hypoglycaemia. *Br J Diabetes Vasc Dis* 2011; 11(Suppl 1): 10–12.
62. Edelman SV, Blose JS. The impact of nocturnal hypoglycemia on clinical and cost-related issues in patients with type 1 and type 2 diabetes. *Diabetes Educ* 2014; 40: 269–279.
63. Nirantharakumar K, Marshall T, Kennedy A, *et al.* Hypoglycaemia is associated with increased length of stay and mortality in people with diabetes who are hospitalized. *Diabet Med* 2012; 29: e445–e448.
64. Andayani TM, Ibrahim MIM, Ahmad HA. Assessing the impact of complications on the direct medical costs of type 2 diabetes mellitus outpatients. *Int J Cur Phar Res* 2010; 2: 32–35.
65. Simon J, Gray A, Clarke P, *et al.* Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *BMJ* 2008; 336: 1177–1180.
66. Mafauzy M. Diabetes control and complications in private primary healthcare in Malaysia. *Med J Malaysia* 2005; 60: 212–217.
67. Mafauzy M. Diabetes control and complications in public hospitals in Malaysia. *Med J Malaysia* 2006; 61: 477–483.
68. Ministry of Health Malaysia. Clinical Practice Guidelines – Management of Type 2 Diabetes Mellitus, 5th edn. 2015 http://www.mems.my/file_dir/14963565685527d8749429c.pdf Accessed March 09, 2017.
69. Chan JC, Gagliardino JJ, Baik SH, *et al.* Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). *Diabetes Care* 2009; 32: 227–233.
70. Chow WL, Goh S-Y, Ying WS, *et al.* Treatment of poorly controlled type 2 diabetes (T2DM) patients with insulin glargine – An economic analysis. In *Poster presented at 2009 SingHealth Congress*.
71. Garg SK, Gottlieb PA, Hisatomi ME, *et al.* Improved glycemic control without an increase in severe hypoglycemic episodes in intensively treated patients with type 1 diabetes receiving morning, evening, or split dose insulin glargine. *Diabetes Res Clin Pract* 2004; 66: 49–56.
72. Chan JC, Malik V, Jia W, *et al.* Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
73. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 2003; 26: 881–885.
74. Wang JS, Tu ST, Lee IT, *et al.* Contribution of postprandial glucose to excess hyperglycaemia in Asian type 2 diabetic patients using continuous glucose monitoring. *Diabetes Metab Res Rev* 2011; 27: 79–84.

75. Kalra S, Balhara YP, Sahay BK, *et al.* Why is premixed insulin the preferred insulin? Novel answers to a decade-old question. *J Assoc Physicians India* 2013; 61: 9–11.
76. Ogle G, Beran D, Raab R, *et al.* Global access and availability of insulin. *Diabetes Voice* 2006; 51: 22–25.
77. Salti I, Benard E, Detournay B, *et al.* A population-based study of diabetes and its characteristics during the fasting month of Ramadan in 13 countries: results of the epidemiology of diabetes and Ramadan 1422/2001 (EPIDIAR) study. *Diabetes Care* 2004; 27: 2306–2311.
78. Mihardja L, Delima , Manz HS, *et al.* Prevalence and determinants of diabetes mellitus and impaired glucose tolerance in Indonesia (a part of basic health research/ Riskesdas). *Acta Med Indones* 2009; 41: 169–174.
79. Cockram CS. The epidemiology of diabetes mellitus in the Asia-Pacific region. *Hong Kong Med J* 2000; 6: 43–52.
80. Norris SA, Osmond C, Gigante D, *et al.* Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts. *Diabetes Care* 2012; 35: 72–79.
81. Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord* 1998; 22: 1164–1171.
82. Fukushima M, Usami M, Ikeda M, *et al.* Insulin secretion and insulin sensitivity at different stages of glucose tolerance: a cross-sectional study of Japanese type 2 diabetes. *Metabolism* 2004; 53: 831–835.
83. Iwahashi H, Okauchi Y, Ryo M, *et al.* Insulin-secretion capacity in normal glucose tolerance, impaired glucose tolerance, and diabetes in obese and non-obese Japanese patients. *J Diabetes Investig* 2012; 3: 271–275.
84. Henry CJ, Lightowler HJ, Newens K, *et al.* Glycaemic index of common foods tested in the UK and India. *Br J Nutr* 2008; 99: 840–845.
85. James GD, Baker P, Badrick E, *et al.* Type 2 diabetes: a cohort study of treatment, ethnic and social group influences on glycated haemoglobin. *BMJ Open* 2012; 2: pii: e001477.
86. Turner RC, Cull CA, Frighi V, *et al.* Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999; 281: 2005–2012.
87. Global survey results reveal need for improved hypoglycaemia management for people with type 2 diabetes [article online], 2011. Available from: http:// www.businesswire.com/news/home/20110915005636/en/ Global-Survey-Results-Reveal-Improved-Hypoglycaemia-Management Accessed March 09, 2017.
88. Lee JY, Wong S. Development and implementation of signs- and symptoms-based insulin adjustment algorithm. *Am J Health Syst Pharm* 2010; 67: 1503–1506.
89. Benaji B, Mounib N, Roky R, *et al.* Diabetes and Ramadan: review of the literature. *Diabetes Res Clin Pract* 2006; 73: 117–125.
90. ASEAN. ASEAN Statistical Yearbook 2014. Nations TAoSA, Ed. 2014, pp. 1–236.
91. Pew Research Centre. Mapping the global muslim population [article online], 2009. Available from: http:// www.pewforum.org/2009/10/07/mapping-the-global-muslim-population/ Accessed March 09, 2017.
92. Soeatmadji DW, Rosandi R, Sasiarini L. Indonesian guideline of type-2 DM management during Ramadan, 2015, (in Indonesian).
93. Ministry of Health Malaysia and Malaysian Endocrine & Metabolic Society. Practical guide to diabetes management in Ramadan, 2016. Available from: http://www.mems.my/ article.php?aid=605 Accessed March 09, 2017.
94. Ibrahim M, Abu Al Magd M, Annabi FA, *et al.* Recommendations for management of diabetes during Ramadan: update 2015. *BMJ Open Diabetes Res Care* 2015; 3: e000108.
95. Nor Azlin MI, Adam R, Sufian SS, *et al.* Safety and tolerability of once or twice daily neutral protamine hagedorn insulin in fasting pregnant women with diabetes during Ramadan. *J Obstet Gynaecol Res* 2011; 37: 132–137.
96. Soewondo P, Soegondo S, Suastika K, *et al.* The DiabCare Asia 2008 study – outcomes on control and complications of type 2 diabetic patients in Indonesia. *Med J Indones* 2010; 19: 235–245.
97. Jimeno CA, Sobrepeña LM, Mirasol RC. DiabCare Asia 2008 Survey on glycaemic control and the status of diabetes care and complications among patients with type 2 diabetes mellitus in the Philippines. *Philipp J Intern Med* 2012; 50: 15–22.
98. Blak BT, Smith HT, Hards M, *et al.* A retrospective database study of insulin initiation in patients with Type 2 diabetes in UK primary care. *Diabet Med* 2012; 29: e191–e198.
99. Pontiroli AE, Miele L, Morabito A. Metabolic control and risk of hypoglycaemia during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. *Diabetes Obes Metab* 2012; 14: 433–446.
100. Pathan MF, Sahay RK, Zargar AH, *et al.* South Asian Consensus Guideline: use of insulin in diabetes during Ramadan. *Indian J Endocrinol Metab* 2012; 16: 499–502.
101. International Diabetes Federation. International Diabetes Federation. Global Guideline for Type 2 Diabetes: recommendations for standard, comprehensive, and minimal care. *Diabet Med* 2006; 23: 579–593.
102. Paz-Pacheco E. Diabetes Clinical Practice Guidelines (CPGs) for the ASEAN region: Country Initiatives for Collectively Enhanced Diabetes Care in the Region. JAFES 2011; 26: http://asean-endocrinejournal.org/index.php/JAFES/article/ view/99/341 Accessed March 09, 2017.
103. American Diabetes Association. Standards of medical care in diabetes–2010. *Diabetes Care* 2010; 33(Suppl 1): S11–S61.
104. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia [article online], 2006. Available

from: http://www.who.int/diabetes/publications/Definition%20and%20diagnosis%20of%20diabetes_new.pdf Accessed March 09, 2017.
105. CPG Secretariat, Ministry of Health Malaysia. Management of Type 2 Diabetes Mellitus [article online], 2015. Available from http://www.acadmed.org.my Accessed March 09, 2017.
106. Ministry of Health Singapore. Diabetes Mellitus (Summary Booklet). Available from: https://wwwmohgovsg/content/moh_web/healthprofessionalsportal/doctors/guidelines/cpg_medical/2014/cpgmed_diabetes_mellitushtml 2014 Accessed March 09, 2017.
107. Perkeni. Konsensus Pengendalian dan Pencegahan Diabetes Mellitus Tipe2 di Indonesia 2011 [Consensus Control and Prevention of Diabetes Mellitus type 2 in Indonesia 2015] [article online], 2011. Available from http://www.scribd.com/doc/5060272/Konsensus-Pengelolaaln-dan-Pencegahan-Diabets-Melitus-Tipe-2-di-Indonesia-2006#scribd Accessed March 09, 2017.
108. Unite For Diabetes Phillipines. Philippine Practice Guidelines on the. Diagnosis and Management of Diabetes Mellitus. Available from: http://obesityorgph/v4/wp-content/uploads/2014/07/Diabetes-United-for-Diabetes-Philpdf, 2014 Accessed March 09, 2017.
109. Bouldin MJ, Low AK, Blackston JW, *et al.* Quality of care in diabetes: understanding the guidelines. *Am J Med Sci* 2002; 324: 196–206.
110. Jenssen TG, Tonstad S, Claudi T, *et al.* The gap between guidelines and practice in the treatment of type 2 diabetes A nationwide survey in Norway. *Diabetes Res Clin Pract* 2008; 80: 314–320.
111. Widyahening IS, van der Graaf Y, Soewondo P, *et al.* Awareness, agreement, adoption and adherence to type 2 diabetes mellitus guidelines: a survey of Indonesian primary care physicians. *BMC Fam Pract* 2014; 15: 72.
112. Meneilly GS, Cheung E, Tuokko H. Counterregulatory hormone responses to hypoglycemia in the elderly patient with diabetes. *Diabetes* 1994; 43: 403–410.
113. Ligthelm RJ, Kaiser M, Vora J, *et al.* Insulin use in elderly adults: risk of hypoglycemia and strategies for care. *J Am Geriatr Soc* 2012; 60: 1564–1570.
114. Chan TY. Estimates on the incidence of antidiabetic drug-induced severe hypoglycaemia in Hong Kong. *Pharmacoepidemiol Drug Saf* 1998; 7: 411–414.
115. Khunti K, Alsifri S, Aronson R, *et al.* Rates and predictors of hypoglycaemia in 27,585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. *Diabetes Obes Metab* 2016; 18: 907–915.