http://rjdnmd.org
Rom J Diabetes Nutr Metab Dis. **25**(2):197-208
doi: 10.2478/rjdnmd-2018-0023

COST-EFFECTIVENESS OF THE INTERVENTIONS TO AVOID COMPLICATIONS AND MANAGEMENT IN DIABETES MELLITUS: A NARRATIVE REVIEW FROM SOUTH-EAST ASIAN PERSPECTIVE

Shazia Qasim Jamshed [1, ✉]***, Akshaya Srikanth Bhagavathula*** [2]***, Abdul Kareem Al-Shami*** [1]

[1] Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia, Pahang, Malaysia
[2] Department of Clinical Pharmacy, School of Pharmacy, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

received: June 01, 2017 *accepted*: May 29, 2018
available online: June 15, 2018

Abstract

Background and Aims: *Asians accounts 60% of the world's diabetic population with a different burden on young and middle-aged. The objective is to critically evaluate the published literature relevant to cost-effectiveness analysis of interventions to avoid complications followed by the management of diabetes mellitus in South-east Asia.* ***Methods:*** *PubMed, ScienceDirect International Pharmaceutical Abstracts (IPA), Proquest and Google Scholar thoroughly searched within the period of November-December 2015. Only research and reviews published in the English language within the period of January 2000-November 2015 considered. The extracted details and particulars from the included studies account for interventions, outcomes, and modeling methods.* ***Results:*** *A total of seven studies from Japan, Singapore, Cambodia and two each from India and Thailand were included. Incremental cost-effectiveness ratios (ICERs) per quality-adjusted-life-year (QALY) accounted as an outcome in more than half of the reviewed studies. Most of the economic evaluations of DM management and preventive interventions in each country focused on different interventions and alternatives for comparison. However, type 1 DM patients showed better outcome when using specific insulin regimens utilized in the southeastern Asian countries followed by the implementation of Thai DM-self management support program (DM-SMS) via healthcare professionals.* ***Conclusion****: Alternatives to pharmacologic approaches such as insulin regimen and oral anti-diabetic agents showed a significant difference*

key words: *cost-effectiveness analysis, interventions, quality-adjusted-life-years, diabetes mellitus.*

Background and aims

Currently, Asians account 60% of the world's diabetic population afflicted with diabetes and encompass inconsistent burden on young and middle-aged [1]. This increased prevalence in Asian populations is due to more visceral fat, the onset of diabetes in younger age, nutrition transitions, and increasingly sedentary lifestyles being the major contributing factors along with dense population in different

✉ Pharmacy Practice, Kulliyyah of Pharmacy, International Islamic University Malaysia, Kuantan, 25200, Pahang, Malaysia. Tel. 0060129099638; *corresponding author e-mail*: pharmacist1992@live.com

countries [1-5]. Furthermore, in Asian countries, this is rampant in an incongruous fashion and of diverse nature in different ethnic and cultural subgroups, also dependent on the how fast the urbanization is gaining momentum coupled with socio-economic characteristics of Asian people [6]. However, to decrease the epidemic in Asia several integrated strategies are initiated. Preventive policies in terms of long-term life style change in the form of switching towards healthy meals, emphasis on early detection and continuous care through multidisciplinary care programs are initiated to diminish the risk and complications in the general population and high-risk individuals [7].

Cost effective analysis (CEA) is a suitably advantageous means to make valid and genuine costs comparison. These analysis consists in compiling incremental cost-effectiveness ratios (ICERs), calculated as a proportion of the difference in the costs to the difference in effectiveness in between the evaluated intervention and comparison intervention [8-10]. In recent global economic burden of diabetes study, it estimated that it reaches nearly US$ 1.3 trillion, and it is hypothesized that this burden may be larger in middle-income countries than the high-income countries [11]. Additionally, society is afflicted with compromised quality of life affecting the patients and their caregivers due to high intangible costs of the disease. In 2012, it was estimated that $245 billion was the cost of diagnosed disease [12]. This accounted for $176 billion for direct medical expenses and $69 billion for reduced productivity [12].

Few studies assessed the cost-of-illness quantified economic burden of diabetes from different parts of the world. For example, as per Seuring et al. cost-of-illness of type 2 diabetes reported that the annual direct cost ranges from $4129 per capita and indirect cost ranges from $45 to $16915 per capita [13]. Furthermore, the International Diabetes Federation's (IDF) Diabetes Atlas, 2015 estimated US$673 billion expenditures related to diabetes [14]. These studies provided the global direct and indirect economic burden of diabetes from the different world region but did not offer any economic cost of interventions focusing on preventing complications and management of diabetes mellitus (DM), especially among high diabetes burden countries.

We aimed to critically evaluate the published studies relevant to cost-effectiveness analysis of interventions to avoid complications followed by the management of DM in South-east Asia.

Materials and Methods

Search Strategy. A comprehensive search strategy performed for categorizing published literature. The keywords commonly used in this search strategy included 'pharmacoeconomics,' 'pharmacoeconomic studies,' 'cost-effectiveness analysis,' 'economy analysis,' 'intervention,' 'treatment,' 'diabetes mellitus,' 'type 2 diabetes', 'Asia' and any equivalent terms in thesauruses. A combination of the keywords also employed as advanced search strategy criteria. The types of interventions are also searched in the document abstracts. Studies using scientific electric databases like PubMed, Science Direct, ProQuest and Google Scholar. The hands-on search of bibliographies also performed. The search was finally limited to full-text articles from South-east Asian countries published in the English language from January 2000 to 2015.

Inclusion criteria. Research articles that directly evaluated the cost of interventions in management and prevent complications. Studies were designated based on: (a) patients having DM; (b) assessed the cost-effectiveness through interventions focusing on preventing complication and management of DM, and (c)

Cost-effective interventional studies conducted on South-east Asian population. After meeting these criteria, studies included that utilized interventions rather than quantitative assessment of DM outcomes such as quality of life, the effect of intervention and prevention of complications and management. All the currency conversions made according to the international dollar (INT$) or US dollar (USD$); 2015 purchase power parity.

Results

A total of 127 articles identified through an electronic search of databases. Of these, 112 studies were not from the South-east Asian countries and thus were excluded, the remaining 15 studies that met the criteria included, but 8 studies from these excluded due to duplication. Finally, seven studies justify the inclusion criteria and therefore, part of this review.

Studies from Japan, Singapore, Cambodia, India, and Thailand reviewed. Table 1 and Table 2 highlight the important features of included studies [15-21].

Table 1. Literature Review Matrix.

No.	Reference	Region	Perspective	Population	Modelling	Timescale	Discount
1.	Flessa and Zembok [15]	Cambodia	Ministry of Health of Cambodia	Type 2 diabetic patients	Markov model	20 years	No discounting
2.	Chirakup et al. [16]	Thailand	Government hospital policymaker	Uncontrolled type 2 diabetic patients	Markov diabetes model	40 years	3% annually
3.	Goh et al. [17]	Singapore	Health care and societal	Type 2 diabetic patients with suboptimal glycaemic control	CORE diabetes model (Markov model)	Lifetime	3%
4.	Wake et al. [18]	Tokushima, Japan	Patient and health policy	Type 2 diabetic patients	Simulation model	10 years	3% annually
5.	Ramachandran et al. [19]	India	Health care system	Type 2 diabetic patients having impaired glucose tolerance (IGT)	Hypothetical model	3 years	No discounting
6.	Khwakhong et al. [20]	Bangkok, Thailand	Healthcare provider's and societal	Type 2 diabetic patients	NA	6 months	NA
7.	Ahmad et al. [21]	India	NA	Type 2 diabetic patients who undergone surgery	NA	During perioperative period	NA

NA- not applicable

Table 2. Study characteristics details.

No.	Reference	Intervention	ICER /ICUR	QALY	Sensitivity analysis
1	Flessa and Zembok [15]	Oral Anti-Diabetic (OAD) vs Insulin therapy	In this Cambodian study, cost-effective intervention means ICER lesser than 1,000 US$. OAD-therapy - 100 US$ per YLS ICER; extremely cost-effective. -A rise of treatment from 13% to 25%-has ICER (102 US$ per YLS) Insulin therapy -ICER: 451 US$ per YLS provided access better from 12.5%- 25%. A rise from 12.5% -100% (457 US$ with r = 5%.	NA	
2	Chirakup et al. [16]	Pioglitazone 45 mg once a day versus Rosiglitazone 8 mg daily	A comparison of total costs within the pioglitazone group and rosiglitazone group reflected higher cost in the pioglitazone group. ICER reflected on the payment of 161,777 Baht (US$ 4681) for one life year gained or either pay186,246 Baht (US$ 5389) for QALY earned.	Pioglitazone group-improved clinical outcomes Incremental cost per QALY gained-186,246 baht (US$ 5389).	%HbA1c change
3	Goh et al. [17]	Biphasic Human Insulin (BHI) versus biphasic insulin (BIAsp-30) *part 30*	ICER (healthcare perspective) = BIAsp-30 dominant ICER (societal perspective) = BIAsp-30 dominant Estimation of long-term outcomes indicated that treatment with BIAsp-30 resulted in an incremental benefit of 0.36 QALYs over continued treatment with BHI at a cost saving.	The life expectancy for patients on BIAsp-30 was 11.67 ±0.19 years, 0.36 years more than the patients receiving BHI (11.32 ±0.19 years). Compared with patients receiving BHI, there was an increase of 0.39 QALYs gained in patients treated with BIAsp 30.	One-way sensitivity analysis

Table 2. *Continued*.

No.	Reference	Intervention	ICER /ICUR	QALY	Sensitivity analysis
4	Wake et al. [18]	MIT versus CIT MIT-multiple insulin injection therapy CIT-conventional insulin injection therapy	NA	The incremental cost per QALY was $16 002 for MIT.	t-test
5	Ramachandran et al. [19]	lifestyle modification (LSM) vs metformin	In a 3-year experimental time, the ICER was: INR 47,341 ($1,052-LSM) INR 49,280 ($1,095-metformin) INR 61,133 ($1,359-LSM and metformin)	NA	
6	Khwakhong et al. [20]	Healthcare professional-led DM-SMS program	Cost-utility analysis-Comparison between DM-SMS program and usual care; Variables: incremental cost and incremental QALYs; Incremental Cost (in Baht): 688 (healthcare provider perspective); 1,927 (societal perspective); Incremental QALY: 0.02	Cost-utility evaluation reflected 34,400 and 96,350. This is related to per QALY gain from the healthcare provider's and societal perspectives, respectively	One-way
7	Ahmad et al. [21]	Using different insulin regimens	ICER = Rs.7.21 on each extra patient on the treatment regimen B (split-mixed NPH/regular). ICER = Rs.20.17 on each extra patient on the treatment regimen D (detemir/aspart). No peri-operative complications with both regimens	NA	Chi-Square test, One-way ANOVA

ICER- incremental cost-effectiveness ratio; ICER- incremental cost-effectiveness ratio; QALY- quality-adjusted life-year; BHI-biphasic human insulin; NA- not applicable

Three studies [15-17] used Markov model while the other two studies used simulation model [18] and hypothetical model [19], another two studies [20-21] did not mention about any modeling system used. All seven studies were from different perspectives such as Ministry of Health [15], government hospital [16], patient [18], and health care system [19]. Two studies [17,20] were having the same perspective which was health care provider and societal. Ahmed et al. study did not include any perspective [21].

The direct medical cost to classify a patient with impaired glucose tolerance (IGT) was Indian Rupees (INR) 5,278 (1 USD$=64.1 INR (2015); US$82.3) per capita. Direct medical costs of interventions over the 3-year trial period were INR 2,739 (US$42.7) per subject in the control group, INR 10,136 (US$158.1) with LSM, INR 9,881 (US$154.1) with metformin, and INR 12,144 (INT$189.4) metformin plus LSM [19]. Cost-effectiveness to prevent one case of diabetes with LSM was INR 47,341 (US$738.5), with metformin INR 49,280 (INT$768.8), and with LSM and metformin INR 61,133 (US$953.71) [19].

Type 2 diabetes mellitus patients are expected to gradually increase from 145,000 (the year 2008) to 264,000 (the year 2028) in the region of Cambodia [15]. In 2008, the diagnosed T2DM patients would sustain costs of around 2 million US$ to cover for their treatment. More than half of this percentage (57%) would be consumed for OAD-therapy and the remaining part used for treatment with insulin. In the year 2028, around 2 million US$ will show an upsurge to around 4 million US$. [15].

A look at the scenario of Thailand reflected that the T2DM screening is cost-effective provided there is high sensitivity test and low unit price. The simulation outcome called for focusing the high-risk groups. Nevertheless, an amplified obtainability of oral anti-diabetic and insulin therapy is highly cost-effective [20]. The cost-utility results were 34,400 THB (US$1005.8) and 96,350 TBH (US$2817.2) per QALY gain from the health care provider's and societal perspectives, respectively. According to the sensitivity analysis, the cost affected the incremental cost-utility ratio (ICUR) to a high degree [20].

In the evalaution of the cost-effectiveness of different insulin regimes in type 2 indian diabetics, a notably substantial difference ($p<0.001$) in the mean costs of the regime A, B, C and D observed. The cost-effectiveness performed stepwise in a manner of regime A versus B and regime C versus D [21]. Incremental cost of the treatment for regime B was INR 7.21, whereas for regime D, INR 20.17 per added patient but without any peri-operative complications. However, the percentage of the incidence of the complications and the total cost was comparatively low with regime A [21].

Interestingly, in a base case analysis, all costs reduced to the present value at an annual rate of 3%. Sensitivity analyses performed to assess the robustness of the results for observing the changes in the values of imperative variables [18]. Multiple insulin injection therapies (MIT) reduced the relative risk in the progression of retinopathy by 67%, photocoagulation by 77%, the progression of nephropathy by 66%, albuminuria by 100% and clinical neuropathy by 64%, relative to conventional insulin injection therapy (CIT). Moreover, MIT extended the time for patients to be free of complications [18]. It is observed 2.0 years for the advancement of retinopathy (*P*B0.0001), 0.3 years for photocoagulation (*P*B0.05), one and a half year for progression of nephropathy (*P*B0.01) and clinical neuropathy more than 2 years (*P*B0.0001).

The total cost (discounted at 3%) per patient during the 10-year period for each group was $30310 and 31525. The discount of full costs in MIT over CIT was primarily due to cost reduction regarding management of complications. The study reported that MIT is more beneficial than CIT regarding both cost and as well as effectiveness [18].

In the base-case analysis, the pioglitazone group had improved clinical outcomes and higher lifetime costs. The incremental cost per QALY gained was 186,246 baht (US$5445). The

most sensitive to the final outcomes were the effect of pioglitazone on the percentage of glycosylated hemoglobin decrease [16].

In a study by Hussein et al. [22] Indonesian, Malaysian, Filipino and Singaporean diabetic patients switched from biphasic human insulin (BHI) to biphasic insulin aspart 30 (BIAsp 30). These ASEAN subgroup participants exhibited well-tolerated and significantly increased glycemic control along with improvement in the mean quality of life who showed poor control on BHI.

Discussion

Based on our current review, a total of seven studies described cost-effectiveness analysis of interventions to manage diabetes mellitus and prevent diabetic-related complications. Out of seven studies, six studies reported about the interventions for managing diabetes mellitus [15-18,20,21]. Meanwhile, four studies reported on the intervention to prevent diabetic-related complication [16-18,21]. ICERs per QALY often become the standard outcomes for economic evaluation since it can improve the comparability of studies and provide information which can aid policy makers to decide regarding resource allocations [21].

Management of diabetes mellitus. Three forms of insulin preparation generally used in diabetes; rapid acting, intermediate- acting, and long-acting insulin [23]. Typically, rapid-acting one is absorbed swiftly with lesser action duration [24]. As for intermediate acting insulin, its onset of action is between 2-4 hours and can last up to 20 hours [25]. Lastly, long acting insulin has biological action up to 24 hours of action [24].

Despite that action, there are many combination therapies of insulin being studied [26]. Premixed Regular + NPH, Split-mixed NPH + Regular, Split-mixed Glargine + Lispro, Split-mixed Detemir + Aspart are some of popular combination approved to manage type 2 diabetes mellitus [27]. In a study by Ahmad et al. study [21], for the estimation of ICER, the group A (premixed NPH/ regular in a ratio of 30:70) was compared to group B (split-mixed NPH/regular). Likewise, group C (split-mixed glargine/lispro) was compared to D (split-mixed detemir/aspart).

There is a significant difference when these regimens were used during the peri-operative period. Over the period of usage, 50% of the group that used premixed NPH/regular experience complication side effect while the highest number of patient that did not experience complication were from a group that uses detemir/aspart. In between that two extreme groups, the group that treated with glargine/lispro recorded 62.3% complication. This study also emphasized the complication that being measured was no postoperative complication after using insulin regimen prescribed. In a comparison of those regimens, a patient that received regimen B recorded ICER of 7.21 INR per case. Meanwhile, for regimen C gives ICER of 20.1 INR per patient case. Thus, Ahmad et al. (2011) concluded that NPH/regular regimen were cost effective compared to the glargine/lispro and detemir/aspart regimens.

The other management strategies proposed to treat diabetes were conventional insulin therapy (CIT) and multiple insulin therapy (MIT). According to UK Prospective Diabetes Study (UKPDS) Group [18], MIT is a method of insulin administration by using an injection or external pump for 3 or more times a day guided by a frequent blood glucose monitoring while CIT is a therapy usually involves one to three daily injections that are the same every day. The types of insulin that you take and the number of injections and dose sizes are determined based on how much food you eat, when you eat, how

much activity you have in a typical day and other factors. The Wake et al. study [18] emphasized on intensive insulin therapy as it helped in keeping the patient free diabetes complications for a pronlong period of time. From pharmacoeconomical standpoint, the total cost (discounted at 3%) per patient (10 years period) under MIT was US$ 30,310 10 and US$ 31,525 for CIT. Likewise, Wake et al. decided to test their points by doing a simulation study. As per simulation the treatment cost in MIT increased almost twofold followed by the incremental cost per QALY was US$16,002. As reported that US$1099 per year per patient cost was used for the treatment of patients with standard insulin therapy. Meanwhile, for MIT, the cost of US$3324 per year per patient was adapted. This study conclusively suggested that multiple insulin therapies could delay the diabetes related complication and augment the quality of life and thus more cost effective compared to conventional insulin therapy.

A study compared the cost-effectiveness of thiazolidinediones in T2DM patients receiving sulfonylureas and metformin [16]. This study has been conducting in Thailand and the time horizon for the simulation was 40 years. This study considered only direct medical costs of each treatment from the health care provider perspectives. In this study, the analytical used was Markov model. By using current clinical studies and epidemiological studies, the prediction of long-term costs and future outcomes of the diabetic patients is possible. In this study, they compared the use of rosiglitazone and pioglitazone used in uncontrolled T2DM who were already on a combination of metformin and sulfonylurea. Maximum dose to achieve best glycemic control was 45 mg orally once daily and 8 mg once daily orally for pioglitazone and rosiglitazone respectively. The results showed that patient with pioglitazone shows a lower incidence of diabetes complication compared to a patient with rosiglitazone. Results also showed that pioglitazone improves patient life expectancy and quality-adjusted life expectancy. Cost-effectiveness of pioglitazone treatment is in right upper quadrant of incremental cost effectiveness scatter plot. This means the treatment with pioglitazone is both more expensive and effective compared to rosiglitazone.

In other studies, the researchers compared the effectiveness of lifestyle modification and metformin in T2DM from health care perspectives as well. This study was conducted in India by Ramachandran et al. [19] for 3 years. In his study, he used hypothetical model for his analytical tools. This study was conducted by randomly separate all subject into four group which are group 1, control group with standard health care treatment, group 2, subjects with advise on lifestyle modifications, group 3, a subject treated with metformin and group 4, subject treated with metformin and advised with lifestyle modifications. LSM contain the counseling regarding the diet and daily routine or exercise of the subjects. Results show that cost of intervention for group 4, followed by group 2 and group 3. Control group show lowest direct medical cost. Further, Khwakhong et al. [20] studied about the cost of effectiveness of Self-management support program which leads by professional health care provider in T2DM. This study aimed to evaluate the effectiveness of healthcare provider roles in providing guide and support to Thailand through the SMS program compared with usual health care. The quality of life of the patients is taking as their markers. This study found that DM-SMS program total cost was 25692 bath. This show that, the total cost is way higher compared to standard care. This study concluded that, by using QALY, this

program is not recommended based on healthcare view.

Prevention of diabetes-related complications. Four cost-effectiveness studies were reported on the intervention to prevent diabetic-related complications [16-18,21]. Wake et al. [18] randomized controlled trial done on Japanese patients for 10 years (Kumamoto study) and Shichiri et al. compared results of an 8th year of the Kumamoto study data [28]. The results obtained from these studies were supported the findings of UKPDS study [29] that the intensive or MIT can reduce the risk of diabetic microvascular complications in type 2 diabetes mellitus patients better than the CIT. MIT is a method of insulin administration by using an injection or external pump for 3 or more times a day guided by a frequent blood glucose monitoring [30]. Most of the results were compared with a larger and longer RCT study done in USA by the Diabetes Control and Complication Trial (DCCT) upon type 1 diabetes mellitus patients. Even though the cost of treatment, annual treatment cost for outpatient and cost per QALY by using MIT is higher than the cost for CIT, these studies come into a consensus that MIT can effectively prolong the free-disease period for retinopathy, nephropathy, and neuropathy among the patients. The annual treatment cost for outpatient in Japan by using MIT does not differ much from the CIT cost. However, the MIT cost is much higher than the CIT cost in the DCCT study. They found out that these differences are due to the differences in the costs of outpatient services applied in their respective countries. Overall, the cost that the patients have to pay will be increased by 30% if they choose to use MIT. However, since the complications can be avoided, the cost for complications management can be reduced by 50% with MIT. The cost effectiveness of regimen has not yet been reported in this study, but according to DCCT, if it is based on the cost per year life saved, MIT is considered as cost-effective [30].

Another study to measure the effectiveness of insulin regimens to avoid complications in T2DM patients [31], however, it specifies the types of insulin used and the effectiveness parameter measured based on the number of patients that will have no post-operative complications in the end. The subjects allocated four different groups according to their insulin types:

Group A (n=74) with premixed NPH/regular (30:70); Group B (n=75) with split-mixed NPH/regular; Group C (n=69) with glargine/lispro; Group D (n=71) with detemir/aspart. According to their results, Group A has the lowest mean cost spent for their medication and hospital stay. However, it has the lowest number of patients with no post-operative complications (NPOC) whereas Group D with the highest number. On the other hand, low total insulin dose used and less hospital stay recorded from patients in Group C. Based on the ICER results; higher cost needed for every extra benefit provided by B and D as compared to A and C respectively. Although C and D are more efficient in reducing or preventing complications as compared to A and B, the costs used for the former are much higher than the latter. Therefore, A and B (especially A) considered as more cost-effective than the use of C and D, especially glargine. A research buttresses this outcome in the UK, which reported of glargine and detemir as the minimum percentage of cost-effectiveness per QALY in comparison to the regular insulin.

Therefore, since the use of A and B can save cost while C and D can effectively reduce the complications incidence but with a higher cost, it now depends on the patients'

affordability to make a choice for their diabetic management.

Chirakup et al. study [16] stated that the life expectancy and quality-adjusted life expectancy of a patient receiving pioglitazone treatment much longer compared to a patient receiving rosiglitazone as they have a higher reduction in the incidence of diabetic-related complications. However, since this study is a first study conducted to examine the cost-effectiveness of pioglitazone versus rosiglitazone, thus many studies for evaluation of cost-effectiveness between both drugs should be done in the Asian country to recommend the most cost-effective drugs to a patient in future. However, in Gah et al. study conducted in Singapore assessed the long-term cost-effectiveness of switching BHI to biphasic insulin as part 30 (BIAsp-30) [17]. There was an increase of 0.39 QALYs gained with a cost savings of SG$14,180 from a healthcare perspective, and SG$15,097 from a societal perspective in a patient receiving BIAsp-30. The main reason for result improvement was due to reduction and delay of diabetes-related complication incidence in a patient receiving BIAsp-30. Thus, from the reported impact of diabetic-related complications in Singapore, the use of BIAsp-30 was dominant and provided better advantages compared to BHI in a poorly controlled diabetes patient. The result reported by Goh et al. [17] correlated with the result reported from UK, US, Sweden, Poland and South Africa where the BIAsp-30 was found to be cost-effective and dominant over BHI [32].

Limitation. This narrative review regarding prevention of diabetic-related complications and management of diabetes mellitus accounts for the studies conducted in South-east Asian region. We found difficulties in trying to find the related material as not much work published so far in this context. Besides, all the cost-effectiveness studies used different interventions to evaluate outcomes. Therefore, the result obtained unable to be compared with another study which used different interventions. Apart from that, study populations were heterogeneous as the patient's gender, age, comorbidities a concomitant drug taken varied between studies. Additional research expects to evaluate further the cost-effectiveness of diabetes mellitus in this particular region.

Conclusion

Irrespective of developing or developed region diabetes mellitus is a pathoology with significant indisposition towards othe illnesses thereby escalating healthcare expenditure. With that, the long-term treatment will affect the cost and healthcare expenditure in general. Thus, many developing countries are preparing for the study of the cost effectiveness of the alternatives treatment. Based on the review of the studies, it shows that many studies account the perspectives of hospital or healthcare provider. Therefore, the cost is the main factor in consideration. Interestingly, few alternatives have higher total cost when compared to the standard cost but have better outcomes too. To evaluate the cost effectiveness, it should depend on country GDP per capita. Along with that alternative, prevention of occurrence and complication of diabetes thoroughly implemented. Thus, the health care expenditure will be able to be minimized and optimize the scarce resources.

Acknowledgments. This study is under Research Initiative Grant Scheme (RIGS) 15-097-0097, International Islamic University Malaysia

REFERENCES

1. Rhee E-J. Diabetes in Asians. *Endocrinol Metab (Seoul)* 30(3): 263-269, 2015.

2. Ramachandran A, Snehalatha C, Shetty AS, Nanditha A. Trends in prevalence of diabetes in Asian countries. *World J Diabetes* 3(6): 110-117, 2012.

3. Zou X, Zhou X, Ji L, et al. The characteristics of newly diagnosed adult early-onset diabetes: a population-based cross-sectional study. *Sci Rep* 7: 46534, 2017.

4. Hu FB. Globalization of diabetes. *Diabetes care* 34(6): 1249-1257, 2011.

5. Kong AP, Xu G, Brown N, So WY, Ma RC, Chan JC. Diabetes and its Comorbidities—where East meets West. *Nat Rev Endocrinol* 9(9): 537-547, 2013.

6. Nanditha A, Ma RC, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. *Diabetes Care* 39(3): 472-485, 2016.

7. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4· 4 million participants. *Lancet* 387(10027): 1513-1530, 2016.

8. Li R, Qu S, Zhang P, et al. Economic evaluation of combined diet and physical activity promotion programs to prevent type 2 diabetes among persons at increased risk: a systematic review for the Community Preventive Services Task Force. *Ann Inter Med* 163(6): 452-460, 2015.

9. da Rocha Fernandes J, Ogurtsova K, Linnenkamp U, et al. IDF Diabetes Atlas estimates of 2014 global health expenditures on diabetes. *Diabetes Res Clin Prac* 117: 48-54, 2016.

10. Leal J, Ahrabian D, Davies MJ, et al. Cost-effectiveness of a pragmatic structured education intervention for the prevention of type 2 diabetes: economic evaluation of data from the Let's Prevent Diabetes cluster-randomised controlled trial. *BMJ open* 7: e013592, 2017.

11. Bommer C, Heesemann E, Sagalova V, et al. The global economic burden of diabetes in adults aged 20–79 years: a cost-of-illness study. *Lancet Diabetes Endocrinol* 5(6): 423-430, 2017.

12. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care **36(4):** 1033–1046, 2013.

13. Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. Pharmacoeconomics **33(8)**: 811–831, 2015.

14. IDF. IDF Diabetes Atlas, 7th ed. Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org. Accessed 11 May 2017

15. Flessa S, Zembok A. Costing of diabetes mellitus type II in Cambodia. *Health Econ Rev* 4: 24, 2014.

16. Chirakup S, Chaiyakunapruk N, Chaikledkeaw U, et al. Cost-effectiveness analysis of thiazolidinediones in uncontrolled type 2 diabetic patients receiving sulfonylureas and metformin in Thailand. *Value Health* 11(1): S43-51, 2008.

17. Goh SY, Tan SC, Lim LC, Chua B, Hunt B. Cost-effectiveness of switching from biphasic human insulin (BHI) to biphasic insulin aspart 30 (BIAsp-30) in type 2 diabetes patients with suboptimal glycaemic control in Singapore. *J Diabetol* 6(1): 2, 2015.

18. Wake N, Hisashige A, Katayama T, et al. Cost-effectiveness of intensive insulin therapy for type 2 diabetes: a 10-year follow-up of the Kumamoto study. *Diabetes Res Clin Prac* 48(3): 201-210, 2000.

19. Ramachandran A, Snehalatha C, Yamuna A, Mary S, Ping Z. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians. *Diabetes Care* 30(10): 2548-2552, 2007.

20. Khwakhong P, Jiamjarasrangsi, Wiroj Sattayasomboon Y, Tuicompee A. Cost-effectiveness of a healthcare professional-led self-management support program for type 2 diabetic patients in Bangkok public health centers, Thailand. *J Med Med Sci* 4(2): 56–62, 2013.

21. Ahmad M, Wafai ZA, Khan ZY, Seth V. Evaluation of the Cost-Effectiveness of Different Insulin Regimes during the Peri- Operative Period in Type-2 Diabetics in India. *J Clin Diagnostic Res* 5: 1064–1068, 2011.

22. Hussein Z, Lim-Abrahan MA, Jain AB, Goh SY, Soewondo P. Switching from biphasic insulin to biphasic insulin aspart 30 in type 2 diabetes: results from the ASEAN subgroup of the A_1chieve study. *Diabetes Res Clin Prac* 100(1): S24-S29, 2013.

23. Zaykov AN, Mayer JP, DiMarchi RD. Pursuit of a perfect insulin. *Nat Rev Drug Disc* 15: 425-439, 2016.

24. Singha A, Anne BM, Chakrabarti SK, Ghosh S, Chowdhury S, Bhattacharya R. Glycaemic control using different regimens of intermediate-and short-acting insulin in childhood type 1 diabetes mellitus: an experience from a tertiary care centre. *Int J Diabetes Dev Ctries*, 2016.

25. Zhuo X, Zhang P, Barker L, Albright A, Thompson TJ, Gregg E. The lifetime cost of diabetes and its implications for diabetes prevention. *Diabetes care* 37(9): 2557-2564, 2014.

26. Sheldon B, Russell-Jones D, Wright J. Insulin analogues: an example of applied medical science. *Diabetes Obes Metabol* 11(1): 5-19, 2009.

27. King DK, Glasgow RE, Toobert DJ, et al. Self-efficacy, problem-solving, and social-environmental support are associated with diabetes self-management behaviors. *Diabetes care* 33(4): 751-753, 2010.

28. Shichiri M, Kishikawa H, Ohkubo Y, Wake N. Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients. *Diabetes care* Suppl 2: B21-B29, 2000.

29. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352(9131): 837-853, 1998.

30. Pugh JA. Intensive insulin therapy reduced microvascular and neurologic outcomes in type 1diabetes mellitus. *Ann Int Med* 120: 30, 1994.

31. Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. *Can Med Assoc J* 180(4): 400-407, 2009

32. Liebl A, Prusty V, Valensi P, et al. Ten years of experience with biphasic insulin aspart 30: from drug development to the latest clinical findings. *Drugs* 72(11): 1495-1520, 2012.