



Review Article

Review on Comparison of Diabetic Patient Adherence to Anti-diabetic Medication (Oral Hypoglycemic Agents vs Injectable Insulin)

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ABSTRACT

Objective – The purpose of this study was to determine the extent of adherence rate of anti-diabetic medication in oral and injection forms and factors of non-adherence to medication.

Research design and methods – Literature search (1976 -2015) was performed to identify reports with data on compliance rate with Oral Hypoglycemic Agents (OHAs) and subcutaneous (s/c) insulin administration and included data about characteristics of patients (age, race, education level, etc.) to determine factors of non-adherence with medications. Total 17 reports included in analysis. Qualified reports with adequate data was found in 3 prospective electronic monitoring OHAs studies, 8 retrospective studies of OHAs adherence rate and 6 retrospective s/c insulin studies.

Results - In the retrospective and prospective analyses on OHAs showed that adherence rate was ranged from 12.4% to 88%. Among retrieved articles, more than half of the amount of studies (6 out of 11 studies) contained similar result and high adherence rate, ranging from 75% to 90% adherence to OHAs. Mean age of the studies are more than 50 years old. There is no prospective electronic monitoring studies on insulin adherence rate. Young patients found in studies of prescribed insulin doses due to Type 1 diabetes. All the conducted studies, uptill now regarding insulin, revealed that the adherence rate was not exceeded than 75%.

Conclusions – This review showed that patients adherence rate with OHAs was higher as compared to the patients under s/c insulin treatment. One of the major factors of low adherence rate of anti-diabetic medications along with the usage of insulin was cost of insulin, while; others included were less knowledge about the medication, fear of needle, low executive functioning and number of injection daily. Prospective electronic monitoring on insulin should develop to improve accuracy of data collection. Number of OHAs per day should be low but may raise problem of over consumption of medications. The purpose of this review was to help the physician and patients to improve medication adherence.

INTRODUCTION

Diabetes mellitus (DM) had ranked at 8th position in leading causes of death in the world, about 1.5 million of deaths in 2012. The statistics published by World Health Organization (WHO), shows that Diabetes mellitus contributed 2.2% of deaths in the world upto the year 2012 (1). International Diabetes Federation (IDF) released a report of prevalence of Diabetes Mellitus. A study conducted in 2014, showed that 387 million people have been suffered from the diabetes and prevalence rate was also enhanced by 2035 Diabetic patients, which will rise to 202 million in future (2). DM defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes is a complex disease that require different aspect to work together and demolish it (3). Diabetes classifies into various types but the main classification is type 1 DM, type 2 DM and gestational diabetes. Type 1 diabetes also known as Insulin Dependent Diabetes Mellitus (IDDM). It is due to cell-mediated autoimmune destruction of the β -cells of the pancreas. Markers of the immune destruction of the β -cell include islet cell auto-antibodies and auto-antibodies to insulin (3). Most of the diabetes patients are under type 2 diabetes mellitus (90%-95%). Type 2 diabetes is also known as Non-Insulin Dependent Diabetes (NIDDM). It is due to insulin deficiency or with insulin resistance that occurs in adults, mostly. There are different causes that originates type 2 diabetes e.g. obesity, different from Type 1 diabetes, it does not have autoimmune destruction of β - cells (3). Gestational patients are the pregnant women having hyperglycemia with the other signs and symptoms of diabetes. All of the diabetic patients require to get more attention on diet, exercise and also adherence to guideline of medication.

Anti-diabetic medications defined as medicines that help to control blood sugar levels in people with diabetes mellitus (4). Anti-diabetic drugs may be subdivided into six groups: insulin, sulfonylureas, alpha-glycosidase inhibitors, biguanides, meglitinides, and thiazolidinediones. Oral hypoglycemic agents (OHAs) are oral anti-diabetic agents that used in treatment of type 2 diabetes mellitus commonly but it cannot treated type 1 diabetes mellitus in monotherapy but need combination with insulin treatment (5). Subcutaneous Insulin injections known as hormone that made by beta cells in the pancreas in our body. It helps to controlled blood glucose levels maintained under normal range in the body. It is made by β -cells

in the pancreas to maintain our blood glucose levels within the normal range (6). Other non-insulin injections including albiglutide, dulaglutide, exenatide, exenatide extended-release, liraglutide and pramlintide.

Among oral hypoglycemic agents, metformin is the only oral anti-diabetic medication that majorly decreases macro vascular complications and death. Metformin is also more effective than sulphonylurea in reducing glucose level. But if it is used in higher doses, may arise some gastrointestinal side effects (9). Sulfonylurea, oral hypoglycemic agent, by increasing insulin levels to lower glucose but on the other hand it may increase risks of cardiovascular events (7). However, insulin had reported to reduce cardiovascular risks such as retinopathy, nephropathy, small vessel arterial disease and neuropathy (8). Most of patients that have severe diabetic complications, may use insulin to lower glucose level and other medicational treatments (7). A study shows that many patients that under diabetic medication had poor adherence to treatment including prescribed one or more oral hypoglycemic agents and more serious with insulin (10). Type 2 diabetes increase rapidly especially, older age and overweight patient. There are a few factors that cause increase in the severity of diabetic patient, one of these factors is poor adherence to medication. Whereas study shows that young patients with type 1 diabetes also have problems of adherence to glycemic control treatment including insulin regimens (11).

This systemic review is to compare patient adherence to anti diabetic medication in oral regimens versus subcutaneous injection forms and find out factors of non-adherence to anti-diabetic medication in oral and injection form.

RESEARCH DESIGN AND METHODS

This review was conducted within Google Scholar and Diabetes Care (January 1978 - October 2015). From the literature search, we identified articles that related or containing information on rate of adherence of diabetic patients with oral anti-diabetic medication and insulin injection. When searching both Google Scholar and Diabetes Care, the databases were first screened against the inclusion criteria that fulfill our review requirement. The first level of screening of the articles of searched that related to the main topic. After the first level screening, the searched articles undergo second level screening by comparing with inclusion criteria. Those articles that meet the inclusion criteria have been studied in detailed.

Inclusion criteria

The articles must contain following information that given in the study:

1. Included patients with diabetes mellitus (including type 1, type 2 diabetes or both)
2. Assessed adherence to anti-diabetic medication (oral medication and insulin)
3. Focused on patients only
4. Doses of medications and the adherence rate must be showed
5. Methodology and data analysis must be explained used to determine the adherence rate.

The most important data or report of articles were included medications adherence rate. If the article not contained any adherence rate but shows data that related to adherence to medication like percentage of adherent patient also included in this review. The articles that were without medications adherence rate were excluded. Articles that also included adherence to treatment, diet, exercise, etc. without medications adherence rate also excluded. The studies conducted in primary care, community setting and hospital setting were included. The methodology of studies like questionnaire, data retrieval from healthcare system and survey were accepted in this review. Researcher will screened the data that must be adhere to inclusion criteria so that can be retrieved to include in this analysis.

Search strategy (Diagram 1)

Search strategies were adapted from Google Scholar and Diabetes Care. The keywords that used to search those articles in database were “patient adherence” and “patient compliance” with “diabetes mellitus”, “medication”, “anti-diabetic medication” and “insulin”. From the headings, we focused on “patient adherence to medication”, including other subheadings. We also screened relevant review articles or meta-analysis and other publications. Those unpublished articles or trials do not include into searching because it was equivalent to time consuming and creating the problems in selection. From the systemic search resulted in Google Scholar and Diabetes Care, we got adequate data on adherence with oral anti-diabetic medication and insulin.

Adherence assessment

Definition of adherence to medication in this review as extent to which patients take medications as prescribed by their health care providers (12). From the medical dictionary, the meaning of “adherence”

was quality of clinging or being closely attached or more precisely described as the process in which a person follows rules, guidelines or standards, especially as a patient follows a prescription and recommendations for a regimen of care (13). The synonym of “adherence” was “compliance” which was in similar meaning. Patients must adhered to the instruction or advice of physician about the doses, amount of medications took and time taken of medication. Adherence rate was defined as percentage of prescribed doses of medication actually taken by patient over a specified period (12). Adherence rate included data of doses (amount of pills taken) and data of timing (taking pills within a specific period). Patients that had poor adherence like lack of followed instructions of physicians were considered as non- adherence. The adherence rate will be expressed in percentage and rate of adherence that above 90% considered as good adherence to medications.

Data extraction and Data analysis

Data extraction carried out by reviewers from the articles that had review in third level screening that relevant to the topic. Reviewer extracted data from the articles independently considered as important aspect of the review articles. Data that extracted including the topic, author name, place that carried out studies, types of medication (oral or injection), duration of medication taken, adherence rate or percentage of adherent patient. Reviewer assessed trial quality and extracted the data required. After data extracted, reviewer reconfirmed the data that extracted was related to the topic. If contained any problems or questions, reviewers found out more information to determine the data was suitable and required.

There are different ways of data collected from the articles. Retrospective database study was conducted by retrieved patients healthcare information from some organization that manage the database of patients like Health Management Organization. The database may contained record of prescription medications and refills. The database may linked to laboratory, clinics and healthcare centre for the patient medical visit data and other health service record. These population-based surveys provide an overview of drug utilization during a period of time. Prospective monitoring was electronic monitoring technology that collected data like medication collected from monitored container, medication dosing and others. This provides medication usage level data from individual patient. The quality assessment of individual trial carried out by scoring a list. The rating scale was “yes”, “no” or “don’t know”. The articles that fulfilled criteria about 50% and above considered

as “Good”. The results collected were compared and determined that article’s quality and provided different grades. Overall quality graded as Good, Medium or Poor. The extracted data was entered into Excel sheet that was suitable for analysis. The data were undergo for comparison between the adherence and non-adherence rates among diabetics. Descriptive statistics (means, range) present data from selected reports, data tabulated by different methodology (retrospective database study, prospective monitoring) and type of medication.

RESULTS

From the search of computerized database identified, first level searching base on the keywords, identified about 10,250 publications that were related to the topic. Second level of review by comparing with inclusion criteria from first level screening reports. By studying the abstract of articles, determine

methodology and result suitable for the review. From this stage identified 89 reports, relevant to the topic. Third level of review article was in detail reports that filtered from second level. Review on the methodology and data analysis to ensure the reports were suitable and adhere to the inclusion criteria that we set. There are 17 articles that met the inclusion criteria (Diagram 1).

There are only 3 studies under prospective monitoring (14, 26, 27) and 14 studies under retrospective study (15-25, 28-30) 15-25, 28). There are 9 studies that included Oral Hypoglycemic Agents (OHAs) (14, 17-18, 20, 22, 24-27) and 6 studies that included insulin injection (16, 19, 21, 28-30). 2 studies that included combination therapy (OHAs and insulin) (17, 28) and 2 studies did not specified class of medication (15, 23).

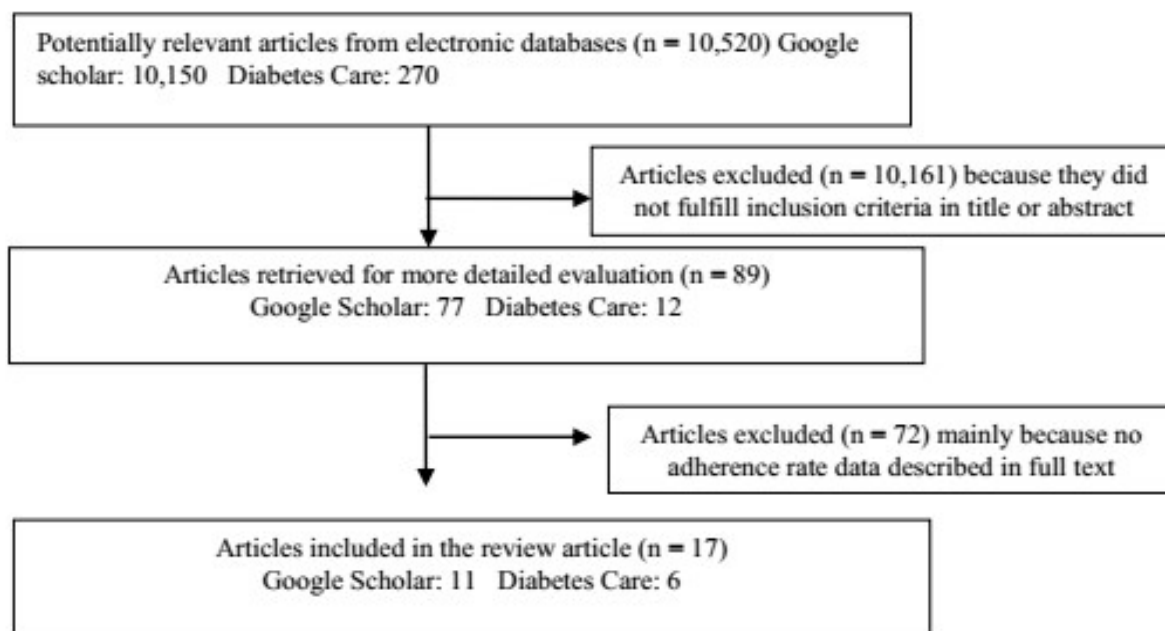


Diagram 1 – Progress of search strategy

There was no prospective study contain adherence rate of insulin injection but 3 studies contain adherence rate of OHAs are under prospective monitoring (14, 26, 27). Among the retrospective study, all 6 studies included (16, 19, 21, 28, 29, 30) insulin injection data and 8 studies included (16-18, 20, 22, 24, 25, 28) OHAs data.

Oral Anti-diabetic Medication

In the retrospective studies, the adherence rate was ranged from 12.4% to 88% (Table 1). The non-comparative studies among retrieved articles contained studies that had similar results and high adherence rate, ranging from 79% to 90% (18, 20, 22-25) adherence to OHAs under the duration of 3 to 36

months of observation. The mean age of patients in these studies are 50 years old and above, indicated that the population of diabetic patients are older. It was also found that some studies compared the patients with different regimens, related to the adherence towards medication. high educated (tertiary) patients had lower adherence rates than low educated (illiterate) patients (40% vs 63%) (16). Patients that did not followed exercise recommendation had lower adherence rate as compare to the patients that had more than 3 times exercise a week (59% vs 68%) (16). Comparing medication knowledge between patients, high percentage of medication knowledge patient had higher adherence rate as compare to low medication

knowledge patient (54.8% vs 0%) (17). Patients under monotherapy had higher adherence rate than combination oral ant diabetic agents and insulin (52%

vs 40.5%) (17). Prevalence of non-adherence for patients under statin was lower as compare to patients under metformin (23% vs 43%) (18).

Table 1 - Studies of rate of adherence to Oral Hypoglycemic Agent in patients with Diabetes Mellitus

Author	Population	Types of Medication	Duration of study (months)	Age	Amount of Patient	Adherence rate	Methodology
Richard Grant, 2007 (14)	HMO, England	Hypoglycemic agent	12	55.4 ± 12.2	2,065	79.8 ± 19.3	prospective study
Barbara J.Mason, 1995 (26)	clinic	Sulfonylurea	10	/	21	74.5	prospective study
Arsenio H.P. Paes, 1997 (27)	Community	hypoglycemic agent	6	69	91	67.2±30	prospective study
Boon-how chew, 2015 (16)	Malaysia	hypoglycemic agent	12	56.9±10.18	668	57.7	retrospective study, cross-sectional study
Manell Pladevall, 2004 (18)	HMO, USA	Metformin	36	64	677 (n = 304 for metformin)	83	retrospective study
Joel M. Schechter, 2002 (20)	USA	hypoglycemic agent	15	59	829	79.7±21	Retrospective study
Elizabeth A. Walker, 2006 (22)	Clinical Centre	metformin	3	/	2155	77	retrospective study
David A. Sclar, 1999 (24)	Medicaid	hypoglycemic agent	12	59±10	975	39.4 (persistence for 6 month)	retrospective study
Francesca Venturini, 1993 (25)	HMO	Sulfonylurea	24	59±11	786	83±22	Retrospective study
P. Michael Ho, 2006 (28)	HMO	hypoglycemic agent	12	65.9±11.1	11532 (9076 of adherent patients)	57.6	retrospective cohort study
Nur Sufiza Ahmad, 2013 (17)	Malaysia	monotherapy	7	55.95±9.13	557	51.5	retrospective study, cross-sectional study survey
		combination hypoglycemic agent				46.9	
		combination hypoglycemic agent + insulin				40.5	
P. Michael Ho, 2006 (28)	HMO	hypoglycemic agent + insulin	12	65.9±11.1	11532 (9076 of adherent patients)	12.4	retrospective cohort study
James Bagonza, 2015 (15)	Eastern Uganda	Antidiabetic medication	12	50.9±14.6	521	83.3	retrospective study, Questionnaire
Michel Tiv, 2012 (23)	France	Antidiabetic medication	12	65	3637	88	retrospective study, Questionnaire

In a study conducted by Micheal *et al* (28) showed that increase in medication adherence were associated with improved outcomes. Strong evidence linking between adherence rate and HbA1c and LDL levels, each 25% increase in adherence to OHAs and statins was associated with -0.05% reduction in HbA1c and LDL levels. There were only 3 studies that performed

prospective monitoring to evaluate the adherence rate of medication by the diabetic patients (14, 26, 27). The range of cohort was 21 to 2065. The ranging of adherence rate was narrow as compared to retrospective study, 68% to 80%. The observation of studies from 6 to 12 months (Table 1).

Most of the prospective studies were using Medication Event Monitoring System (MEMS) container that is a medication bottle cap with spring-loaded device. When patient opened, it will triggered microprocessor that record date and time of opening.

The electronic monitoring device showed adherence rates decreased when larger OHAs doses were prescribed for daily intakers of medications.

Table 2 - Studies of rate of adherence to s/c Insulin in patients with Diabetes Mellitus.

Author	Population	Types of Medication	Duration of study (months)	Age	Amount of Patient	Adherence rate	Methodology
L.A.Donnelly, 2007 (19)	Scotland	insulin	12	62±12	1099	70.6±17.7	retrospective study, Observational records-based study
Boon-how chew, 2015 (16)	Malaysia	insulin	12	56.9±10.18	668	55.7 (1 type), 53.9 (more than 1 type)	cross-sectional study
Kelly McNally, 2010 (21)	USA	insulin pump	36	10.5 ± 1.0	235	60.86 ± 8.10	Retrospective study
P. Michael Ho, 2006 (28)	HMO	insulin	12	65.9±11.1	11532 (9076 of adherent patients)	9.5	retrospective cohort study
Musarrat Riaz, 2014 (29)	HMIS, Pakistan	insulin	9	17.9±6.4	194	11.9	retrospective study, questionnaire
Anthonia O Ogbera, 2012 (30)	Diabetic Centre, Lagos	insulin	6	52.85	160	8.6	retrospective study

Mason *et al* (26) studied that adherence rate for patients taking sulfonylurea by using electronic monitoring was 74.5%, while self-reported adherence comparatively were higher (92.4%). Another study conducted by Grant *et al* (14) showed adherence rate and medical intensification. This study showed that the patients with highest adherence rate

were more likely have regimens intensified than patients in lower adherence. This showed that medication adherence to initially prescribed drug was strongly related to medication intensification. The study provides a link between the patient behavior and physician action. This observation may increase attention of physician and patient on effective management of diabetes on earlier phases and may provide a way to avoid of micro as well as macro complications.

Insulin injections

For studies, that include insulin are very limited and no prospective monitoring on insulin uptake. All 6 studies are under retrospective study (16, 19, 21, 28-30). In related studies, range of age is very wide, ranging from 10-66 years old (Table 2). Compare to OHAs data, mean age of 10.5 ± 1.0 children and 17.9±6.4 adolescence are included in data of insulin injection for treatment of IDDM. Large amount of patients are under observation, ranging from 235 to 11532 patients. Duration of study or observation from 6 to 36 months. The overall adherence rate for insulin use is significantly low as compare to OHAs use show on Table 2. All studies comprised of adherence rate with insulin in Table 2 not higher than 75%. Micheal (28) showed that patient rates of adherence that under insulin treatment, non-adherence rate higher than

adherent patient (11% vs 9.5%). Comparing adherence rate of OHAs and insulin, adherence to OHAs far more higher adhered than that of adherence to insulin (57.6% vs 9.5%) (28). Non-adherent patients may have more risks for all-cause mortality as compare to adherent patients (5.9% vs 4.0%) and risks of all-cause

hospitalization were also comparatively higher than patients (23.2% vs 19.2%) (28). In 2010, Nally *et al* (21) demonstrated the relationship between executive functioning (e.g. ability to set goals or task and ability to adapt to treatment regimens), medication adherence and glycemic control in children or pre-adolescence (mean age 10.5 ± 1.0 years) with type 1 diabetes. To improve accuracy of study, researcher collected data and measured by Behavior Rating Inventory of Executive Functioning (BRIEF), Diabetes Self-Management Profile (DSMP) and glycemic control. Patient adherence towards a single type of insulin was higher than more than one types of insulin (56% vs 54%) (16). Furthermore, Boon How Chew (16) reported that the patient's rate of adherence to OHAs were higher than rate of adherence to insulin treatment (58% vs 56%). Based on type 2 diabetes, Donnelly (19) contributed adherence rate of number of injections per day and relationship between HbA1c levels with adherence level. From the collected and analysed data, it was showed that patients with one injection of insulin per day had higher rate of compliance than more than one injection per day (78.3%±17.8 vs 60.8%±21.7) and HbA1c levels significantly increased at low compliance rate.

CONCLUSION

This systemic review shows that the adherence rate of OHAs is relatively higher than s/c injections of insulin, administered once or more in a day. Patients with oral anti diabetic medications are considered as mild diabetes patients. Boon and Micheal (16, 28) recorded compliance rate of insulin and OHAs, a clear association between the both medications that showed compliance rate of OHAs significantly higher than insulin. Young patients with type 1 diabetes not only low adhered to insulin but also dietary and lifestyle advices (29). A review conducted by Davies (4) on adherence of insulin between type 1 and type 2 diabetes, indicated few factors that caused patients low adherence. Some other factors that affect on the compliance rates such as fear of injections and embarrassment of injecting in public were also considered. In discussion of this study (33) advised initiating therapy with a pen device and decrease financial problems of patients by applied insurance scheme.

One of the main factor found in both studies of Riaz *et al* in 2014 (29) and Ogbera *et al* in 2015 (30) was the cost of insulin. For the patients that earned a salary required quarter of his/her salary to spend on insulin (30). Insulin cost is higher for type 2 diabetes treatment due to the requirement of 4 injections per day and use insulin analogues (30). Patients that do not adhered to the insulin regimens, the complication of diabetes may increase for them. This leads to increase cost of health care due to more co-morbidities. Government should concern about the patients in difficulties especially on cost of healthcare, provide insurance scheme that will reduce the cost burden of treatment not only for diabetes mellitus but also for the other disease.

Furthermore, the side effects of insulin also causes non adherence of medication by type 1 diabetes patients. In the study of Ogbera, 51 patients experienced hypoglycemia, 19 patients experienced skin changes and weight gained and 7 patients experienced skin atrophy and hyperpigmentation (30). Especially women, due to weight gained and skin changes, they rather chose not adhered to insulin than showed any side effects after using insulin. The medical care service influencing patient compliance. Rate of non-adherence of medications increased due to patients did not understanding to their prescribed drug and treatment (29). Physician did not provide sufficient information to the patients about the insulin like way to administered and side effects. Fear of injection also considered in factors of non-adherence to insulin treatment (29, 30).

For type 1 diabetics, that still children and adolescence has low executive functioning as showed in a study (21). Executive functioning was strongly linked to medication adherence and self-management. Adherence rate will directly interfered the rate of glycemic control. Executive functions defined as umbrella term for management of cognitive processes, including working memory, reasoning, task flexibility and problem solving as well as planning and execution (31). Parents must provide family support to improve their skills on organization, planning and problem solving.

Adherence rate of medication strongly relate to the number of tablet(s) per day. Based on the results from the studies included in this review (17, 21) suggested that prescribe an easy dose regimen with one tablet per day may increase compliance of medication. However, one tablet per day may causes higher possibility of overconsumption compare to twice daily and three times per day as show it the data of

Nally's study (21). Overconsumption among the patients with once daily regimen can be explained patients had additional intake of tablet due to patients felt insecure about whether he/she had taken medicine or not and felt that not under 24 hours therapeutic coverage because only one tablet per day.

MEMS device provided an effective function by identifying outpatient of medication adherence and contribute to metabolic control (26). Inaccurate of self-assessment of adherence in patients cause physicians have difficulty to identify adherence rate of medications accurately. MEMS can increase awareness of adherence for both patients and prescribers. Thus, MEMS can considered as most useful diagnostic tool to identify patient's rate of adherence to medication. The information may provide prescriber or physician assist in treatment decision and improve metabolic control. The electronic monitoring only restricted to studies of OHAs. Similarly of this review, is lack of electronic monitoring system for insulin dosage regimens. It will be a great improvement and increase sensitivity of data on studies of rate of adherence to insulin. Further, studies with electronic monitoring of diabetic medications may identify the problems of patients and improve treatment outcomes (10). This may lead to improve glycemic control and reduce overall healthcare costs as high cost of insulin treatment showed in studies (29, 30) and decrease economic burden of diabetes mellitus.

The main limitation or inaccuracy of this review article is the methodology used to analyses adherence rate of medication. Although the studies included data about factors of non-adherence but still lack of evaluation on ways to improve adherence rate of medications. In retrospective study, that includes mean of age, duration of observation, definition of adherence and ways to collect data. Some of the retrospective studies may include all patient but some studies only include part of cohort base unclear condition. Type and name of the medication should record, so that we could analyze rate of adherence of various medication either OHAs or insulin and adherence rate when initiation of new medication. Some studies only stated anti-diabetic medication but not clarified which type of medication they focused (15, 23).

From this review, it is clearly stated that low adherence rate of medication for diabetic patient will cause increase in HbA1c level. The adherence rate of insulin is lower than OHAs. So implication is instead of increase dose, changing medication, combination with second drug when blood glucose level and HbA1c level are high, clinicians should provide counseling patient especially patients that under insulin treatment for curing type 1 and type 2 diabetes to improve adherence rate of insulin. Due to the route of administration of insulin at current stage is only s/c injection, company, government and universities should give more support on research of various route of administration of insulin that have similar effect as injection insulin and does not have side effects like oral route. One of the research by Zhang *et al* (31) successfully delay the onset and reduce the incidence of diabetes in mice over a 1-year period in animals administered with 1 mg of porcine insulin orally but yet no metabolic effect in decreasing blood glucose level. The adherence of OHA also depend on amount of medications, the lesser the amount of OHAs the higher the adherence rate. Developing methods that can improve the medication adherence like modified patient's behavior, higher the adherence rate could significantly improve glycemic control.

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