Exploring the relationship between medication adherence and hospitalization rate in patients with type 2 diabetes mellitus

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Abstract

Medication adherence is defined by the World Health Organization (WHO) as "the degree to which the person's behavior corresponds with the agreed recommendations from a health care provider, Adherence to therapies is a primary determinant of treatment success. The aim of the current study to compute the level of medication adherence in hospitalized and non-hospitalized patients in order to compare between them and demonstrate the effect of non-adherence on hospitalization rate. Sixty patients were participating in the current study (30 hospitalized, 30 non hospitalized) with age ≥ 18 years old, using morisky questionnaire and general questionnaire to collect information that relate to the patient lifestyle, diet, age, sex etc. It was found that 60% of hospitalized patients involved in the study had low adherents, 26.6% medium and only 13.3% were high adherents compared to non-hospitalized with 33.3% being high adherents, 33.3% low and medium adherents, and the direct relationship between decreased adherence and increased hospitalization rates, also noticed the effects of age, complexity of treatment, patient- provider interactions and unwanted side effects of medications on the rates of adherence. The study found that low adherence was higher in hospitalized patients; the rate of high adherence was increased in non-hospitalized patients. Adherence to prescriptions is linked to age, patients' beliefs, education about their health, their trust in health care workers.

Keywords: diabetic mellitus, insulin, HbA1c, Polyuria

Introduction

A rise in plasma blood glucose is a clinical illness known as diabetic mellitus (DM). Among its numerous causes, type 1 or type 2 diabetes are the most frequent ones. T2DM has a more insidious beginning in which there is a functional insulin deficit brought on by an imbalance between insulin levels and insulin sensitivity. Although it is multifaceted, age and fat are the two main causes of insulin resistance (1). Polyuria, which frequently occurs at night, polydipsia, polyphagia, blurred vision, numbness or tingling in the hands or feet, extreme fatigue, slowly healing wounds, and an increased risk of infections were among the symptoms of diabetic mellitus. Hyperglycemia is a complication of diabetes that can lead to both acute and chronic complications. Acutely, severe symptoms, metabolic decompensating, and hospitalization may arise from elevated glucose and insufficient insulin. Diabetes-specific 'micro- vascular' complications affecting the kidneys (nephropathy), feet (neuropathy), and eyes (retinopathy) are brought on by chronic hyperglycemia (2).

A variety of therapies are necessary for the effective management of DM due to the disease's complex physiology and treatment. Patient involvement and diabetic education are essential to management. Patients who can control their diet (restrictions on carbohydrates and total calories), exercise frequently (above 150 minutes per week), and self-monitor their blood sugar levels will fare better. In order to avoid unintended consequences, treatment must frequently last a lifetime. Maintaining glucose levels between 90 to 130 mg/dL and a HbA1c of less than 7% is the ideal range. Although glucose control is essential, overly strict management might result in hypoglycemia, which can have dangerous or lethal consequences [26]. First-line therapy for T2DM patients includes food and lifestyle change

guidance. If glycaemic objectives are not met as a result, or if a patient has a high HbA1c and significant symptomatic hyperglycemia at diagnosis, oral anti-diabetic medications are typically administered. Nonetheless, in several nations, the protocol calls for starting medication as soon as diabetes is diagnosed (3,4,5,6). The most widely utilized classes of oral antidiabetic medications to treat type 2 diabetes are four well-established ones. These consist of alpha-glucosidase inhibitors, metformin, thiazolidinediones, insulin secretagogues, sulfonylureas, and biguanides. Three new medicines that target endogenous regulators of glucose homeostasis are pramlintide, exenatide, and sitagliptin (3).

The degree to which people take their drugs as directed by their medical professionals is known as adherence to a medication regimen. Adherence was meant to replace the idea of patients as people who only followed instructions, and it assumes the patient agrees with the recommendations (7). The percentage of a patient's recommended medicine dosages actually taken over a given period of time is typically used to calculate the patient's rate of adherence. The term "adherence" has been further defined by some researchers to encompass information on dosage compliance (taking the recommended number of pills daily) and dose timing (taking pills within a designated period). Patients with acute disorders tend to adhere to treatment plans more frequently than those with chronic ailments; patients with chronic conditions, on the other hand, have surprisingly low persistence rates, which peak after the first six months of therapy (8, 9). Physicians have a low ability to identify no adherence, and efforts to increase adherence have yielded inconsistent outcomes. Additionally, effective solutions are typically very expensive and complex (9, 10, 11, and 12). Medication adherence is the primary cause of disease progression, mortality, and rising health care expenses (11). Non adherence to medications can be intentional or non-intentional. Methods to measure adherence illustrates in table 1 (13).

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	Patients can hide pills in the mouth and then discard them; impractical for routine use
Measurement of the level of medicine or metabolite in blood	Objective	Variations in metabolism and "white-coat adherence" can give a false impression of adherence; expensive
Measurement of the biologic marker in blood	Objective; in clinical trials, can also be used to measure placebo	Requires expensive quantitative assays and collection of bodily fluids
Indirect methods		
Patient questionnaires, patient self-reports	Simple; inexpensive; the most useful method in the clinical setting	Susceptible to error with increases in time between visits; results are easily distorted by the patient
Pill counts	Objective, quantifiable, and easy to perform	Data easily altered by the patient (e.g., pill dumping)
Rates of prescription refills	Objective; easy to obtain data	A prescription refill is not equivalent to ingestion of medication; requires a closed pharmacy system
Assessment of the patient's clinical response	Simple; generally easy to perform	Factors other than medication adherence can affect clinical response
Electronic medication monitors	Precise; results are easily quantified; tracks patterns of taking medication	Expensive; requires return visits and downloading data from medication vials
Measurement of physiologic markers (e.g., heart rate in patients taking beta-blockers)	Often easy to perform	Marker may be absent for other reasons (e.g., increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	Easily altered by the patient
When the patient is a child, questionnaire for caregiver or teacher	Simple; objective	Susceptible to distortion

Table 1: Method to measure adherence

The validated Morisky Medication Adherence Scale-8 (MMAS-8) questionnaire is a useful instrument for assessing non-adherence in a range of patient demographics. The MMAS-8 scale is a low-cost, easy, self-reported instrument for evaluating chronic medication adherence that is especially made to make it easier to identify obstacles to anti-diabetic medication adherence in real-time, which is crucial in clinical practice. The MMAS-8 is self-report questionnaire

with 8 questions (items) whose wording of the questions/items are formulated to avoid answering "yes" to questions regardless of their content (14).

Subjects and Methods:

Sixty Adult-patient with T2DM male and female (age ≥ 18 years old) with conventional treatment of oral anti-diabetic-treatment were enrolled randomly as samples in current study. Thirty patients were “hospitalization patients” taken from Al-Kadhimain teaching hospital Baghdad/ Iraq, between "January 2024 to March 2024". Another Thirty were “non-hospitalization patients” taken from random Pharmacies in Baghdad. They were treated according to clinical practice guidelines “conventional treatment of oral anti-diabetic treatment” and disease severity under supervision of consultant internists. Pregnant and nursing mothers were excluded. The Questionnaire (1) to determine general health and medication information about the patient then the results calculated by finding the percentage of each question involved. Questionnaire (2) MMAS-8 for rates of adherence was used. Items 1 through 7 have response choices "yes" or "no" whereas item 8 has 5-point Likert response choices. Each—no" response is rated as "1" and each "yes" is rated as "0" except for item 5, in which each response "yes" is rated as "1" and each "no" is rated as "0". For item 8, if patient chooses response "0", the score is "1" and if they choose response "4", the score is “0”. Responses “1, 2, 3” are respectively rated as “0.25, 0.75, 0.75”. Total MMAS-8 scores can range from 0 to 8 and have been categorized into three levels of adherence: high adherence (score = 8), medium adherence (score of 6 to < 8), and low adherence (score< 6) (14).

Questionnaire (1)

1. **Patient name:**
2. **Age:**
3. **Sex:** ☐ Male ☐ Female
4. **How long have you been diagnosed with DM?**
   ☐ Less than 5 years ☐ 5 - 10 years ☐ 10 - 15 years ☐ 15 years or more
5. **Is DM an inherited disease in your family? "Family history"**
   ☐ Yes ☐ No
6. **Do you eat healthy or fat-rich meals?**
   ☐ Healthy (Regular diet with low sugar/carbohydrates) ☐ Fat rich meals
7. **Rate your physical activity**
   ☐ Low ☐ Moderate ☐ High
8. **Do you often check your blood glucose level?**
   ☐ Yes ☐ No
9. **If answer (yes), in which test?**
   ☐ Fasting blood sugar test ☐ Random blood sugar test ☐ HbA1c test
10. **How often do you communicate with your doctor about your medication and health?**
    ☐ Each month ☐ Each 3 months ☐ Each 6 months
11. **Do you use any drugs for your DM?**
    ☐ Yes ☐ No
12. **How many drugs do you take?**
    ☐ One ☐ Two ☐ Combination
13. **Which drug is use?**
    ☐ Metformin (biguanide)
    ☐ Sulfonylureas
    ☐ Thiazolidinediones (TZDs)
    ☐ Dipeptidyl peptidase 4 inhibitors (DPP-4)
    ☐ Glucagon-like peptide 1 receptor agonists (GLP-1)
    ☐ Sodium-glucose cotransporter 2 inhibitors (SGLT-2)
    ☐ α-glucosidase inhibitors
    ☐ Meglitinides
    ☐ Bile acid sequestrants
    ☐ Amylin analog

14. **Does the medication that you are currently taking is the same one you took when you discovered your disease?**

☐ Yes ☐ No

15. **Do you take your medication at the scheduled time?**

☐ Yes ☐ No

16. **When you feel bad, have you ever discontinued taking your medication?**

☐ Yes ☐ No

17. **Have you ever forgotten to take your medication?**

☐ Yes ☐ No

18. **When you feel better do you sometimes stop taking your medication?**

☐ Yes ☐ No

19. **Sometimes if you feel worse when you take the medication do you stop taking it?**

☐ Yes ☐ No

20. **I take my medication only when I am sick**

☐ Yes ☐ No

21. **In the LAST WEEK, HOW MANY TIMES did you fail to take your prescribed dose?**

☐ Never ☐ 1-2 times ☐ 3-5 times ☐ 6-10 times ☐ > 10 times

22. **Has your doctor ever prescribed insulin to you?**

☐ Yes ☐ No

23. **Do you tell your doctor or your pharmacist about the drug's problems?**

☐ Yes ☐ No

24. **Have you ever lost your consciousness because of low blood sugar? "hypoglycemia"**

☐ Yes ☐ No

25. **Have you ever been admitted to the hospital? And why? Answer Only for outpatients**

☐ Yes ☐ No

26. **Are you aware that DM is a chronic condition and may cause several serious conditions for body organs? But these complications happen to a lesser extent if you take your medication as scheduled.**

☐ Yes, I'm aware ☐ No, I didn't know

Questions	Yes	No
1. Do you sometimes forget to take your medication?		
2. People sometimes miss taking their medications for reasons other than forgetting. Over the past 2 weeks, were there any days when you did not take your medication?		
3. Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?		
4. When you travel or leave home, do you sometimes forget to bring your medication?		
5. Did you take all your medication yesterday?		
6. When you feel like your symptoms are under control, do you sometimes stop taking your medication?		
7. Taking medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your treatment plan?		
8. How often do you have difficulty remembering to take all your medication? Never/rarely Once in a while Sometimes Usually All the time		

Table (2): MMAS-8 questionnaire

Results

Table 3: the results of Questionnaire 1

		Out patients	In patients
Gender in %	Female	40%	36.6%
	Male	60%	63.3%
Mean age		47.4	59.8
Is DM inherited in your family?	Yes	70%	66.6%
	No	30%	33.3%
What test do you use to check your blood glucose level?	Fasting blood sugar test	30.6%	29.8%
	Random blood sugar test	24.4%	19.2%
	HBA1C test	34.6%	25.5%
	I don't check my blood sugar levels	10.2%	25.5%
How often do you communicate with your doctor about your medication and health?	Each month	6.6%	0%
	Each 3 months	30%	10%
	Each 6 months or more	63.3%	90%
How many drugs for DM do you take?	One	20%	13.8%
	Two	17.1%	24.1%
	Combination	62.8%	62.1%
Which drug do you use?	Metformin	41.7%	44.8%
	Sulfonylureas	20.8%	36.2%
	TZDs	5.9%	0%
	DPP-4	14.9%	13.8%
	SGLY-2	16.4%	3.5%
	Others	0%	1.7%
Is the medications you are taking now is the same one that you took when you discovered your diagnosis?	Yes	23.3%	36.6%
	No	76.6%	63.3%
Do you take your medication at the scheduled time?			
	Yes	90%	70%
	No	10%	30%

		Out patients	In patients
When you feel bad have you ever discontinued taking your medication?	Yes	20%	33.3%
	No	80%	66.6%
Have you ever forgot to take your medication?	Yes	33.3%	76.6%
	No	66.6%	23.2%
When you feel better do you stop taking your medication?	Yes	20%	63.3%
	No	80%	36.6%
If you feel worse when you take your medication do you stop taking it?	Yes	20%	36.6%
	No	80%	63.3%
I take my medications only when I'm sick?	Yes	13.3%	46.6%
	No	86.6%	53.3%
In the last weeks how many times you failed to take your medications?	Never	76.6%	63.3%
	1-2 times	20%	10%
	3-5 times	0%	20%
	6-10 times	0%	6.6%
	More than 10 times	3.3%	0%
Have your doctor ever prescribed insulin to you?	Yes	40%	86.6%
	No	60%	13.3%
Do you tell your doctor or pharmacist about drugs problems?	Yes	83.3%	73.3%
	No	16.6%	26.6%
Have you ever lost consciousness because of low blood sugar? (hypoglycemia)	Yes	33.3%	43.3%
	No	66.6%	56.6%
Have you ever been admitted to hospital?	Yes	40%	
	No	60%	
Are you aware that DM is a chronic condition that have several serious complications?	Yes	100%	83.3%
	No	0%	16.6%

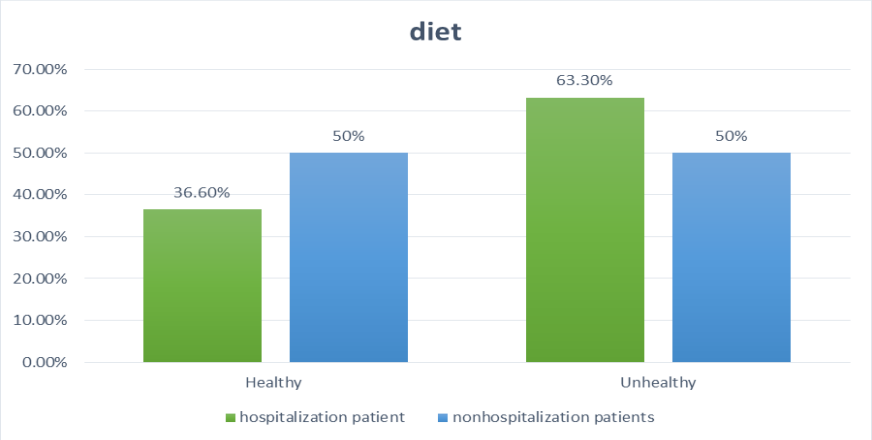

Figure 1: results of diet for hospitalization & non-hospitalization patient

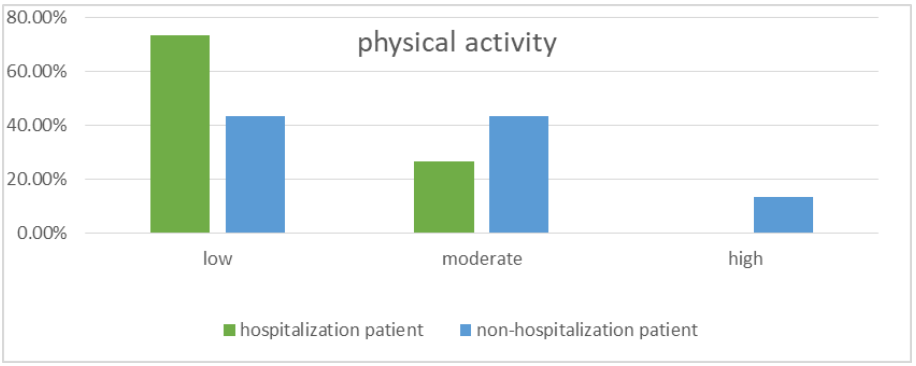

Figure 2: results of physical activity for hospitalization & non-hospitalization patients

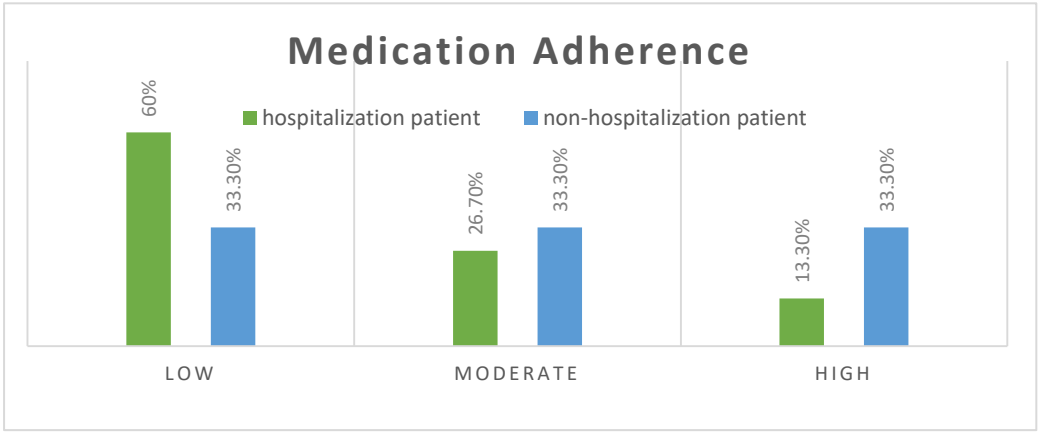

Figure 3: classification of adherence MMAS-8 score

Discussion

In order to achieve therapeutic goals, medication adherence is a crucial aspect of patient care. The main cause of patients not receiving the full range of health advantages that medications might offer is poor adherence. Dr Derek Yach, Executive Director, non-communicable Diseases and Mental Health, World Health Organization, stated that it wastes health care resources, results in medical and psychosocial complications of disease, lowers patients' quality of life, and increases the risk of drug resistance. When combined, these immediate effects make it more difficult for health care systems to meet global population health

targets (15). In the current study though using morisky scale it was found that 60% of patients who are hospitalized had low adherence while in non-hospitalization patients 33.3% were low adherents, 33.3% non-hospitalization patients with high adherence level were compared to 13.3% in hospitalized individuals, the direct relationship between decreased adherence and increased hospitalization rate can be noticed and this agree with the retrospective observational study that done by Pednekar., *et al* (16). Also, the age may have effects, it was found that the mean age for hospitalized patients were 59.8, while in non-hospitalization patients were 47.4, this could be explained by the fact that increased age causes increase rates of forgetfulness (917). Since 76.6% of hospitalized patients have forget to take their medication in some occasions while 33.3% in non-hospitalization patients.

Another interesting result is increased the number of drugs that should be taking could reduce the level of patient adherence 86.2% of hospitalized patients were using two drugs and combinations of several drugs ,also the fact that most of patients involved in the current study were diagnosed with other chronic diseases like hypertension, hypothyroidism, HF that requires taking additional medications, Patients with T2DM will likely need to take medication for the rest of their lives, and the complexity of their regimen will likely grow as a result of the chronic, progressive nature of the disease. The treatment that has been given has become more complex during the past 20 years as knowledge of the illness has constantly grown (18). In the current study it was found that 43.3% of in patients suffered from hypoglycemia caused them to lose consciousness also explain the fact that 36.6% have discontinued taking their medication when they felt worse, while in non-hospitalization patients 33.3% suffered from hypoglycemia and 20% discontinued taking their medication. This result can be explained by non-adherence could also be due to adverse events associated with medications. The majority of patients with T2DM are overweight or obese at diagnosis, and some of the current therapeutic options are associated with weight gain and hypoglycemia.

When thinking about long-term therapy, it is crucial to think about such tolerability difficulties. In an analysis of data from 2,074 T2DM patients in the USA between 2006 and 2008 who were taking more than one OHA but not insulin, the majority (71.7%) reported having at least one tolerability problem in the previous two weeks (hypoglycemia, constipation/diarrhea, headaches, weight gain, and water retention), and 49.7% reported having more than two problems. There was a strong correlation between the quantity of tolerability problems and the probability of non-adherence [19]. It has also been demonstrated that interactions between diabetic patients and their medical professionals affect medication adherence. Research has indicated that enhanced communication between patients and healthcare professionals can alleviate patient discomfort and increase adherence and glycemic control. Patients who receive more information about treatment options and decisions are also more likely to adhere to their prescribed regimen (20). This explained the result of the current study since 90% of hospitalized patients communicate with their doctors every 6 months or more while in non-hospitalization patients 30% communicate with their doctors every 3 months.

Physical activity has a great effect on controlling diabetes, 73.3% of hospitalized patients were low physical activity while 43.3% of non-hospitalization patients have low physical activity demonstrates the effect of activity on hospitalizations rate in a large-scale short study, Low-volume physical exercise, defined as 15 minutes per day or 90 minutes per week, was associated with a 14% lower risk of all-cause mortality and a 3-year improvement in life expectancy (21). It is crucial to remember that low to moderate-intensity daily physical activity should be regarded as an alternative and supportive exercise therapy regimen for diabetics, in addition to moderate-to-vigorous physical activity (22).The effects of health and unhealthy diet appears clearly in the present study since it was found that among hospitalized patients 63% were on unhealthy diet compared to 50% in non-hospitals patients. Numerous studies, such as the Diabetes Prevention Program

(DPP), provide the strongest evidence for the prevention of T2DM. The DPP showed that a rigorous lifestyle intervention that led to weight loss might, over the course of three years, cut the incidence of T2DM in persons who were overweight or obese and had impaired glucose tolerance by 58% (25). A sustained decrease in the rate of conversion to T2DM has been observed in the follow-up of three large studies involving lifestyle interventions for the prevention of diabetes: the Da Qing Diabetes Prevention Study (23) showed a 43% reduction at 20 years; the Finnish Diabetes Prevention Study (DPS)(24) showed a 43% reduction at 7 years; and the U.S. Diabetes Prevention Program Outcomes Study (DPPOS) showed a 27% reduction at 15 years and a 34% reduction at 10 years (25).

Conclusion

Low adherence was higher in hospitalized patients; the rate of high adherence was increased in non-hospitalized patients. Adherence to prescriptions is linked to age, patients' beliefs, education about their health, their trust in health care workers. The complexity of prescriptions may make it even difficult for the patients to commit to their medications especially when the majority of them have other chronic diseases requiring daily medications. Also increases the rate of hospitalization was related to low physical activity and unhealthy diet.

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References

1. Kaul, K., Tarr, J. M., Ahmad, S. I., Kohner, E. M., & Chibber, R. Introduction to diabetes mellitus. Diabetes: an old disease, a new insight. 2013; 1-11.

2. Grootenhuis, P. A., Snoek, F. J., Heine, R. J., & Bouter, L. M. Development of a type 2 diabetes symptom checklist: a measure of symptom severity. Diabetic Medicine. 1994;11(3), 253-261.

3. Trevor, A. J., Katzung, B. G., Masters, S. B., & Kruidering-Hall, M. Pharmacology examination & board review. New York: McGraw- Hill Medical. 2010; pp. 121-132.

4. Ralston, S. H., Penman, I. D., Strachan, M. W., & Hobson, R. (Eds.). Davidson's Principles and Practice of Medicine: Davidson's Principles and Practice of Medicine E-Book. Elsevier Health Sciences. 2018.

5. Howland, R. D., Mycek, M. J., Harvey, R. A., & Champe, P. C. Lippincott's illustrated reviews: Pharmacology. Philadelphia: Lippincott Williams & Wilkins. 2006; pp. 103-57.

6. DiPiro, J. T., Talbert, R. L., Yee, G. C., Matzke, G. R., Wells, B. G., & Posey, L. M. (Eds.). Pharmacotherapy: a pathophysiologic approach. 2021.

7. Steiner, J. F., & Earnest, M. A. The language of medication-taking. Annals of internal medicine. 2000; 132(11), 926-930.

8. Jackevicius, C. A., Mamdani, M., & Tu, J. V. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. Jama. 2002; 288(4), 462-467.

9. Haynes, R. B., McDonald, H. P., & Garg, A. X. Helping patients follow prescribed treatment: clinical applications. Jama. 2002; 288(22), 2880-2883.

10. Burnier, M. Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. Blood pressure monitoring. 2000; 5, S31-S34.

11. Miller, L. G., Liu, H., Hays, R. D., Golin, C. E., Beck, C. K., Asch, S. M., ...& Wenger, N. S. How well do clinicians estimate patients' adherence to combination antiretroviral therapy?. Journal of general internal medicine. 2002; 17, 1- 11.

12. Murri, R., Ammassari, A., Trotta, M. P., De Luca, A., Melzi, S., Minardi, C. & AdICoNA Study Group. Patient-reported and physician-estimated adherence to

HAART: social and clinic center-related factors are associated with discordance. Journal of general internal medicine. 2004; 19, 1104-1110.

13. Wagner, J. H., Justice, A. C., Chesney, M., Sinclair, G., Weissman, S., Rodriguez-Barradas, M., & VACS 3 Project Team. Patient-and provider- reported adherence: toward a clinically useful approach to measuring antiretroviral adherence. Journal of clinical epidemiology. 2001; 54(12), S91-S98.

14. Okello, S., Nasasira, B., Muiru, A. N. W., & Muyingo, A. Validity and reliability of a self-reported measure of antihypertensive medication adherence in Uganda. PloS one. 2016; 11(7), e0158499.

15.Rassool, G. H. Failure to take prescribed medicine for chronic diseases is a massive world-wide problem. Journal of Advanced Nursing. 2004; 45(4), 447-447.

16.Pednekar, P., Heller, D. A., & Peterson, A. M. Association of medication adherence with hospital utilization and costs among elderly with diabetes enrolled in a state pharmaceutical assistance program. Journal of Managed Care & Specialty Pharmacy. 2020; 26(9), 1099-1108.

17. Gold PE and Korol DL. Forgetfulness during aging: an integrated biology. Neurobiol Learn Mem. 2014; 112:130-8.

18. Grant, R. W., Pirraglia, P. A., Meigs, J. B., & Singer, D. E. (). Trends in complexity of diabetes care in the United States from 1991 to 2000. Archives of Internal Medicine. 2004; 164(10), 1134-1139.

19. Ingelsson, E., & McCarthy, M. I. Human genetics of obesity and type 2 diabetes mellitus: past, present, and future. Circulation: Genomic and Precision Medicine. 2018; 11(6), e002090.

20. Pollack, M. F., Purayidathil, F. W., Bolge, S. C., & Williams, S. A. Patient-reported tolerability issues with oral antidiabetic agents: associations with

adherence; treatment satisfaction and health-related quality of life. Diabetes research and clinical practice. 2010; 87(2), 204-210.

21. Mingrone, G., Panunzi, S., De Gaetano, A., Guidone, C., Iaconelli, A., Leccesi, L& Rubino, F. Bariatric surgery versus conventional medical therapy for type 2 diabetes. New England Journal of Medicine. 2012; 366(17), 1577-1585.

22. Wen, C. P., Wai, J. P. M., Tsai, M. K., Yang, Y. C., Cheng, T. Y. D., Lee, M. C., & Wu, X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. The lancet. 2011; 3. 78(9798), 1244-1253.

23. Diabetes Prevention Program Research Group. (). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. New England journal of medicine. 2002; 346(6), 393-403.

24. Diabetes Prevention Program Research Group. (). 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. The Lancet. 2009; 374(9702), 1677-1686.

25. World Health Organization. WHO Global report on diabetes; 2016.

26. Umpierre, D., Ribeiro, P. A., Kramer, C. K., Leitao, C. B., Zucatti, A. T., Azevedo, M. J., ... & Schaan, B. D. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. Jama. 2011; 305(17), 1790-1799.