

Hypertension: Health Literacy and its Effect on Patient's Self-Monitoring, Knowledge and Medication Adherence

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Abstract

Background: Self-monitoring blood pressure (SMBP) plus clinical support can improve access to care and quality of care for individuals with hypertension while making blood pressure control more convenient and accessible across the population. **Aim:** To examine the effect of health literacy on hypertensive patient's self-monitoring, knowledge and medication adherence. **Patients and method:** A quasi-experimental research design has been utilized. **Setting:** In hypertension unit in internal medicine department at Assiut University Hospital, Egypt. **Sample:** Study was done on 90 patients who were fulfilled the inclusion and exclusion criteria. **Tools:** Tool I Patient assessment sheet. It divided into three parts; Socio-demographic patients' characteristics, medical assessment, Part II: Blood Pressure Self -Monitoring and Part III: patient awareness questionnaire sheet Tool II: Morisky Medication Adherence Scale (MMAS 8). And Tool III: Health literacy booklet. **Results:** a highly significant statistical differences between mean systolic and diastolic blood pressure before health literacy and after every 2 weeks, There is a highly significant statistical difference between pre & post health literacy regarding to patients knowledge and also for medication adherence ($P < 0.0001$). Regarding to correlation between knowledge scores and medication after health literacy there is a highly significant statistical difference. **Conclusion:** Health literacy has significant impact on the studied patients which driven to advancement of hypertension management in these patients. Too, increase in their knowledge and adherence to their medications. **Recommendations:** Activating the role of community-based physician service intervention including patient education and patient-centered objective support

Key words: Health literacy; Self-monitoring blood pressure; Medication adherence, Knowledge

Operational definitions:

Self- Monitoring Blood Pressure (SMBP): Technically refers to the regular measurement of a patient's own blood pressure

Health literacy: Defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions.

Introduction

Hypertension is a global phenomenon and is common to all human populations with the exception of some primitive communities that live in social confinement, for example, within the Amazon basin. It accounts for up to 6% of adult deaths around the world. Some reports recommend that, there are one billion individuals around the world, who might have hypertension as of 2030. It is believed that there is a global epidemic of unknown proportions as abnormally elevated blood pressures are often asymptomatic. In fact the primary diagnosis of hypertension is often made when the person presents with a myocardial infarction or a stroke. Hypertension is hence properly often referred to as the "silent killer" (Sunil & Gregory, 2015)

Blood pressure readings consist of two figures- first the systolic pressure and the second diastolic pressure. The reading is given as, for example, 140 over 90 mm Hg. The systolic pressure is the higher reading caused by the contraction of the heart, while the lower pressure in the arteries is the diastolic number, during the brief 'resting' period between heartbeats (Cruickshank, 2013).

Currently, most guidelines worldwide define hypertension as systolic BP levels in greater than 140 mmHg or diastolic BP levels excess of 90 mmHg; normal BP is 120/80 mmHg or lower. any BP level between those two ranges is called now either prehypertension or borderline hypertension. Large numbers of individual both in developed and developing countries all through the world will eventually develop hypertension at a few point in their lifetime (Venkata, 2015)

Elevated blood pressure that is not caused by another condition or disease is called essential or basic hypertension. In case it happens as a result of another condition, it is called secondary hypertension (Mark, 2011)

Essential hypertension: can result from different variables, including blood plasma volume and action of the hormones that regulate of blood volume and pressure. It is additionally affected by environmental factors, such as stress and lack of exercise. **Secondary hypertension** has specific causes and is a complication of another issue. (Suzanne et al., 2016)

It is maintained that elevated blood pressure causes sweating, anxiety, sleeping problems, and becoming

flushed. In any case, in most cases, there will be no symptoms at all. If blood pressure reaches the level of a hypertensive emergency, an individual may experience headaches and nosebleeds. (Samy & George, 2012)

The American Heart Association (AHA) guidelines (2017) define the following ranges of blood pressure:

	Systolic (mmHg)	Diastolic (mmHg)
Normal blood pressure	< 120	<80
Elevated	Between 120 & 129	Less than 80
Stage 1 hypertension	Between 130 & 139	Between 80 and 89
Stage 2 hypertension	At least 140	At least 90
Hypertensive crisis	> 180	>120

Self-measured blood pressure monitoring (SMBP), also called as monitoring blood pressure at home, SMBP is the regular measurement of blood pressure measured by the patient outside the clinical area, either at home or somewhere else. SMBP requires the utilize of a home blood pressure measurement device by the patient to assess blood pressure at different points in time, (Tucker et al., 2017).

SMBP furthermore clinical support can improve quality of care for people with hypertension while making blood pressure control more convenient and available over the population. Clinical support incorporates standard one-on-one counseling, web-based or telephonic support devices, and educational classes (William, 2015).

Health Literacy in Nursing advances verbal and written communication techniques that nurses can utilize to effectively meet the individualized needs of a progressively diverse patient population in an effort to improve patient provider communication across the entire continuum of care. It provides strategies for creating culturally suitable written materials in plain language that patients can read and take after when they arrive home (Terri, 2017) .

Numerous kinds of SMBP plus additional support interventions have effectively lowered blood pressure in patients with HTN. Common components of successful SMBP plus additional support interventions are: Conveyance of intervention by trained health care providers (e.g., pharmacists, nurse practitioners, physician assistants, health educators) Regular patient communication of SMBP readings to providers. A patient/provider “feedback loop” in which provider support and counsel are customized based on patients’ reported information, (Merai et al, 2016).

Knowledge is a vital component to control hypertension, which is relative to lower rates of ceasing interventions, taking after the interventions behavior, and superior control on disease by patients. As a result, careful evaluation of hypertension has been considered as an indistinguishable portion of general care of the patients, (Beata et al., 2016).

Inadequate medication adherence is a critical cause of poor blood pressure control. The cornerstone of the effective management of hypertension is adherence to prescribed medications and preventive measures. The role of adherence is particularly important when the treatments are not giving the anticipated clinical outcomes, as, in patients with resistant hypertension, (Burnier, 2014).

Significance of the study:

Hypertension (HTN) or, elevated blood pressure, is a major risk factor for heart disease, stroke, and kidney disease. It influences about one-third of American adults aged 18 or older (67 million individual) (Yoon et al,2015). HTN as a rule requires lifetime management, and keeping up long-term medication adherence, and lifestyle modification can be challenging for patients. Assessment of the knowledge and medication adherence practice is significant for the patient's improvements and wellbeing as well as avoiding disease complications, also applying of self-monitoring blood pressure remains the cornerstone of controlling individual's blood pressure.

Aim of the study:

The aim of this publication is to examine the effect of health literacy on hypertensive patient’s self-monitoring, knowledge and medication adherence.

Hypotheses:

After health literacy patients will experience an increase ability to control /regulate their blood pressure, increase in their knowledge and adherence to their medications, than before .

Patients and methods

Research design: quiz experimental (pre/ post-test) research design was utilized to conduct this study.

Setting: The study was conducted in hypertension unit in internal medicine department at Assiut university hospital.

Sample: A purposive sample of (90) adult hypertensive patients, their age ranged from 18 – 65 years.

Tools for data collection:

Tool I: Patient assessment sheet :

It developed by the researchers based on the literature review.

It consisted of main three parts:

Part I: Socio-demographic patient variables & medical assessment. It included: Patient's name, age, marital status, level of education and occupation. Medical assessment includes: risk factors assessment for developing HTN, duration of disease, medications received, chronic disease assessment, nutritional status assessment, laboratory investigations, smoking , and previous family member history of the disease

Part II: Blood Pressure Self -Monitoring: before health literacy and every 2 weeks for 3 months.

Part III: patient awareness questionnaire sheet:

The aim of this part was to assess the patient awareness about self -monitoring blood pressured includes (definition of blood pressure, normal ranges of BP, important for monitoring, normal Frequency of monitoring, proper posture during measuring BP and precautions before measuring BP) medication, bathing, and follow up.

Scoring system:

Six questions for assessing patients' awareness regarding self -monitoring blood pressure for chronic low back pain treatment.

The answer divided into correct = 2 mark, incomplete answer = 1 mark, and wrong answer= zero .

Total score was ranged from 0 to 12 and this score. The maximum score was 12 degree the minimum score was zero. Classified into three categories: less than 50% was poor knowledge, 50%-70% was fair knowledge, and more than 70% was good knowledge.

Tool II: Morisky Medication Adherence Scale (MMAS 8): Self-reported medication adherence was measured by (Morisky et al., 2008).

Scoring system:

It consists of 8 items, with binary scoring for the first seven items and a 5-point Likert score for the last item. The last item contributes a score between zero and one in 0.25-point increments on a 5-point scale assessing the frequency patients forget take medications (never =1, once in a while =0.75, sometimes =0.5, usually =0.25, and all the time =0). The total score is a summation of all MMAS-8 items and ranges between 0 and 8, with scores of 8 reflecting high adherence, 7 or 6 reflecting medium adherence, and < 6 reflecting low adherence.

Tool III: Health literacy booklet:

This tool was developed by the researchers based on the review of the relevant literatures to provide hypertensive patients with needed instructions to provide knowledge, skills and to increase patients control over HTN.

The study was carried out on three phases:

Phase I: Preparatory phase:

1-The study tools were formulated after an extensive national and international literature review.

2- The content and validity of the tools checked by five special nursing and medical experts.

3-A pilot study was conducted on 10% (9 patients) of sample in a selected setting to evaluate the applicability and clarity of the developed tools.

Sample size :

The sample was 90 patients was selected by using the following equation according to Steven, (2012)

$$n = \frac{N \times p(1-p)}{\left[\left[N - 1 \times (d^2 \div z^2) \right] + p(1-p) \right]}$$

N=total patient population size of 360 who admitted in hypertension outpatients clinic at Assiut University Hospital. During May 2019 to July 2019 by n=90

Z = confidence levels is 0.95 and is equal to 1.96

D= the error ratio is = 0.05

P= the property availability ratio and neutral = 0.50

Phase II: Implementation phase:

- An official permission was obtained from the head of internal medicine department at Assiut university hospital.
- Oral permission for voluntary participation was obtained from patients and the purpose of the study was explained.
- From March 2019 to May 2019 sampling was started and completed. This study was carried out in morning shift.
- Patients were visited by researchers in hypertension unit to start line of communication, clarify the purpose of the study and fill out tool(I). then follow up by telephone .
- Each patient involved in the study was interviewed by the investigators after one month in the clinic for follow up.
- The researcher met every patient and assess the socio-demographic data, medical assessment, and patient’s knowledge, the degree of adherence to HTN medications, and patient’s control over their diseases using Tool(I, II).
- Health literacy booklet was used to provide the patients with needed theoretical and practical information using Tool (III).

Phase III: Evaluation phase:

Evaluate the effect of teaching nursing instructions on patient’s adherence to drugs, and control over HTN using Tool (II)three months after implementing the instructions.

Ethical Considerations:

The study was following the common ethical guidelines of clinical research according to the principles of **Helsinki Declaration, (1996)** for medical research.

- Confidentiality and anonymity were guaranteed.
- Patients had the freedom to participate and or withdraw from the study whenever they want.
- Opportunities were provided for participants to ask questions at any time, and the researcher.
- No names appeared on any results and a coding system known only to the researcher will be developed and used.

Validity and Reliability: The tools were tested for content validity by 5 experts of academic medical and nursing staff from the faculty of nursing at Assiut University. Modifications were done accordingly, and then the tools were designed in its final format and tested for reliability by using internal consistency for the tools measured using Cronbach test, the tools proved to be reliable (0.87) .

Statistical design:

Data collected and entered by Microsoft Excel 2016 program, the SPSS version (21) (Statistical package for social science) used for statistical analysis of data. The frequency used to calculate count and percentage of qualitative data e.g. gender, where descriptive used to calculate the mean ± standard deviation for quantitative data (e.g. Age). Chi-square & ANOVA test used to test the relation between qualitative variables. n.s P > 0.05 no significance, ** P < 0.01 moderate significance and *** P < 0.001 highly significance

Results:

Table (1) Frequency distribution of the studied sample as regards Socio-demographic characteristics (N=90)

Socio-Demographic characteristics	Studied patients	
	N.	%
Gender:		
• Male	28	31.1%
• Female	62	68.9%
Residence:		
• Urban	21	23.3%
• Rural	69	76.7%
Age:		
• 18-35	21	23.3
• 36-50	34	37.8
• 51-65	35	38.9
Mean± SD(range)	45.21±12.52 (37)	
Education Level:		
• Illiterate	49	54.4%

• Read and write	7	7.8%
• Secondary education	20	22.2%
• University	14	15.6%
Marital Status:		
• Single	14	15.6%
• Married	76	84.4%
Occupation:		
• Farmer	21	23.3
• House wife	62	68.9
• Office work	7	7.8

Frequency test

Table (1): As regard sex the highest percentages was females (68.9%) .Regarding residence; the result found that the highest percentage was living in rural areas (76.7%). Regarding age; it was found that (38.9%) of the patients their age was 51 -65 years, with mean±SD of 45.21±12.52,Also it was found that 54.4% was illiterate. The highest percentage was married (84.4%). More than half of them was house wife (68.9%).

Table (2) Frequency distribution of the studied sample as regards Medical data & Risk factors

Medical data	Studied Patients	
	N =(90)	%
Presence of Medication		
• 1 drug	76	84.4%
• 2 drugs	14	15.6%
Duration of HTN		
• 1-3 yrs.	41	45.5%
• 4-6 yrs.	21	23.3%
• 7-9 yrs.	28	31.1%
Frequency of self-monitoring(SM)Before		
• Yes	0	0
• No	90	100.0%
Chronic Disease		
DM		
• Yes	28	31.1%
• No	62	68.9%
CAD		
• Yes	28	31.1%
• No	62	68.9%
CKD		
• Yes	7	7.8%
• No	83	92.2%
Other Medical Problems		
• Yes	7	7.8%
• No	83	92.2%
Nutritional Status		
• Low weight	0	0.0%
• Standard	0	0.0%
• Over weight	27	30.0%
• Obese	56	62.2%
• Morbid obesity	7	7.8%
Family History		
• Yes	48	53.3%
• No	42	46.7%
Smoking		
• Yes	28	31.1`%
• No	62	68.9%

Cholesterol Level		
• Normal	28	31.1%
• High	62	68.9%

Table (2): represents that most of the patients (84.4%) receiving 1drug for hypertension, more than half of them complaining from hypertension from 1-3 yrs. All of them didn't do self- monitoring of blood pressure before. 68.9 % of them not complaining from diabetes mellitus or coronary artery disease , also 92.2% not complaining from chronic kidney disease or other medical problems. As regarding nutritional status more than half of them 62.2% were obese. 53.3% of patients with family history of hypertension. Most of them didn't smoke and had high level of cholesterol

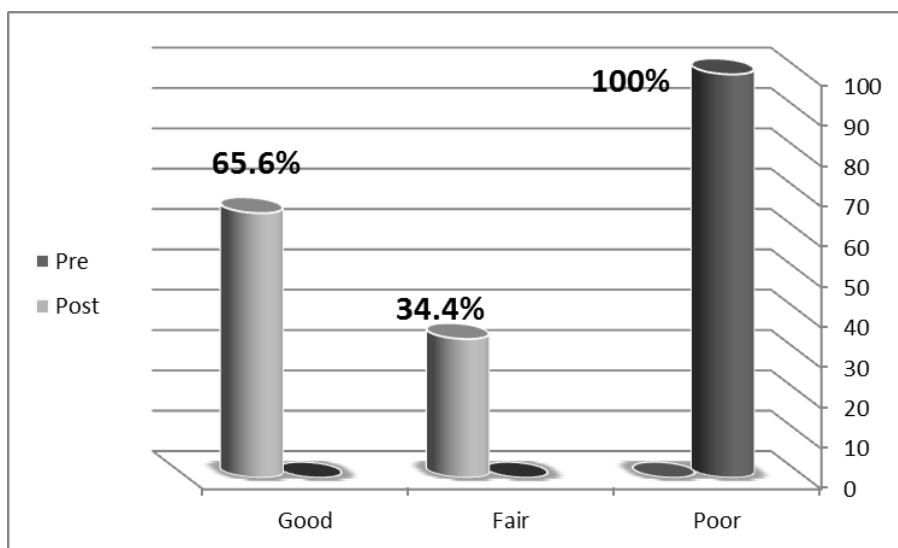
Table (3): Blood pressure self-monitoring of patients before health literacy and every 2wks after till 12 weeks.

Blood Pressure	Before health literacy	After 2 weeks	After 4 weeks	After 6 weeks	After 8 weeks	After 10 weeks	After 12 weeks
	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD	Mean ±SD
• Systolic	166.88 ±15.55	164.00 ±13.4	153.2 ±9.46	140.44 ±7.48	133.11 ±5.330	123.88 ±5.126	117.44 ±7.276
• Diastolic	97.33 ±9.094	94.89 ±9.025	86.11 ±6.98	77.44 ±6.100	71.11 ±3.160	70.00 ±0.00	70.00 ±0.00
P value		.000* **	.000 ***	.000* **	.000** *	.000** *	.000** *

One sample T test ANOVA test
 *** highly Significant p at <0.05

Table 3: shows that there is a highly significant statistical differences between mean systolic and diastolic blood pressure before health literacy and after every 2 weeks .

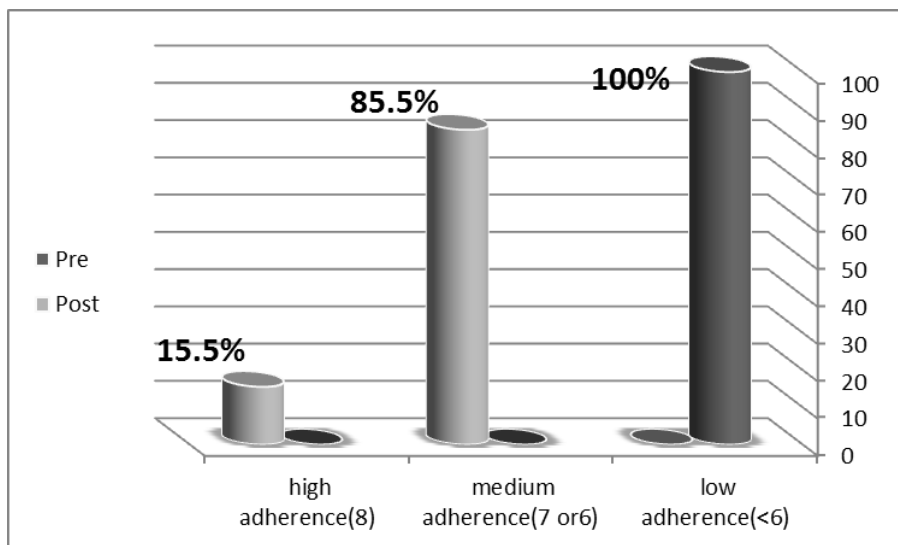
Figure (1): Comparison between patients knowledge between pre &post health literacy (N. =90)



Chi square test
 *** highly Significant p at <0.05

Figure (1) describes that there is a highly significant statistical difference between pre &post health literacy regarding patients knowledge

Figure (2): Comparison between studied patients' medication adherence scores pre & post health literacy (N.=90)



Chi square test * highly Significant p at <0.05**

Figure (2) showed that; there is a highly significant statistical difference between pre & post health literacy regarding to medication adherence

Table (4): Relation between medication adherence scale, knowledge score & Socio-demographic data for the studied patients after health literacy

Item	Medication adherence		Knowledge Score		P 1	P2
	Medium	High	Fair	Good		
Age in years:						
18--35.	8	13	1	18	0.0001***	0.002*
36-50.	34	0	12	17		
51-65	34	1	18	35		
Gender:						
• Male.	21	7	7	21	.091 ns	.239ns
• Female.	55	7	24	38		
Address						
• Arbun	9	12	4	17	.0001***	.118ns
• Rural	67	2	27	42		
Marital status:						
• Single	7	7	1	13	.001**	.029ns
• Married	69	7	30	46		
• Divorced	-	-	-	-		
• Widow	-	-	-	-		
Level of education:						
• Illiterate	48	1	24	25	.0001***	.0001***
• Reade & Write	7	0	1	6		
• Secondary	19	1	6	14		
• University	2	12	0	14		
Occupation :						
• Office work	1	6	0	7	.0001***	.040*
• Farmer	20	1	7	14		
• House wife	55	7	24	24		

Chi-Square test ns= non-significant *Significant at p. value<0.05

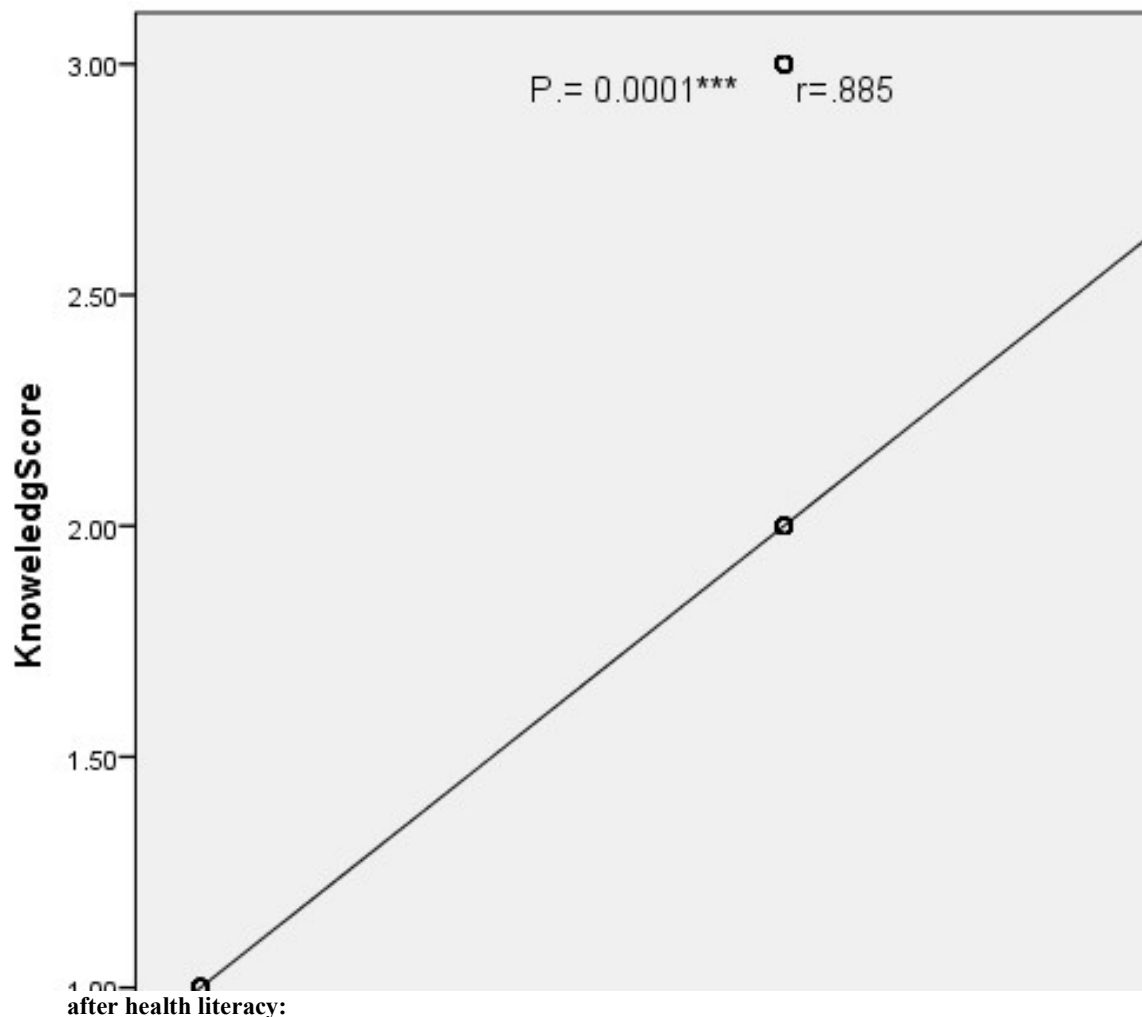
P1 = P value between Socio demographic & Medication adherence scores

P2 =P value between Socio demographic & patients knowledge score

This table depicts the relation between socio-demographic and medication adherence; there is a significant

difference in all parameters except gender, however regarding to knowledge there is significant difference in age, level of education and occupation only.

Figure (3): Correlation between knowledge score and medication adherence for the studied patients



Data presented in figure (3) reveals that there was a highly significant statistical difference between knowledge scores and medication adherence after health literacy.

Discussion:

The population-wide viability of hypertension treatment is still inadequately. The basic factor contributing to an unsatisfactory response to pharmaceutical treatment is destitute medication adherence. The management and control of hypertension are conceivable with a combination of medication and strict lifestyle changes. Published studies indicate that ~60% of patients treated for hypertension stopped treatment within 6 months (Marcum et al., 2013).

Our aim in this study was to examine the effect of: health literacy on self-monitoring, patient knowledge and medication adherence for blood pressure regulation.

According to socio-demographic data: the present study resulted that: as regard sex the highest percentages was females. Regarding age; it was found that less than half of the patients their age were 51 -65 years, with mean±SD of 45.21±12.52, and more than half of them were illiterate. This is compatible with Pirasath et al., (2017) who found that most of the patients were females, and their age ranged from 60 to 70 years old.

In congruence with a study done by Fernanda et al., (2019) who concluded that low levels of health literacy may be associated with fewer years of schooling. Also Hae-Ra et al., (2018) noted in his study that most

of participants were primarily middle-aged with mean 38.9- 62.2, female, and had a low level of formal education.

In our study the highest percentage was married. More than half of them were house wife. This is compatible with **Bentley et al., (2017)** who reported that most of the patients were married, and less than half of them were retired. Furthermore, **Fateme et al., (2018)** confirmed that the mean (SD) of participants' age was 60.58 ± 11.14 years,

As regard to nutritional status, our results found that; more than half of them were obese. Most of them don't smoke and with high level of cholesterol. This was agreed with **Bekele et al., (2017)** who resulted that most of the patients overweight, however the highest percentage of them smokers,

We found that most of the participant patients receiving 1drug for hypertension, more than half of them complaining from HTN from 7-9 years. Most of the patients not complaining from diabetes mellitus or coronary artery disease, also the majority not complaining from chronic kidney disease or other medical problems. This is in the same with **Gülay and Fevziye, (2017)** who suggested that less than half of the participants had one chronic disease at least and few of them had previously been diagnosed with hypertension.

However this point not in the line with **Saleem et al., (2011)** who reported in his study "Association between Knowledge and Drug Adherence in Patients with Hypertension in Quetta, Pakistan" that the mean duration of hypertension for the studied patients was 3.01 ± 0.94 years

The current study revealed that all of studied patients didn't perform self- monitoring of blood pressure before. The researchers think this can be due to the low level of education at most of the studied patients, in addition to the lack of information available to them and the low culture of society towards the disease.

Also majority of the studied patients with high cholesterol level, this is compatible with **Masaaki et al., (2018)** who found in his study "Lifestyle Habits Adjustment for Hypertension and Discontinuation of Antihypertensive Agents" that among his study subjects which were 50 patients with hypertension male/female : 25/25 ,have hyperlipidemia was 32% versus 52%, respectively, and Consultations in median were 4.0 versus 4.0 times,

As regard to self -monitoring blood pressure (SMBP):

The result of this study declares that there was a highly significant statistical difference between mean systolic and diastolic blood pressure before health literacy and after every 2 weeks. This was consistent with **Richard et al., (2018)** who found that Self-monitoring, with or without telemonitoring, when utilized by common specialists to titrate antihypertensive medication in individuals with inadequate controlled blood pressure, leads to essentially lower blood pressure than titration guided by clinic readings. With most specialists and many patients utilizing self-monitoring, it could become the cornerstone of hypertension management in essential care.

Also in the same line with **Jacqueline et al., (2016)** who mentioned that; a health literacy sensitive multi-level intervention may similarly lower (systolic blood pressure) SBP in patients with low and higher health literacy. Practical health literacy suitable strategies and methods can be implemented in essential care settings using a quality enhancement approach. **Katherine et al., (2017)** found self-monitoring alone is not related with lower blood pressure or better control, but in conjunction with co-interventions (including systematic medication titration by doctors, pharmacists, or patients; education; or lifestyle counseling) leads to clinically significant BP reduction, which continues for at least 12 months. The implementation of self-monitoring in hypertension ought to be accompanied by such co-interventions.

Chun et al., (2016) demonstrated that after intervention, advancement with statistical significance were watched in patients' health literacy, nutrition behaviors, exercise, capacity and recurrence of blood pressure monitoring, controlling salt intake and taking anti-hypertension medication.

As regard to study patients' Knowledge scores:

The exciting study showed there is significant statistical difference between pre &post health literacy regarding to patients knowledge. This was matched with the study of **Shaoying et al., (2018)** who concluded that the person with low health literacy is likely to have inadequate knowledge of hypertension. However, there is poor evidence to prescribe that health literacy is associated with outcomes of hypertension independently. **Xiaorou et al., (2018)** found that in his study "A4367 Effect of education on health literacy of hypertensive patients", the health literacy score are significantly elevated after intervention.

Patients' knowledge on hypertension is a significant independent determinant of a greet adherence. Other independent determinants include non-pharmaceutical treatment and standard blood pressure measurements. (**Beata et al., 2016**). Patients with satisfactory health literacy were more effective in control and treatment of their disease (**Jamileh et al., 2016**)

Regarding to patients' adherence to medication:

In this study, results revealed that there is a highly significant statistical difference between pre &post health literacy regarding to medication adherence. This was in the line with the results by the study of **Vichi et al.,**

(2015) who documented significant post-intervention improvements in medication adherence among hypertensive patients.

However the results of the study of **Nam et al., (2018)** suggested that: To successfully advance health related quality of life in this population, medication adherence and health literacy of patients ought to be considered when developing health interventions, including subjective health and exercise.

Arijit et al., (2016) concluded that the preponderance of evidence suggests a positive impact of counseling on adherence, clinical and humanistic outcomes.

As regarding to relation between socio-demographic and medication adherence there is a significant difference in all parameters except gender, however regarding to knowledge there is significant difference in age, level of education and occupation only. This is consistent with results of **Roya et al., (2018)** who reported that age of patients, duration of disease and physical activity were related variables with health literacy in studied patients and only these variables were appropriate for expectation of health literacy level of patients. Also, **Shi, et al., (2017)** and **Wang, et al., (2017)** concluded that instructions and employment had a critical relationship with health literacy.

Regarding to correlation between knowledge score and medication adherence for studied patients after health literacy: in this study the results revealed that a highly statistical difference between knowledge scores and medication adherence after health literacy. Our findings are constant with **Hawa et al., (2018)** who resulted in his study that patients with low hypertension knowledge were less likely to adhere to change lifestyle and medication compare with patients who had high knowledge.

Also **Tibebu et al .,(2017)** in his study which is conducted in Ethiopia which examined "factors associated with adherence to recommended lifestyle modifications practices among 404 patients managed for hypertension" that knowledge about hypertension was an independent predictor of adherence with heart healthy lifestyle practice and medication.

Conclusion:

Health literacy had significant impacts on the studied patients which driven to advancement of hypertension management in these patients. Too, increase in their knowledge and adherence to their medications.

Recommendations:

- Activating the role of community-based physician/nurses service intervention including patient education and patient-centered objective support.
- Replication of the study utilizing a larger probability sample acquired from distinctive geographical regions.

Declaration of conflicting interests:

The authors declare that there is no conflict of interest.

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