RESEARCH ARTICLE

ASSESSMENT OF PHARMACIST'S EDUCATION TO REDUCE METFORMIN ADVERSE REACTION

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ABSTRACT

Introduction: Gastrointestinal (GI) adverse reactions are the main complaint of patients receiving metform in and caused approximately 5% of patients to the extent that discontinue their medication or compliance impaired. **Objective:** The study aimed was to reduce GI disturbance in patients receiving met form in with a primary endpoint to improve patient's outcome by reducing HbA1c and patient satisfaction. **Methodology:** This study was conducted on 203 patients receiving met form in and can't tolerate GI disturbance. The intervention is to conduct patient's education and counseling using pharmacist's skills and knowledge. Patient's improvement outcome was measured using HbA1c and visual analog scale (VAS) for pain. Student t-test was used to compare HbA1c before and after education. **Results:** The most common GI symptoms reported were flatulence, abdominal pain, loss of appetite, nausea, heartburn, vomiting and others. Pharmacist intervention went with many methods to overcome GI adverse effects. This study showed a significant HbA1c reduction after patient's education and counseling. The impact of the education was also shown in VAS with a linear regression of the pain and patients satisfaction. **Conclusion:** Pharmacist intervention including medication review, patient counseling, telephone and face-to-face follow-up were associated with lower GI disturbance, improved patients' quality of life, higher patients' adherence and therefore decreased HbA1c. The main implication of this study that "patient education" reduced GI side effect, increase patient compliance, and improve patient's quality of life.

INTRODUCTION

Metformin dimethylbiguanide is an oral glucose-lowering medication, considered as the drug of choice as a first line of treatment either as monotherapy or in combination with other drugs for treatment of type 2 diabetes mellitus (DM) due to its efficacy, low cost, low risk of hypoglycemia and low risk for inducing lactic acidosis as a side effect. It is also used as a part of the treatment of polycystic ovary syndrome(PCOS). It works along with diet and exercise to decrease blood sugar. Restricted proof proposes metformin may prevent the cardiovascular diseases and complications of diabetes (Maruthur, 2016; HanyLashen, 2010; Yi-Wei Wang, 2017). The high prevalence of the disease demands full and effective disease management. According to the health information survey in 2013 at the Kingdom of Saudi Arabia for patients with diabetes, it is estimated that 1.851.080 persons over the age of 15 years were diabetic and will increase to more than 4.300000 in 2030. Estimate utilization of metformin in type 2 diabetes annual costs of 300 million (SAR) and this number will be increased to 750 million (SAR) in 2030 (Team, 2018). Gastrointestinal (GI) adverse reactions were the main complaint of patients receiving metformin tablet. The most widely recognized GI side effects associated with metformin

were diarrhea, nausea, and vomiting (incidence rate 20%–30%). Two pathophysiological mechanisms had been proposed to explain the GI side effects, including metformin-induced release of serotonin in the intestinal mucosa and reduced absorption of bile salts. Strategies to manage this common clinical problem were fragmented and based on little proof (Cubeddu, 2000; Carter *et al*., 2006). Decreasing intestinal absorption of glucose by metformin could be another pharmacological mechanism of inducing GI disturbance. The GI symptoms occurred with variable degrees in patients and in most cases, it resolved spontaneously. It is recommended that people take *metformin* with meals as this both increases its absorption in the *stomach* and reduces side effects. Moreover, gradual administration of metformin can reduce the severity of side effects and titrating the dose will lessen the GI disturbance and allow tolerance to improve (Bonnet, 2017). GI disturbance are also associated with poor compliance and cause approximately 5% of patients to discontinue or impair their adherence tomedications[8,9,10].Poor medication(s) adherence led to hyperglycemia and therefore a high level of HbA1c. Consistently high blood glucose levels can lead to diabetic complications that involve *cardiovascular disease, nerve damage (neuropathy)*, k*idney*damage (nephropathy), eye damage (retinopathy) and foot damage (Papatheodorou, 2016). On the other hand, UK Prospective Diabetes Study UKPDS

proof that controlling blood glucose in type 2 diabetes reduced the risk of microvascular complications (King, 1999). There are many approaches to improve glycemic control and achieve HbA1c target value and decreases the probability of having diabetic complications that include, effective screening, monitoring, counseling and consistent follow up of the patients (Venkatesan *et al.*, 2012). Pharmacist role in patient education giving appropriate training as pharmacist experience that changes strategies and improve patient health outcomes. Ambulatory care pharmacists are able to provide self-management support to their patients (Dent, 2009). Also enhancing medication management during transitions of care and diminishing readmission rates. Pharmacists have the ability to educate patients about the importance of continued therapy and adherence; also to dissipate any uncertainties that patients may have regarding their medications. Moreover, pharmacists improve patients' therapeutic outcomes throughout patient's medication discharge counseling. Pharmacists counseling and follow-up after discharge have multiple effects on the emergency department visits, hospital readmission, and costs (Sanii *et al.*, 2016). Additionally, "the pharmacist" is the last health wellbeing expert to encounter the patients, and should play a crucial role in patient education on drug usage and consequently decrease of medication errors[16]. The extent of pharmacist's involvement in the education for patients on drug use was much clearer in their instructions than other healthcare professionals (Alkhawajah, 1992). This project depends on pharmacist's skills and knowledge by performing effective and comprehensive patient's education and counseling.

The impact of this study is to reduce GI disturbance after metformin intake; and also to improve patient's quality of life and improve disease outcomes, performing patient's education and most importantly is to show that counseling will achieve the seoutcomes by using the following instructions:

- Taking medication after the meal in a timely manner.
- Gradually escalate the dose of Metformin.
- Doing some exercises.
- Changing lifestyle.
- Crush the tablet as a powder form.
- Changing eating habits and food style such as increasing good fat intake, decreasing carbohydrate, and reducing heavy meals.

Objective and Aim: Elaboration on patients who cannot tolerate metformin in a routine dose is a matter of concern specifically if it is associated with the gastrointestinal adverse reaction(s). The hypothesis of this study would consider that pharmacist's education wouldreduce GI adverse reaction and improve patient's outcomes. This study aimed to reduce gastrointestinal (GI) disturbance in the patient receiving metformin with a primary endpoint is improving patient outcome by reducing HbA1c.

METHODOLOGY

Pharmacist responsibilities included a range of care for patientsstarting from dispensing medications, educate patients on the use of medications, monitoring patient health and progress to optimize their response to medication therapies. Pharmacists also must ensure drug purity and strength and make sure that drugs do not interact in a harmful way. This study wasa cross-sectional cohort to find out the ability of

pharmacist's education on metformin side effect with the primary endpoint was to improving patient outcome by reducing HbA1c. Study subjects could be identified as patients who cannot tolerate metformin in adequate amount by the followings:

- Patients rejected to continue taking metformin because of previous experience with metformin side effect.
- Pharmacy records showed that although it was the time to make a refill for all medications, yet patient(s) deniedor rejected to receive metformin tablets because s/he didn't take metformin.
- Personal communication, that patients identified themselves to pharmacists that they disliked metformin intake due the side effect.

Patients used to be consented to get their permission to conduct this study during the first visit. Then, patients asked to get laboratory works, visual analog scale(VAS) and asked some questions related to exercise, diet, and other activities related to diabetes mellitus. Visual analog scale(VAS) is a common tool for the self-measurement of pain and other side effects[18].

The intervention of pharmacist during six visits conveyed by two physical visits of the patients (visit 1 to visit 6). Then the patient have the choice to have more visits or got the data through a telephone call. Patients follow-up and the requested activities during each visit is shown as follow:

Activity / Visit number at	V1	V2	V3	V4	V5	V6
/ Week number	W0	W1	W2	W4	W8	W12
Patient consent form signature	√					
Laboratory work such as HbA1c *+ Blood glucose	√	√	√	√	√	√
Patients' adherence to metformin (intervention)	√	√	√	√	√	√
A questionnaire to assess the other meds, diet, exercise…	√					√
Visual analog scale to assess the severity of GI/SE	√	√	√	√	√	√

* HbA1c will be in first and last visits only

The main intervention was to conduct patient's education and counseling using pharmacist's skills and knowledge with the following instructions:

- Taking medication after the meal in a timely manner.
- Gradually escalate the dose of Metformin.
- Doing some exercises.
- Changing lifestyle
- Crush the tablet as a powder form.
- Changing eating habits and food style such as increasing fat, decreasing carbohydrate, and reducing heavy meals.

Inclusion andExclusion criteria: All patients receiving metformin and complaining of GI upset or other side effect were included in this study; whereas, pediatric, pregnant women, type1 DM and patients with GI disorder were excluded from this study.

Sample size and study site location: Sample size calculated according to Creative Research System with confident level 95%, confident interval 90% and estimated that type2 diabetes who were receiving metformin as 100,000 populations in KSA Riyadh. Selected site areas are King Abdullah bin Abdul-Aziz University Hospital, King Salman bin Abdul-Aziz Hospital, and Security Forces Hospital.

Statistical Consideration: The data was transferred from excel sheet to SPSS 25 to have descriptive analysis, frequency, and percentage of the variables. A demographic analysis of the current situation presented as a table, graph and chart. A student t-test will be applied to compare between HbA1c before and after the intervention as needed.

Ethical Consideration: An ethical certificate was obtained from Princess Norah bintAbdulrahman University (PNU) Health Science Research Center with IRB log number was 18-0118.

RESULTS

This study was applied on 203 patients who were receiving metformin and can't tolerate the gastrointestinal adverse effects. Metformin was indicated for 191 (94%) with diabetes DM and 12(6%) with polycystic ovary syndrome PCOS. Most of them were females 123 (61%) and 80 (39%) were males, with an average age of 44.6 years (± 10.8 SD). Treatment with metformin wasoften associated with gastrointestinal (GI) side effects. The findings in this study was shown in table 2, that most common GI symptoms reported from the patients were flatulence (34%), abdominal pain (34%), loss of appetite (24%), nausea (20%), heartburn (20%), vomiting (14%) and other symptoms like diarrhea and constipation by (35%). Gastrointestinal adverse reaction affect patient's adherence to their medications, it was found at visit one (baseline), that 142 (70%) of the patients were using metformin despite the undesirable side effect while 61(30%) of the patients were intentionally missed the dose because they couldn't tolerate the adverse reaction.

After pharmacist's intervention by performing patient's education and counseling using one or more of the instructions that have been mentioned previously, the adherence was improved in all patients dramatically. A significant improvement for HbA1c average after the interventions, showedfrom 8.2 % (± 1.3 SD) at the baseline (first visit) to 7.7% (± 1.1 SD) at the last visit (with $p < 0.05$). The impact and influence of pharmacist's intervention through education was also shown in visual analog scale (VAS). The results showed a linear regression for the GI pain and patients satisfaction during the six visits. Patients showed positive satisfactions for reducing their complaints after metformin intake. About 134 (66%) of the patients were expressed their feeling that they had no pain neither any adverse drug reaction at the last visit comparing to all had pain on the first visit (baseline). Figure 1 showed a linear relationship between pharmacist's education and metformin intake with less side effect. At baseline, only 76 (37%) patients were following specific diet system, and 54 (27%) patients were performing exercises. Resultsat visit six (last visit) showed that 98(48%) followed healthy diet and 71(35%) did exerciseafter pharmacist's intervention.Pharmacist's intervention went with several methods on the way of patient's education to overcome the metformin (GI) adverse effects, some patients were used one or more method/s to overcome GI disturbance. Results also showed that majority of patients (67%) had metformin intake after healthy meals, (35%) of the patients switched from immediate-release metformin to metformin-XR, (14%) of the patients disappeared with time, (12%) of the patients did some exercises, (7%) of the patients decreased the dose of metformin, (3%) of the patients crushed the tablets and the others (8%) showed that none of the methods helped them, as

illustrated infigure 2. However, it was found that the best time for metformin intake was to be with meal to reduce GI adverse effect, in this study it was found that 109 (54%) of patients taking before meals or on empty stomach.

Table 1. Metformin Gastrointestinal (GI) side effects

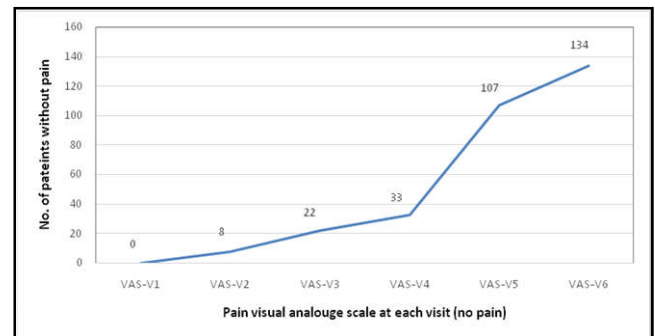| GI symptoms	Number of patients	Percentage
Nausea	41	20%
Abdominal Pain	69	34%
Vomiting	28	14%
Flatulence	70	34%
Loss of Appetite	49	24%
Heartburn	40	20%
Others	72	35%

Figure 1. Visual Analogue Scale (VAS) shows a linear regression of the pain and adverse reaction and the satisfaction of patients receiving metformin after pharmacist education throughout six visits
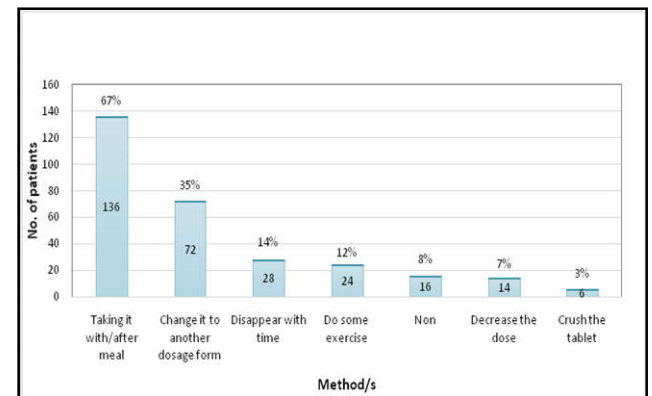

Figure 2. Different education methods on how to overcome the adverse drug reaction of metformin showing the frequency and percentage of each educational method.

DISCUSSION

The study was designed to measure the impact of the education and counseling on reducing gastrointestinal (GI) disturbance in patients receiving metformin. This study applied on 203 patients, 191 patients with DM and 12 patients with PCOS and all of them were complaining of GI disturbance. The most common GI side effect has been reported abdominal pain, bloating, and retching follow diarrhea, heartburn, and nausea. Due to the fact that metformin transportation via organic cation transporterthat will increase metformin concentration in the intestine and will result in severe side effect. The most common GI side effect has been reported abdominal pain, bloating, and retching follow diarrhea, heartburn, and nauseaas indicated with percentage in table 1. Theseside effects were associated in 20-30% of patients with metformin intake, in which, will affect the treatment negatively due to intolerance and discontinuation of the drug in patients with diabetes DM (Fatima, 2018). The main responsibilities of the pharmacists

were to review and find out the most suitable medication for their patients. One of the most additional responsibilities was to assure that patients had received their medication in the proper way considering the pharmacodynamics and pharmacokinetics of the drug. This study was emphasizing on the impact of the pharmacists and their input on metformin intake and patients' adherence. Education and counseling played a key role in encouraging patients to adhere to their medications through educating patients; why they're taking a certain medication, how to take it, tips to alleviate adverse reaction, and how it's going to improve their health. One of the most important tips on metformin was that metformin should always be taken with meal. This is a crucial detail that's easily miscommunicated or miss-prescribed when patients didn't get the instructions by the pharmacist and could end up with some patients feel pain and lose their adherence to metformin. It was found that 30% patients have poor adherence with metformin use, the main reason for that was GI intolerability, and the consequences of poor adherence could severely impact treatment outcomes and increase the risk of diabetic complications. Education and counseling have a positive impact on patient's adherence and increasing quality of life (Butt, 2016; Daniel, 2017). Patients none-adherence to metformin could increase patient's complication (Manel Pladevall, 2004), while with better adherence will be associated with decrease HbA1cand therefore will reduce complication (Clifford, 2005); this was exactly what was shown in the United Kingdom Prospective Diabetes Study that reducing HbA1c will decrease diabetes-related complications.

Pharmacist's interventions showed important factor to improve glycemic control in diabetic patients. Pharmacist's interventions could be interpreted by diabetes education and counseling on drug, disease, diet, exercise, lifestyle modification, self-management, assessment and adjustment of anti-diabetic medications, identifying and solving drug-related problems, co-operation with physician and other diabetes health care team, providing materials that reinforce patients to achieve a target goal, and providing additional information on smoking cessation (Blom, 2018). These interventions aimed to patient's adherence, then to improve glycemic control and reducing complications. This study proved that HbA1c levels were significantly reduced with pharmacist's interventions compared with usual care. The mean differences in the change of Hba1c were 0.5% after intervention (Collins, 2011). A visual analogue scale (VAS) isa psychometric measuring instrument used in this study to measure patient's satisfaction. The VAS score ranging from 0-10 qualitative ratio data to measure the reduction of pain intensity and adverse drug reaction or sometimes patient satisfaction (Klimek, 2017). It was frequently used in epidemiologic and clinical research to quantify the intensity or frequency of numerous symptoms. Patients were asked to indicate the intensity of the GI disturbance by marking a horizontal line that was labeled from 0 to 10 where 0 indicated "no pain", 1-3 "mild pain", 4-6" moderate pain," 7-9 "moderate to severe pain" and 10 "severe pain". The impact and influence of pharmacist intervention (figure 1) showed a linear regression of the GI pain and patients satisfaction during the six visits. Pain reduction had been expressed through the VAS scale. The scale showed a linear relationship, which is correlated with pain intensity measured (Williams et al., 2010); similarly this study showed a linear correlation of patient's satisfaction along the period of patient's visits. Pharmacists should not limit themselves on medications and how to utilize it but they should have enough

information about exercise, nutrition lifestyle modificationand other comorbidity diseases. Patients with diabetes were encouraged by the to maintain with healthy diet and exercise regimen. Guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) stressed the importance of diet and exercise in the treatment of all stages of type 2 diabetes (García-Pérez et al., 2013; Kelley, 2017). It had also been found in some research that beside diet control and medical treatment, long-term regular exercise was found to be helpful in glycemic control, body composition and cardiovascular fitness among patients with T2DM, which played a role in weight loss and, consequently, improved well-being among these patients (Mohammad Asif, 2014; Najafipour, 2017). Patient's education improved tolerance to metformin, which was recommended to all patients to take metformin with or after meals. Typically the largest meal of the day since will reduce GI side effects and increase absorption of metformin[7]. This was exactly applied in this study when it was found that the majority of patients (67%) had metformin intake with or after healthy meals. It was also showed improving in metformin intake by switching of metformin using extended release (XR) with 35% of the patients have been improved absorption and reduced GI upset (Lawrence Blonde, 2004). As much as the patient increase intake of fiber and non-starchy vegetables in diet, and eat yogurt daily will reduce GI side effects (http://www.rxeconsult.com /healthcare-articles/ How-To-Prevent- And-Manage-Metformin-Side-Effects-974/2.). It had been shown also that (12%) of patients had continued their exercise and changed their lifestyle after education. Pharmacistused to advisepatients to start with a smaller dose then gradually increased to the original dose; it was also found that (7%) of participated patients had been overcome side effects through this method.

Conclusion

In this study, the main aim was to reduce gastrointestinal (GI) disturbance in the patient receiving metformin. It was found that pharmacist's intervention including; medication review, patient counseling, telephone and face to face follow-up were associated with lower gastrointestinal (GI) disturbance, improved patients' quality of life, higher patients' adherence and therefore decreased HbA1c. Greater efforts are needed to set policies and guidelines in place for pharmacists to be entirely involved in patient's care to improve the medication therapy outcomes for patients with diabetes mellitus.

Acknowledgement

Conflict of Interest

Authors admit that there is no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations.

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