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A Cohort Study of Glycemic Control in Type 2 Diabetes Patients Receiving Metformin and Metformin - based Antidiabetic Medications in A Vietnamese General Hospital

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ABSTRACT

To assess diabetes management in a Vietnamese general hospital, a 1-year cohort study was conducted. Fasting plasma glucose (FPG) level can be controlled in 72% of group 1 (patients received monotherapy "metformin (MET)"), 21% of group 2 (patients received monotherapy followed by dual therapy "MET plus second antidiabetic medications (ADMs)") and 7% of group 3 (patients received monotherapy at beginning and step-up to dual therapy to triple therapy "MET plus two ADMs"). MET was able to reduce FPG by 2.2 ± 2.1 mmol/L ($p<0.01$) in group 1. Addition of second and third ADM was able to reduce FPG level by 4.1 ± 3.4 mmol/L ($p<0.01$) and 4.7 ± 4.2 mmol/L ($p<0.01$) in group 2 and 3, respectively. It is concluded that most of the patients are well-controlled with MET monotherapy.

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Introduction

Diabetes mellitus (DM) has a tendency to spread out all over the world. The prevalence is increased in low and middle income countries (NCD Risk Factor Collaboration [NCD-RisC], 2016). It becomes the top of ten diseases leading to death (World Health Organization [WHO], 2014). The diabetes management plays an important role in reducing mortality and economic burden (WHO, 2016). In Vietnam, the percentage of patient with diabetes increases to 211% compared with the previous decade. The national forecast demonstrates that diabetic population will expand double in every 15 years. Controlling and preventing diabetes is the national priority (Vinh N, 2012). At this time, research reveals that community knowledge about disease, treatment, prevention is low. Around 21.9% of people have an average to high understanding level about DM (Vinh N, 2012). Deficiency of awareness accompanied by the poor health care system, all of which can cause dramatic effects on medical care in patients (Garfield et al., 2003). Numerous strategies are adapted which can be used to prevent and control diseases including physical exercise, nutrition therapy, medication, education, etc (American Diabetes Association [ADA], 2016a). Gold standard of efficacy evidence is randomized controlled trials (RCT), however, they are conducted in perfect environment (Well, 1999). Concordance with development of clinical trials, routine practice has faced challenges over patients' treatment process. Given that diabetic patients have to deal with so many influence factors and that sometimes economic issue, educational level, environment factors, health care system, social support are required involving to hyperglycemia management (TRIAD study group [TRIAD], 2010). Apart from RCT as the core efficacy evidences, real world studies are also important proof (Narayan et al., 2000). Nowadays, metformin is usually recommended as first line treatment in ADA guideline (ADA, 2016b). In developing countries like Vietnam, it could be seen that health care process helps overcome challenges to diabetes management in daily practice. This study is conducted in Lam Dong general hospital in Vietnam, and aimed to observe diabetes care management in newly diagnosed patients who started with metformin and were followed-up for a year.

Objective of the study

To investigate the reduction of fasting plasma glucose (FPG) level in type 2 diabetes patients who were treated with metformin and continued with metformin or step-up to add 1-3 antidiabetic medications on metformin.

Materials and Methods

Data source:

Research data was extracted from the electronic system in Lam Dong general hospital which is the largest hospital in the highland area in Vietnam. Complete electronic medical records were collected from outpatients of internal department with more than 44,000 visits during the period from May 2015 to April 2016. Data include physicians' prescriptions, laboratory test, diagnoses, hospital admission, physical examinations. All chronic patients had national health care insurance.

Methods:

Adult diabetic patients who visited outpatient department during May 2015 and April 2016 were eligible for the study. They were included in the study if they were newly diagnosed with type 2 diabetes mellitus, firstly treated

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with metformin, continued to take antidiabetic medications (ADMs) for at least 3 months, and successively visited hospital until the end of observation period. Exclusion criteria were missing of data i.e., having one data of laboratory test, non-continuous visit to the hospital, using combination therapy or insulin at the beginning of treatment.

According to Vietnamese guideline for treatment of diabetes, monotherapy with metformin (MET) is first line medication to be used. If FPG is uncontrollable, dual, triple and quadruple therapy by adding one ADM at a time is recommended. In this study, patients were divided into 4 groups:

- Group 1 - Patients used metformin (MET) during one year (monotherapy group).
- Group 2 - Patients used MET at the beginning and second ADM was added when FPG was not controllable (monotherapy step-up to dual therapy group).
- Group 3- Patients used MET at the beginning, then went to dual therapy but FPG was still uncontrollable so that the third ADM was added (monotherapy step-up to dual therapy to triple therapy group)
- Group 4 - Patients used MET at the beginning then went to dual therapy and triple therapy but FPG was still uncontrollable so that the fourth ADM was added (monotherapy step-up to dual therapy to triple therapy to quadruple therapy)

Statistical Analyses

Descriptive data were performed for all variables. Difference was statistically analyzed by using t-test if it is normal distribution, otherwise, Wilcoxon-Mann Whitney and $p<0.05$ was set for statistical significance. In addition, correlation was performed to evaluate the relationship between baseline characteristics and reduction of FPG level.

Results:

During May 2015 and April 2016, there were 578 diabetic patients who visited at outpatient department. Of these, 178 patients were newly diagnosed. However, only 97 patients were fulfilled the study criteria. Among these, 72% was in group 1, 21% was in group 2, 7% was in group 3 and none was in group 4. Baseline characteristics of population were presented in Table 1. Generally, patients were 63.5 ± 10.7 years (mean ± SD). Average age declined dramatically from group 1, 2, 3 where mono, dual and triple therapy was given (65.9 ± 10.5; 59 ± 8.5; 54 ± 8.5 years, respectively). It was noteworthy that the percentage of male is higher than that of female in all groups. Among them, there were no marked differences between weight and body mass index (BMI). In terms of comorbidity disease, hypertension and dyslipidemia were found mostly. It was also found that the highest prevalence was in the third group (85%). Baseline FGP level was highest in group 2 with 9.9 ± 2.1 mmol/L, following with group 3 with 9.1 ± 2.1 mmol/L and the lowest was group 1 with 8.7 ± 1.7 mmol/L.

Figure 1 demonstrated progression of FPG level, weight and duration of each treatment option during one year follow-up. Overall, adding second and third ADM to MET caused higher FPG reduction as the reduction of FPG level was 2.2 ± 2.17 mmol/L ($p<0.01$), 4.2 ± 3.3 mmol/L ($p<0.01$), 4.7 ± 3.5 mmol/L ($p<0.01$) in group 1, 2, 3, respectively. The decrease of body weight was noted in metformin monotherapy with 0.7 ± 1.2 kg. During dual therapy of group 2 and 3, weight increase and retention was recognized with 0.62 ± 2.31 kg, 0 ± 0.46 kg, respectively.

Age, baseline FPG level and duration of treatment have negative correlation with reduction of FPG level in all patients (n=97) during their monotherapy. Pearson values of age, FPG, duration of treatment were -0.263, -0.239, and -0.406, respectively (Table 2)

Table 1: Baseline characteristics of population

Baseline characteristic	Monotherapy	Dual therapy*	Triple therapy**	Total patients
Number and percentage of patient n (%)	70 (72)	20 (21)	7 (7)	97(100)
Male (%)	54	55	57	54
Female (%)	46	45	43	46
Age (years)	65.9 ± 10.5	59 ± 8.5	54 ± 8.5	63.5 ± 10.7
Baseline weight (kg)	66.6 ± 6.5	67.8 ± 4.5	68.7 ± 3.2	66.9 ± 4.5
Baseline BMI	26.3 ± 1.5	25.9 ± 1.6	26.3 ± 1.2	26.2 ± 1.5
Hypertension n (%)	50 (71)	15 (75)	6 (85)	71 (73)
Dyslipidemia n (%)	45 (64)	12 (60)	6 (85)	62 (64)
Cardiovascular disease n (%)	11 (15)	4 (20)	2 (14)	17 (18)
Chronic kidney disease n (%)	3(4)	0 (0)	1 (14)	4 (4)
Baseline FPG (mmol/L)	8.7 ± 1.7	9.9 ± 2.1	9.1 ± 2.1	9 ± 1.8

*Dual therapy = metformin with sulfonylurea or metformin with insulin

**Triple therapy = metformin with sulfonylurea and acarbose or metformin with sulfonylurea and insulin.

Figure 1: Changing of fasting plasma glucose (FPG) level and weight in each group within one year follow-up
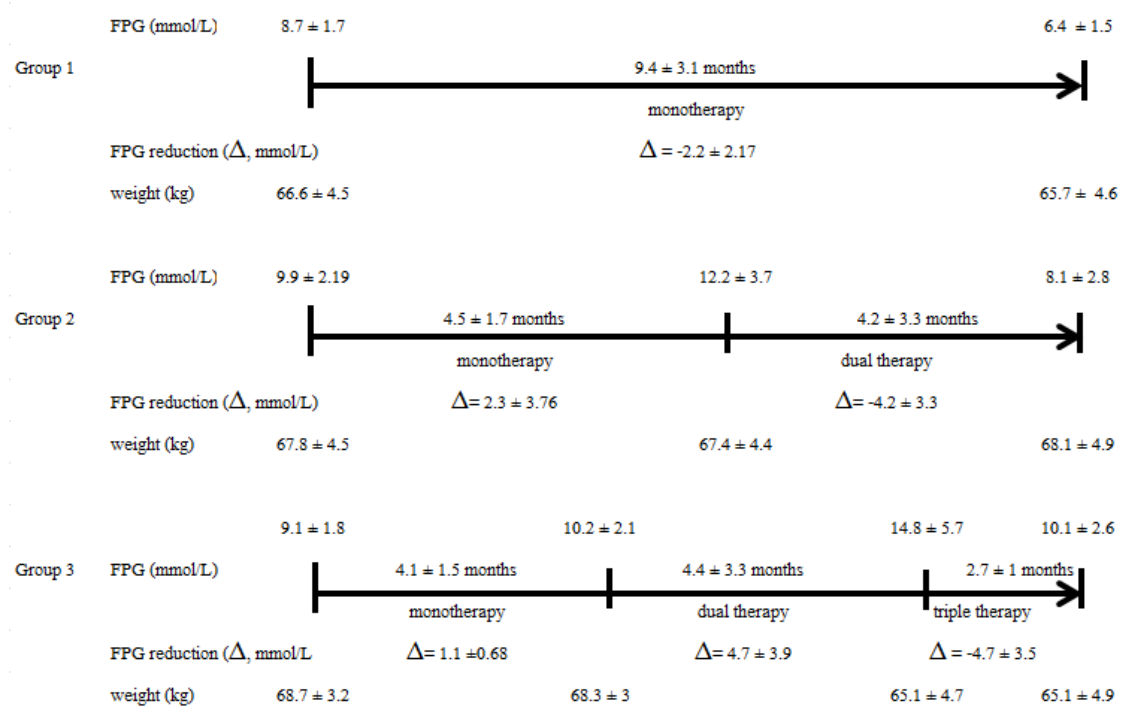
Table 2: Correlation of reduction of fasting plasma glucose (FPG) level with baseline factors in metformin treatment in all patients

Reduction of FPG level	Age	FPG baseline	Duration of MET monotherapy	Weight baseline monotherapy
Pearson correlation	-0.263	-0.239	-0.406	0.025
Sig. (2-tailed)	0.009	0.018	0.0001	0.804

Discussion

Even though retrospective study is secondary data, this study provides a picture of current diabetes care management in routine practice at Lam Dong general hospital. In routine practice, there are numerous factors that can affect management. It is difficult to identify exactly the role of each influence factors (Agency for healthcare research and quality [AHRQ], 2016). Our study showed negative correlation between age and changing FPG. It means that the value of FPG reduction level was higher in elderly patients compared to younger patients. This may be explained by the lifestyle of our Vietnamese people that the elderly patients are mostly retired and have plenty of free time meanwhile the younger people usually work in stressful environments, have heavy workload, live in sedentary life together with all-night parties. As changing lifestyle is the first priority strategy to control blood sugar (ADA, 2016b; Thai Q, 2014), and our elderly patients have more free time than the younger, therefore they can follow the doctor suggestion and have better FPG reduction level. It was found that the knowledge of glycemic profile, the ability to contribute basal and prandial glucose usually plays an important role in total mean blood sugar. In elderly, basal glucose has lower involvement than postprandial when compared with that of younger patients (Munshi et al., 2013). They usually consume less food than the younger, therefore prandial blood will be well-controlled. All of these factors can be linked to the better result in FPG reduction level in the elderly. In addition, these may be the explanation why the average age was lower in group 3 than group 2 and group 1.

Our result demonstrates that duration of treatment with MET has negative correlation with reduction of FPG level. This means the longer duration of treatment has tendency to reduce FPG. Maximum effects of metformin achieves around 6 months in randomized controlled study (Knowler et al., 2002). Group 2 and 3 has duration of monotherapy approximately 4 months, hence reduction of FPG level is less than group 1 who used monotherapy for 9.4 months.

Baseline FPG level also plays a crucial role which can forecast the achievement of goal of treatment (Cook et al., 2007). Each ADM has different efficacy to reduce FPG level and high baseline FPG level will cause the progress of beta cell failure (Scheen, 2003). This reveals difficulty in management and has negative correlation with reduction of FPG level. Whether using combination therapy is appropriate or not awaits further study.

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A retrospective study, conducted in 11 health centers in US, pointed out that intensive therapy with adding second drug occupy 9.3% among the new beginning treatment patients during one year follow-up (Raebel et al., 2014). Other article published in 2015 by Thomsen et al. indicated that 21.37% of patients in Germany received second oral agents within 3 years (Thomsen et al., 2015). In contrast, our study reveals higher percentages, nearly one-third of patients started combination therapy. Hyperglycemia management requires comprehensive treatment. Medication, diet, life-style modification, social support should be adapted to individual patients. In US and Germany, patient programs and heath care system are well established, and are better than that of Vietnam (WHO, 2016b). This may be the explanation why our result show higher percentage of patients compared to US and Germany.

While daily practice usually deals with many environmental factors, FPG level and body weight decline less than that seen in randomized controlled trial (RCT) (2.47 mmol/L and 0.6 - 1.9 kg within 24 weeks) in all metformin monotherapy subjects (AHRQ, 2016; Lawrence, 2004). To be value as changing therapy in hyperglycemic control, FPG level declines more in combination therapy. Our result is accordant with RCT. However, sulfonylurea and insulin can cause weight gain (Mitri, 2009) and in Vietnam only metformin, sulfonylurea, acarbose, insulin glargine, premixed insulin aspart, insulin aspart were available in essential drug list. Therefore the majority of additional ADM in our study were sulfonylurea and insulin, hence, body weight is retained in dual therapy or triple therapy groups.

Conclusions:

This study shows that metformin treatment for type 2 diabetes patients is still effective and suitable for our highland area. Most of patients are well-controlled with MET monotherapy.

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