BASAL INSULIN AS ADD-ON THERAPY TO ORAL GLUCOSE-LOWERING DRUGS IN INSULIN NAIVE PATIENTS WITH TYPE 2 DIABETES MELLITUS IN PRIMARY PUBLIC HEALTH CENTER

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ABSTRAK

*Kontrol glikemik yang efektif sangat penting untuk meminimalkan komplikasi jangka panjang dari diabetes mellitus (DM) tipe 2. Namun, tercatat banyak pasien menghabiskan waktu yang lama di atas kisaran glikemik yang optimal, terutama di layanan kesehatan primer. Sebagian besar dokter pada layanan kesehatan primer, yang bertanggung jawab merawat pasien tersebut, menunda memulai terapi insulin atas beberapa alasan. Tujuan penelitian ini adalah mengevaluasi efikasi dan keamanan insulin detemir yang ditambahkan pada terapi oral untuk individu naive-insulin dengan DM tipe 2. Penelitian dengan desain one group pre- and post-test study ini melibatkan pasien DM insulin-naive yang telah mendapatkan perawatan per oral (n = 64, HbA1c> 8,0%), diambil dari 10 puskesmas di seluruh Surabaya, Indonesia, menggunakan metode simple random sampling. Pasien diobati dengan insulin detemir selama 12 minggu dan dosis insulin dititrasi dengan target glukosa plasma puasa (FPG) <125 mg/dl. Hasil yang dievaluasi meliputi HbA1c, kadar glukosa puasa dan 2 jam post-prandial, risiko hipoglikemia dan berat badan. Setelah 12 minggu, HbA1c mengalami penurunan sebesar 2,53% (dari 11.38% menjadi 8.85%) dengan insulin detemir sekali sehari (p = 0,001). FPG menurun dari 201,75 mg/dl menjadi 152,47 mg/dl (p = 0,001) dan glukosa 2 jam post-prandial menurun dari 287,91 mg/dl menjadi 222,30 mg/dl (p = 0,001). Frekuensi kejadian hipoglikemia sebesar 6,4% (4 kejadian hipoglikemi) dan semua kasus ringan sehingga tidak perlu dirawat di rumah sakit. Hipoglikemia dapat diobati oleh pasien sendiri dengan asupan gula dan makanan, dan dosis insulin detemir disesuaikan. Selain kejadian hipoglikemik, tidak terdapat efek samping lainnya. Rata-rata BMI menurun dari 23.94 ± 4.22 kg/m2 menjadi 23.34 ± 5.60 kg/m2 pada akhir studi. Ini berarti terdapat penurunan berat badan sebelum dan sesudah tera pi insulin walaupun tidak signifikan secara statistik (p 0.37, 95% CI -0,74-1,95). Sebagai kesimpulan terapi insulin basal dengan insulin detemir sebagai terapi add-on pada penderita DM tipe 2 dengan kontrol glikemik yang jelek di Puskesmas terbukti secara signifikan memperbaiki kontrol glikemik kadar gula darah dengan resiko hipoglikemia yang rendah dan tanpa resiko penambahan berat badan.**(FMI 2013;49:128-133)***

Kata kunci: *insulin basal, terapi add-on, obat antidiabetes oral, glikemia, DM tipe 2, berat badan*

ABSTRACT

*Effective glycemic control is very important to minimize longterm complications of type 2 diabetes mellitus (DM). However, it is well documented that many patients spend prolonged periods above optimal glycaemic range, especially in primary public health centers. Most of primary care physicians, who are responsible to manage them, delay to iniate insulin therapy for some reasons. The aim of this study was to evaluate efficacy and safety of insulin detemir added to oral therapy in insulin-naive individuals with type 2 DM. This one group pre- and post-test study involved insulin-naive and previously oral-treated DM patients (n=64, HbA1c> 8.0%), drawn from 10 primary public health center centers all over Surabaya, Indonesia, using simple random sampling method. Patients were treated with insulin detemir for 12 weeks and insulin doses were titrated to target fasting plasma glucose (FPG) < 125 mg/dl. Outcomes evaluated included HbA1c, level of fasting and 2 hours post-prandial glucose, risk of hypoglycemia and body weight. After 12 weeks, HbA1c had decreased by 2.53% (from 11.38% to 8.85%) with detemir insulin once a day (p=0.001). FPG improved from 201.75 mg/dl to 152.47 mg/dl (p=0.001) and 2 hour post-prandial glucose improved from 287.91 mg/dl to 222.30 mg/dl (p=0.001). Frequency of hypoglycaemia events were 6.4% (4 hypoglycaemic events) and all cases were mild events so that they did not need to be admitted in the hospital. Hypoglycaemic events can be treated by the patients themselves with sugar and food intake, and then the dose of detemir insulin was adjusted. Besides hypoglyecemic events, no other side effects were recorded. Mean the pre insulin therapy BMI was 23.94 ± 4.22 kg/m2 to become 23.34 ± 5.60 kg/m 2 at the end of the study. There was a decrease in body weight before and after insulin detemir therapy, but it was not statistically significant (p 0.37, 95% CI -0.74-1.95). In conclusion, the addition of basal insulin to oral antidiabetic drugs in poorly controlled type 2 diabetes patients in primary public health center achieved clinically improvements in glycaemic control with low risks of hypoglycaemia and non-significant body weight increase.**(FMI 2013;49:128-133)***

Keywords: *basal insulin, add-on therapy, oral antidiabetics, glycaemia, type 2 DM, body weight*

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INTRODUCTION

Diabetes Mellitus (DM) is a progressive condition in which the function of beta pancreatic cells will continue to decline and increased blood sugar levels over time. Studies by the United Kingdom Prospective Diabetes (UKPDS) showed that the reduction in glycated hemoglobin (HbA1c) will also reduce the incidence of complications, both microvascular and neuropathic complications. Each 1% reduction in HbA1c alone can reduce the risk of myocardial infarction by 14%, also reduces the risk of microvascular complications by 37% and lowers the risk of death related to DM by 21% (United Kingdom Prospective Diabetes Study (UKPDS) Group 1999). Perkeni Consensus and other general guidelines set HbA1c target of< 7%. However, some studies show there are still a lot of patients with DM who have not achieved the desired therapeutic target (Perkeni 2011).

Report of Basic Health Research (*Riset Kesehatan Dasar/Riskesdas*) in 2007 by the Ministry of Health showed that the prevalence of DM in urban areas of Indonesia to the age above 15 years was 5.7%. DM is also the leading cause of death in the age group of 45-54 years, whereas in urban areas it ranks the second, while in rural areas it ranks the sixth (Ministry of Health Republic of Indonesia 2007). Diabcare research results in 2008 showed the majority of patients with type 2 DM in secondary and tertiary health service centers in Indonesia have poor glycemic control with a mean HbA1c of 8.1% (Soewondo et al 2010). It is apparently still far from the expected target of HbA1c, which is less than 7%.

This poor glycemic control adjustments indicate the need of more intensive therapy in patients with type 2 DM (Soewondo et al 2010). Facts obtained in the field indicate various problems that occur as a result of poor blood sugar control, among others, many patients are reluctant and afraid to use insulin even though their blood sugar remains uncontrolled with the use of oral anti-diabetics only, the reluctance of physicians to use insulin due to lack of knowledge, experience and confidence in insulin use (Rodgers 2004, Hirsch et al 2005, Peyrot et al 2010). In fact, the more the blood sugar uncontrolled, the more the complications arise, and ultimately will make the cost of treatment of DM and its complications higher. This was the reason why this study was conducted, that was to observe the administration of insulin detemir in patients with type 2 DM who had used oral anti-diabetic. As we know, basal insulin, such as insulin detemir, which is only given once a day, is relatively simple and easily implemented by general practitioners at primary public health centers (*Pusat Kesehatan Masyarakat/Puskesmas*).

MATERIALS AND METHODS

This study was part of research conducted at 10 primary public health centers in Surabaya between October 2011 to June 2012. This study was an observational study. Data were collected from patients before and after basal insulin therapy. Basal insulin therapy using insulin detemir was given for 12 weeks. Insulin therapy performed by general practitioners at each primary public health center. The general practitioner has previously received training on insulin therapy. The training was conducted in the form of a workshop held three times face to face. It included regular meetings with research assistants every 2 weeks to monitor insulin therapy run by those general practitioners. The insulin therapy training materials included the use of insulin therapy, the technique of insulin use, insulin use side effects, such as hypo-glycemia and handling, as well as independent blood sugar test.

Inclusion criteria were patients with type 2 DM who had never received insulin treatment, still uncontrolled, those with HbA1c level of more than 8%, had received combination therapy of sulfonylureas and metformin for at least 12 weeks, and were willing to follow the study by signing the informed consent. Exclusion criteria included subjects who had insurance that requires a referral to hospital, hypersensitive to insulin detemir, basal-bolus insulin therapy, which used a combination on basal insulin and prandial insulin, and pregnant women, lactating or planning to become pregnant within the next 6 months period.

In this study, we collected patients' data, including demographic data, body weight, duration of DM, suffered complications and type of drugs given. Patients also underwent fasting blood glucose (FBG), 2 hours post prandial glucose (2hPPG) and HbA1c before and after the study. Patients filled out questionnaires about quality of life before and after therapy. SMBG examination was conducted in order to adjust the insulin dose and avoid the risk of hypoglycemia. SMBG monitoring was done on waking in the morning, after breakfast, before and after lunch and dinner. Monitoring was conducted once every three days. This research had been granted permission from the ethics committee of the Faculty of Medicine, Airlangga University, No. 049/EC/IEC/FKUA/2011 dated November 2, 2011.

This study was a prospective study in which the data were documented in Case Record Forms (CRF) prepared for each patient. Data were obtained through interviews and laboratory tests and other data contained in the medical record. Blood sample for HbA1c examination was obtained from venous blood with EDTA 3 ml for all subjects recruited and analyzed using

High Performance Liquid Chromatography (HPLC). Examination of fasting blood glucose and 2-hour post-prandial was done at the primary public health center by using a glucometer stick. For patients who had received insulin detemir therapy, SMBG records were taken by PHC doctors, and each week they met with the research assistants to report on SMBG recording and insulin dose adjustments that had been and would be done. In the second month, the monitoring was scheduled every two weeks.

The study was conducted at 10 primary public health centers in Surabaya, the Primary public health centers Pakis, Manukan Kulon, Asem Rowo, Tambak Rejo, Ketabang, Mulyorejo, Pacar Keling, Wonokusumo, Takal and Sawahan. The centers were selected based on geographical distribution and had a high prevalence of DM. The management of DM patients is held by medical doctors in those centers. Recruitment in 99 patients was conducted between the months of December 2011 - February 2012.

Data on subject demographic characteristics included age, body mass index, blood pressure, and the duration the subjects suffering from Diabetes Mellitus. Biomarkers indicators included the levels of HbA1c, FBG, and 2hPPG, which were analyzed descriptively by calculating the mean and standard deviation, in addition to calculating the subjects' proportion, including sex, history of anti-diabetics use, side effects of insulin use, as well as its complications. To calculate the difference in body mass index, mean HbA1c levels, FBG level and 2hPPG before and after insulin therapy, paired T-test was performed by first performing a test for data distribution normality to both data groups using Kolmogorov-Smirnoff test.

RESULTS

The total number of patients who participated in this study was 64 patients with characteristics as shown in Table 1. In this study the number of female patients was more than male patients, amounting to 82.8%. The average age of the patients was 53.6 ± 9.87 years. The age of the youngest patient was 33 years old and the oldest 80 years. Body mass index varied from 16.67 - 34.60kg/m2 with an average of 23.94 ± 4.22kg/m2. The average duration of DM was 7.06 ± 4.45 years, with the longest duration 21 years.

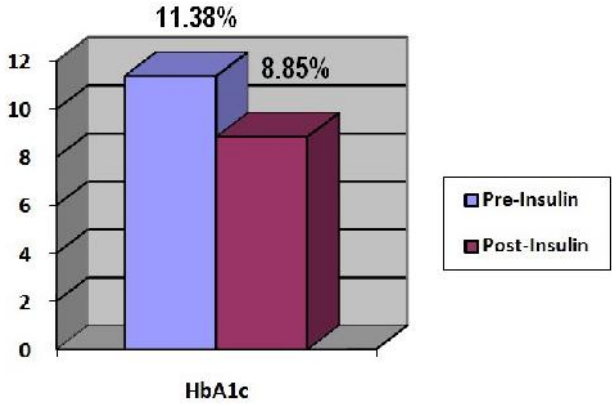
This research also conducted interviews and examination of medical records in the primary public health centers to find out if the patient had experienced DM complications before insulin therapy was provided. Eighteen (28.1%) patients were known to suffering from complications of cardiovascular diseases, such as coronary heart disease, stroke or hypertension, 41 patients (64.1%) claimed not to have cardiovascular complications, and 5 patients (7.8%) claimed not knowing. As for neuropathic complications, 37 patients (57.8%) had suffered from peripheral neuropathy, 25 patients (39.1%) claimed not and 2 patients (3.1%) did not know. For ocular complications such as cataracts, diabetic retinopathy or blurred eye, were obtained in 24 patients (37.5%), while 38 patients (59.4%) did not have, and 2 patients (31%) did not know (Table 2).

Table 1. Patients' Characteristics and Demographics

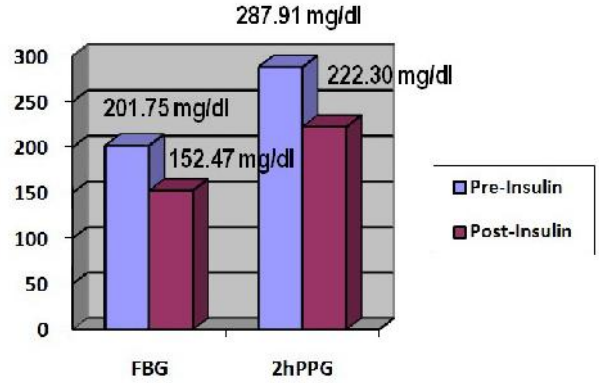
Variables	Data	Range
Total (n)	64	
Sex :		
- Male (%)	17.2	
- Female (%)	82.8	
Age (years)	53.6 ± 9.87	33 – 80
Body Mass Index (kg/m^2)	23.94 ± 4.22	16.67 – 34.60
Duration of Type 2 DM (years)	7.06 ± 4.45	0.5 – 21
HbA1c (%)	11.38±1.97	8.2 – 16.4
Fasting blood glucose (mg/dl)	201.75 ± 79.25	98 – 525
2-hour Post Prandial Glucose (mg/dl)	287.91±96.78	116 – 580

Table 2. Complications obtained in the patients prior to insulin therapy.

Complications	Cardiovascular	Neuropathy	Ocular
Yes	18 patients (28.1%)	37 patients (57.8%)	24 patients (37.5%)
No	41 patients (64.1%)	25 patients (39.1%)	38 patients (59.4%)
Not knowing	5 patients (7.8%)	2 patients (3.1%)	2 patients (31%)



A. Improvement of HbA1c after 12 weeks insulin detemir therapy



B. Improvement of FBG and 2hPPG after 12 weeks insulin detemir therapy

Figure 1A & B. Glycemic control in patients with type 2 DM before and after the administration of insulin detemir therapy.Notes: HbA1c = Hemoglobin A1c; FBG = Fasting Blood Glucose; 2hPPG = 2-hour Post-Prandial Glucose

Final results of the study demonstrated very significant reduction in FBG, 2hPPG and HbA1c, which at the end of the study was compared to the baseline. A total of 64 patients participated in this study had an average of initial FBG 201.75 mg/dL and significantly dropped 49.28 mg/dl to 152.47 mg/dl at the end of the study (p = 0.0001). 2hPPG also significantly decreased 91.22 mg/dl from the level of 287.91 mg/dl to 222.30 mg/dl (p = 0.0001). This study also found significant reduction in HbA1c from baseline, from 11.38% to 8.85% at the end of the study (p = 0.0001), so that the average reduction in HbA1c obtained in patients receiving insulin was 2.53% (Figure 1). Side effects of hypoglycemia were found in 4 patients (6.3%), which was a mild incidence and did not require hospitalization, only requiring insulin dose adjustment. In regard with weight, the pre insulin therapy BMI was 23.94 ± 4.22 kg/m2 to become 23.34 ± 5.60 kg/m 2 at the end of the study. This means there is a decrease in body weight before and after insulin detemir therapy, but was not statistically significant (p 0.37, 95% CI -0.74-1.95). While the systolic blood pressure obtained pre insulin therapy 127.14 ± 17.7 kg/m2 to 126.17 ± 13.74 kg/m 2 at the end of the study, which was not statistically significant (p 0.62, 95% CI -2 , 95 to 4.89). Diastolic blood pressure obtained pre insulin therapy 79.84 ± 8.86 kg/m2 to 81.95 ± 9.33 kg/m 2 at the end of the study, which was also not statistically significant (p 0.10, 95% CI -4. 66 to 0.45).

DISCUSSION

This study found that glycemic control in diabetic patients in primary public health centers was very poor. This is evident from the average HbA1c results of the

patients, which was achieving 11.38 ± 1.97% (Table 1). This result is far from the target set by Perkeni in 2011, which is below 7%. Diabcare Asia 2008 study found that the average HbA1c in patients with DM, who searched for treatment either in primary or secondary primary public health centers, reached 8.1 ± 2.0% (Soewondo 2010). It appears that in fact the average HbA1c in primary public health centers was much higher than HbA1c in Diabcare 2008 research. This is very worrying given the levels of HbA1c is associated with the occurrence of complications in patients with DM. Therefore, it is necessary to intensify therapy in patients with DM. Moreover, UKPDS study showed that a 1% reduction in HbA1c lowers the risk of DM complications by 21% (Stratton et al 2000).

Chronic complications of DM observed in this study showed that 28.1% of the patients suffered from cardiovascular complications, such as coronary heart disease, stroke or hypertension. Neuropathy complications were found in 57.8% of the patients and 37.5% had ocular complications, such as cataracts, diabetic retinopathy or blurred eye (Table 2). It was not much different from the data of DM studies in Indonesia, which shows the prevalence of microvascular complications reaching 27.6 to 53%, macrovascular complications 16-20%, neuropathy 13-78%, and retinopathy reached 17.2 to 42.6% (Soewondo et al 2013).

Litwak et al (2013) also conducted an observational study in 28 countries across Asia, Africa, Europe and South America. They found macrovascular complications in 27.2% of the patients, microvascular complications in 53.5% of patients, renal disorders in 27.9% of patients, eye abnormalities in 26.3% and neuropathy in 38.4% of patients (Litwak et al 2013). It shows that most patients with DM come with a variety of chronic complications. Chronic complications require precise handling and good glycemic control to prevent further complications and slow the progression of existing complications.

In this study, after the administration of basal insulin, that is the insulin detemir as add-on therapy in patients who have received oral anti-diabetic for 12 weeks, there was a significant decrease in HbA1c, amounting to 2.53%, while the average FBG fell by 49.28 mg/dl and 2hPPG of 91.22 mg/dl (Figure 1). In a study of Daily Levemir (SOLVE) with insulin detemir for 24 weeks as add-on therapy in patients with oral anti-diabetic, a decrease of 1.3% was found in HbA1c (Yale et al 2013). PREDICTIVE study is a large prospective observational study in Denmark involving 312 patients with DM type 1 and 77 type 2 diabetic patients to assess the efficacy and safety of insulin detemir therapy for 12 weeks. In patients with type 2 DM HbA1c decreased 0.3% from 8.8% at baseline to 8.5% at the end of the study. Obtained FBG fell by 2.7 mmol/l (48.6 mg/dl) of 10.5 mmol/l at baseline to 7.8 mmol/l at the end of the study (Hermansen et al 2007).

Rosenstock et al (2008) provide insulin detemir as add-on therapy in patients with type 2 DM who have received oral antidiabetic therapy and have not been given insulin (insulin-naïve). He earned a decrease in HbA1c of 1.4% after administration of insulin detemir 52 weeks (8.6% to 7.2%). Fasting blood glucose declined by 3.7 mmol/l (66.6 mg/dl) of 10.8 mmol/l at baseline to 7.1 mmol/l at the end of the study. In our study it appears that the decrease in HbA1c is greater than that in other studies. Greater decrease in HbA1c is likely due by high baseline HbA1c in this study, ie 11.38%, while baselines in the other studies above ranged about 8%.

Hypoglycemic side effects in this study were found in 6.3% of patients. The incidence of hypoglycemia was mild and not required hospitalization, only the adjustment of insulin dose. SOLVE study also showed increased incidence of minor hypoglycemia which was not statistically significant (Yale et al 2013). Side effects of weight gain commonly found in insulin administration were not found in this study. In contrast, this study actually revealed weight reduction, although not statistically significant. This is in line with the PREDICTIVE study that also gains weight loss of 0.6 kg in patients with type 1 DM and 1 kg in patients with type 2 DM (Hermansen et al 2007). The mechanism of weight loss in this study remains unclear, possibly due to the effects of low hypoglycemia, reducing the need for a snack or excessive eating. Other side effects, such as allergies or pain at the injection site, were also not found in this study.

CONCLUSION

Basal insulin therapy with insulin detemir as add-on therapy in patients with type 2 DM with poor glycemic control in primary public health centers significantly improves glycemic control of blood sugar levels with a low risk of hypoglycemia and without the risk of weight gain.

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REFERENCES

Hermansen K, Lund P, Clemmensen K, Breum L, Moller KM, Rosenfalk AM (2007). 3-months results from denmark within the globally prospective and observational study to evaluate insulin detemir treatment in type 1 and type 2 diabetes: The PREDICTIVE Study. The Review of Diabetes Study 4, 89-97

Hirsch IB, Bergenstal RM, Parkin CG, Wright Jr E, Buse JB (2005). A real world approach to insulin therapy in primary care practice. Clin Diabetes 23, 78-86

Litwak L, Goh SY, Hussein Z, Malek R, Prusty V, Khamseh ME (2013). Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational a1chieve study. Diabetology & Metabolic Syndrome 5, 57-67

Ministry of Health Republic of Indonesia (2007). Report on Result of National Basic Health Research (RISKESDAS 2007), Jakarta, Departemen Kesehatan Republik Indonesia

Perkeni (2011). Konsensus Pengelolaan dan Pencegahan Diabetes Mellitus Tipe 2 di Indonesia

Peyrot M, Rubin RR, Khunti K (2010). Addressing barriers to initiation insulin in patients with type 2 diabetes. Primary Care Diabetes 4, S11-S18

Rodgers J (2004). Initiating insulin in primary care: factors to be considered. Journal of Diabetes Nursing 8, 291-293

Rosenstock J, Davies M, Home PD, Larsen J, Koenen C, Schernthaner G (2008). A randomized, 52 weeks, treat to target trial comparing insulin detemir with insulin glargine when administered as add-on to glucose lowering drugs in insulin naive people with type 2 diabetes. Diabetologia 51, 408-416

Soewondo P, Ferrario A, Tahapary DL (2013). Challenges in diabetes management in Indonesia : a literature review. Globalization and Health 9, 63-80

Soewondo P, Soegondo S, Suastika K, Pranoto A, Soeatmadji D, Tjokroprawiro A (2010). The diabcare Asia 2008 study – outcomes on control and complications off type 2 diabetic patients in Indonesia. Med J Indones 19, 235-244

Stratton IM, Adler AI, Neil HA, Mathews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321, 405-412

United Kingdom Prospective Diabetes Study (UKPDS) Group (1999). Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes mellitus (UKPDS 33). Lancet 354, 602

Yale JF, Damci T, Kaiser M, Karnieli E, Khunti K, Liebl A, Baeres FMM, Svendsen AL, Ross SA (2013). Initiation of once daily insulin detemir is not associated with weight gain in patients with type 2 diabetes mellitus. Diabetology & Metabolic Syndrome 5, 56-66