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Original article

Comparative evaluation of biphasic insulin with metformin and triple oral hypoglycemic agents (OHA) in type 2 diabetes patients

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ABSTRACT

Introduction: The prevalence of secondary failure to oral hypoglycemic agents among type 2 diabetes mellitus (T2DM) patients ranges from 30 to 60%. The alternative approaches to overcome this issue are either switching to triple oral hypoglycemic agents (OHA) or intensifying the regimen by adding insulin. **Objective:** To compare the glycemic control achieved with biphasic insulin plus metformin and triple OHA in T2DM patients who were not adequately controlled with two OHA regimen.

Methods: A qualitative prospective study was conducted at Asir diabetes center, Abha, KSA. Poorly controlled T2DM patients with two OHA for at least 1 year with glycated hemoglobin (HbA1c) >7.0% were included. Subjects were divided into group I (a third OHA was added to the existing two OHA regimen) and group II (switched over to Biphasic insulin and metformin). At baseline and 3-month intervals, level of HbA1C, Fasting Plasma Glucose (FPG), Postprandial Plasma Glucose (PPG), Blood Pressure (BP), lipid profile and hypoglycemic episodes were obtained and evaluated for one year.

Results: 41.1% of patients were in group I and 58.9% were in group II. At the end of the study, there was a significant reduction in HbA1c in group II subjects comparing to group I (8.18 ± 1.32 vs 8.79 ± 1.81, p = 0.0238). FPG and PPG were improved also in group II. The mean body weight increased from baseline in group II is +4.48 kg and decreased from baseline in group I (−0.46 kg). 11.3% from group I and 23.7% from group II reported hypoglycaemic incidences.

Conclusion: Biphasic insulin and metformin regimen could be an appropriate therapeutic option for achieving good glycemic control compared with triple OHA in patients with two OHA failure.

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1. Introduction

The prevalence of secondary failure to OHAs among T2DM patients taking oral agents particularly late into the disease, in different populations, ranges from 30% to 60% over 5 years after initiation of therapy (Reidel et al., 2007; Eurich et al., 2005). Since the two OHA regimen has the potential to reduce the HbA1c levels on

an average by only 1.2–2%, addition of a third agent either an oral agent or insulin is required in all patients in the future course of time with advancing T2DM (Sirajudeen et al., 2014). Despite the triple OHA regimen is found to be statistically and clinically more effective in reducing HbA1c (Moon et al., 2017), patients with triple OHA were less likely to complete the regimen due to an additive risk of adverse effects, dose adjustments may become complex or intolerable side effects (Lingvay et al., 2009; Tri Murtiet al., 2010). On the other hand, insulin therapy has been shown to result in significant decreases in fasting plasma glucose (FPG) and HbA1c values (Bloomgarden, 2017). However, large doses of insulin are often required to achieve near-normal blood glucose levels and are associated with weight gain and the risk of hypoglycemia (Sirajudeen et al., 2014). Since both approaches have their respective advantages and disadvantages, this study compared the efficacy and safety in patients with two OHA failure randomly assigned to triple OHA therapy or insulin-based therapy.

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2. Methods

A qualitative prospective cohort study was conducted for a period of two years from June 2013 to June 2015 at Asir Diabetes Center, Asir Central Hospital in Abha, Saudi Arabia. The study was approved by the regional Research Ethical Committee. Both adult male and female insulin-naïve T2DM patients currently on two OHA therapy, with a history of poor glycemic control and HbA1c > 7% for the last one year or more were included in the study. Patients with a history of type 1 diabetes, elevated serum creatinine levels, lactic acidosis, gestational diabetes mellitus, and any other life-threatening complications were excluded from the study. Upon enrollment, study subjects were divided into two groups. In group I study subjects, a third OHA (gliptins or thiazolidinediones) was added to their existing 2 OHA therapy (Sulfonylurea and Metformin), whereas group II included study subjects who were switched over to biphasic insulin and metformin from their existing 2 OHA therapy (Sulfonylurea and Metformin). Study subjects were followed regularly post-drug therapy intervention. HbA1c, Fasting plasma glucose (FPG), Postprandial Plasma Glucose (PPG), Blood Pressure (BP) and lipid profile data were collected from the study center at every three months based on the scheduled follow up visits of study subjects. Hypoglycemic episodes were obtained from patients' home blood glucose monitoring logs. Hypoglycemic episodes were defined as symptoms indicative of low blood glucose accompanied by a documented capillary blood glucose value of <70 mg/dl. The primary objective of the study was to assess the change in HbA1c level at 1 year from the baseline. The secondary objectives were the changes in FPG, PPG, BP, weight, lipid profile and the number of hypoglycemic episodes. Statistical analyses were performed using SPSS software (IBM SPSS software, IBM Corp, V21 Armonk, NY, USA). Descriptive statistics were provided for all collected variables. Categorical data were summarized as frequency and percentage, whereas quantitative data were summarized as mean and standard deviation. Baseline characteristics and change in the primary and secondary outcome parameters from baseline was done using ANOVA followed by Dunnett's test for post hoc analysis. p-value of <0.05 was considered statistically significant.

3. Results

A total of 129 patients were included in the study out of which 41.1% of patients (n = 53) received triple OHA regimen (group I) and 58.9% of patients (n = 76) received biphasic insulin and metformin regimen (group II). Both groups were well matched concerning gender ratio, age, body weight, BMI, HbA1c, and lipid profile with varying proportions of comorbidities [Table 1]. Baseline HbA1c was $10.2 \pm 1.7\%$ for subjects in the triple oral therapy and $10.8 \pm 1.7\%$ in the biphasic insulin plus metformin group. The mean duration of diabetes was numerically longer in group II (11.63 ± 5.9 years) than in group I (8.23 ± 5.54 years). Before the transition, the most common combination used by the participants was sulfonylurea + metformin [Table 2].

The maximal reduction in the mean HbA1c level occurred at the sixth month and then remained stable in group I, whereas the mean HbA1c level kept on decreasing till the end of the study in group II [Fig. 1a, Table 3]. There was a significant reduction in HbA1c in biphasic insulin plus metformin group compared to the triple OHA group (8.18 ± 1.32 vs 8.79 ± 1.81 , $p = 0.0238$).

Percentage of subjects achieved HbA1c values $\leq 7\%$ was 21 in group I and 30 in group II. There was no significant difference in the FPG reduction between the 2 groups (mean reduction from the baseline: 37.7 mg/dl vs 68.9 mg/dl, $p = 0.07$). There was a sharp

Table 1

Demographics and Baseline disposition of study subjects.

Characteristics	Group I N (53)	Group II N (76)	Total for all Patients N (129)	p-value
DEMOGRAPHY				
Male	32 (60.4)	46 (60.5)	78 (60.4)	0.9887
Age (Year)	53.2 ± 8.7	54.1 ± 10.25	53.3 ± 8.7	0.7373
Total duration of diabetes (Mean years \pm SD)	8.23 ± 5.54	11.63 ± 5.9	8.2 ± 5.5	0.02*
CLINICAL				
Blood Pressure, mm Hg				
Systolic*	120.1 ± 13.1	123.8 ± 15.3	123.5 ± 14.7	0.0342*
Diastolic	76.2 ± 7.9	77.6 ± 9.2	77 ± 8.7	0.5913
Biochemical				
HbA1C (%)	10.2 ± 1.7	10.8 ± 1.7	10.6 ± 1.7	0.0573
FPG (mg/dl)	195.6 ± 62	211.8 ± 63.6	205.3 ± 63.3	0.0722
PPG (mg/dl)	236.5 ± 73.8	283.4 ± 82.1	263.9 ± 81.8	0.0004*
Lipid Profile				
HDL (mg/dl)	39.2 ± 9.9	41.2 ± 10.8	40.4 ± 10.5	0.2715
LDL (mg/dl)	120 ± 36.1	116.1 ± 35.6	117.7 ± 35.7	0.5527
TGL (mg/dl)	155.5 ± 79.8	169.4 ± 133.3	163.4 ± 114.2	0.9637
Anthropometric				
Body weight, Kg	77.9 ± 12.7	77.1 ± 16.3	77.4 ± 14.8	0.5103
BMI, kg/m ²	29.8 ± 4.3	30.3 ± 6.9	30.1 ± 6	0.6806

Values are presented as n (%) or mean \pm SD.

* P values < 0.05 (statistically significant).

Table 2

Drug therapy and coexisting conditions at the baseline.

Variables	Group I N (53)	Group II N (76)	Total for all Patients N (129)
Use of hypoglycemic agents			
Metformin + Glibenclamide	31 (58.5)	43 (56.8)	74 (57.4)
Metformin + Glimipride	16 (30.2)	21 (27.6)	37 (28.7)
Metformin + Gliclazide	5 (9.4)	10 (13.1)	15 (11.6)
Metformin + Repaglinide	1 (1.9)	0	1 (0.8)
Metformin + Pioglitazone	0	0	0
Metformin + Rosiglitazone	1 (1.9)	1 (1.3)	2 (1.6)
Coexisting conditions			
Neuropathy	4 (5.88)	16 (21.1)	20 (15.5)
Retinopathy	1 (1.47)	12 (15.8)	13 (10.1)
Diabetic foot ulcer	0	0	0
Diabetic ketoacidosis	0	5 (6.6)	5 (3.9)
Impotence	4 (5.88)	4 (5.3)	8 (6.2)
Ischemic heart disease	5 (7.35)	2 (2.6)	7 (5.4)
Cerebrovascular Aneurism	1 (1.47)	5 (6.6)	6 (4.7)
Depression	4 (5.88)	7 (9.2)	11 (8.5)

reduction in FPG in both groups in the third month and continued to decrease in group II [Fig. 1b].

Reduction in mean PPG was -66.45 mg/dl in group I and 79.64 mg/dl in group II with no significant differences [Fig. 1c]. The change in body weight was statistically significant between the two groups with an increase in BMI by $+0.16$ kg/m² in group I compared to $+1.78$ kg/m² in group II ($p = 0.042$) [Fig. 1d].

Changes in lipid parameters are shown in Fig. 2. The baseline values of LDL, HDL, and triglycerides indicated no differences between the two treatment groups. Subjects in the triple oral therapy group showed a small increase in HDL and triglyceride levels, whereas, subjects in group II showed a small decrease in HDL.

No episodes of major hypoglycemia were recorded during the study period. The proportion of patients experiencing symptoms was not similar in the two groups. Of these study subjects, a total of 6 of 53 patients (11.3%) from group I and 18 of 76 (23.7%) from group II reported hypoglycaemic incidences.

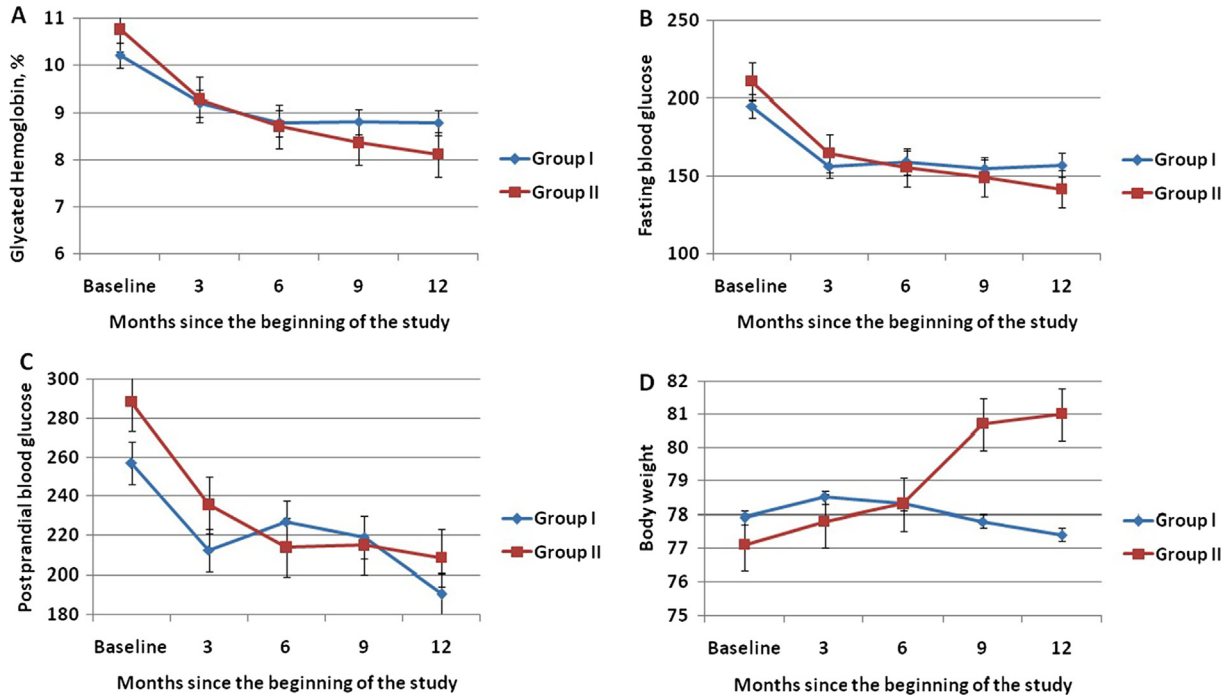


Fig. 1. Temporal assessment of primary and secondary outcomes during the study period. **Fig. 1a** shows mean levels of glycosylated hemoglobin in the four study groups. **Figure-1b** shows mean levels of fasting plasma glucose. **Figure-1c** shows mean levels of postprandial blood glucose. **Figure-1d** shows mean levels of body weight. I bar denote standard deviation.

Table 3
Post intervention impact on primary and secondary outcomes.

Variables	Group I N (53)	Group II N (76)	P value [†]
PRIMARY OUTCOME			
HbA1c(%)			
At 1 year	8.79 ± 1.81	8.18 ± 1.32	0.0238*
Mean change from baseline	-1.42	-2.64	
SECONDARY OUTCOMES			
FPG			
At 1 year	158 ± 44.5	144.7 ± 43.8	0.0765
Mean change from baseline	-37.66	-68.88	
PPG			
At 1 year	200.9 ± 82.4	213.4 ± 67.3	0.4921
Mean change from baseline	-66.45	-79.64	
SBP			
At 1 year	120.89 ± 13.9	124.32 ± 15.9	0.0365
Mean change from baseline	-0.81	1.34	
DBP			
At 1 year	77.26 ± 9.1	77.16 ± 10	0.8559
Mean change from baseline	-0.8491	0.54	
HDL			
At 1 year	41.11 ± 11.7	38.46 ± 9.8	0.3364
Mean change from baseline	1.89	-2.73	
LDL			
At 1 year	104.58 ± 27.4	102.48 ± 32.9	0.3158
Mean change from baseline	-15.43	-15.12	
TGL			
At 1 year	158.74 ± 81.9	161.27 ± 10.5	0.7702
Mean change from baseline	3.26	-13.71	
Body Wt			
At 1 year	77.42 ± 13.2	82.73 ± 15.3	0.1793
Mean change from baseline	-0.46	4.48	
BMI			
At 1 year	29.59 ± 4.6	32.34 ± 6.6	0.0421*
Mean change from baseline	-0.16	1.78	
% of patients achieved HbA1c target—no (%)			
≤ 7%	11 (20.8)	23 (30.3)	
Hypoglycemic incidences	6(11.3)	18 (23.7)	

Values are presented as n (%) or mean ± SD.

[†] The p values are for the comparisons between the groups at 1 year.

* P values < 0.05 are statistically significant.

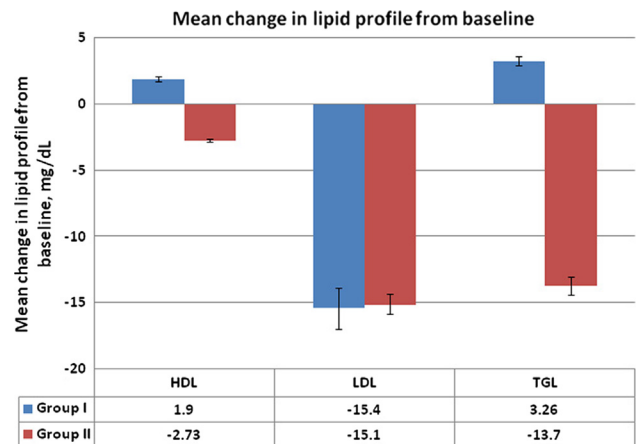


Fig. 2. Mean changes in lipid profile from the baseline. Mean ± SD changes in HDL, LDL and triglyceride levels in the insulin plus metformin group as compared with the tripleOHA group.

4. Discussion

T2DM is characterized by a progressive loss of β -cell function and glycemic control. Suboptimal glycemic control often results in microvascular and macrovascular complications (Ogurtsova et al., 2017), which warrant the identification of effective and simple treatment regimens with high-level glycemic control and good patient compliance and convenience. The most recent ADA consensus statement (American Diabetes Association, Standards of Medical Care in Diabetes-2019) encourages early use of insulin, whereas, commonly used agents such as gliptins and sodium-glucose cotransporter-2 (SGLT2) inhibitors are considered second tier. However, these guidelines faced criticisms such as insulin treatment is associated with hypoglycemia, weight gain, and low

treatment satisfaction and compliance. In light of this dilemma, this study reports the glycemic control, cardiovascular risk factors, weight gain and rate of hypoglycemia.

Although most patients prefer OHAs over insulin, the addition of insulin to oral regimens is a well-established approach that is effective for many patients (American Diabetes Association; Standards of Medical Care in Diabetes 2019). Treatment modalities such as extended reliance on OHAs result in hyperglycemia for long periods, which contributes to microvascular complications and beta-cell destruction that in turn accelerates treatment failure. Wallia and Molitch (2014) reported that insulin-based regimens are effective and safe as a short-term treatment option to gain rapid glycemic control. Therefore, the results of our study demonstrate that long-term continuation of insulin based regimens is effective, safe, and well accepted by patients as compared with a combination of triple OHA regimen.

Significant reduction in glycemic parameters such as the HbA1c, FPG, and PPG in both treatment groups was seen. However, as would be expected, the mean reductions in these parameters were found to be more prominent and statistically significant in group II rather than group I (mean reduction from the baseline: 2.64% vs 1.42%, $p = 0.0238$). These results were consistent with previous researches which reported the combination of insulin and metformin provided better glycemic control and treatment satisfaction (Lingvay et al., 2009; Holden et al., 2016).

In the present study, Group II patients showed considerable and comparable improvement in FPG, PPG and other cardiovascular disease (CVD) risk factors such as systolic BP (SBP), diastolic BP (DBP) and lipid profile. This is in line with the results of the previous study comparing the efficacy and safety of premixed and basal-bolus insulin in the management of T2DM after the failure of two OHAs (Sirajudeen, et al., 2013). However, the patients in this group experienced higher incidences of hypoglycemic events. It confirms that biphasic insulin and metformin regimen is a better option in controlling glycemic parameters may be at the cost of increased adverse events (i.e., greater HbA1c reduction with increased hypoglycemia). This result is similar to the previous studies that reported that biphasic insulin and metformin regimen is more likely to cause hypoglycemia (Hauber and Gale (2006), Qayyum et al., 2008).

Despite instituting intensified therapy, only one-fifth of subjects from group I and one third from group II were able to achieve an HbA1c value below 7%. Barriers in achieving target HbA1c maybe the severity and long duration of diabetes, certain classes of oral hypoglycemic agents are possibly less effective, fear of hypoglycemia by either subjects or physicians limiting further aggressive control, and noncompliance with recommended regimens (Hengameh et al., 2018; Janneth et al., 2018). Non-compliance is expected if polypharmacy is involved in glycemic control and other comorbid conditions of T2DM such as hypertension and dyslipidemia (Noale et al., 2016).

An increase in body weight is one of the major side effects of insulin therapy. A noticeable increase in body weight was observed in those subjects treated with biphasic insulin and metformin (change in body weight from baseline = 4.48 kg). In group I subjects, body weight did not significantly change. In clinical practice, metformin is one of the most widely used agents in both obese and non-obese type 2 diabetes patients as a monotherapy or in combination with insulin, because of its ability to ameliorate insulin resistance and the potential effect of weight loss (Wright et al., 2002; Lund et al., 2009). However, some studies have documented that metformin induces weight loss only when its daily dosage reached 2000–3000 mg (Lund et al., 2009; Siraj 2003). In our study, the mean metformin dose was 1270 ± 387 mg/day, which was similar to a study conducted to evaluate the efficacy of biphasic insulin and metformin in T2DM patients (Yunjuan et al., 2012). More

weight gain associated with premixed insulin use has been reported across trials (Buse et al., 2009; Buse et al., 2011; Highlights of Prescribing Information, 2012). However, dietary management and exercise programs need to be in place as part of the patient's treatment, especially when insulin is initiated.

Although many studies were conducted to find out the best therapeutic strategy after the failure of two OHA regimen in T2DM, the dilemma still exists. Previous studies have reported that an insulin and metformin regimen is effective and safe as a short-term treatment option to gain rapid glycemic control (Lingvay et al., 2007; Lingvay et al., 2009). Data of this study shows that the long-term continuation of this regimen is effective in terms of glycemic control compared with a combination of three OHAs with some commonly known downsides such as weight gain and hypoglycemic events. These consequences can be overcome by tailoring the insulin regimen based on factors, including age, comorbidities, lifestyle, eating patterns, and psychological status of the patient.

This study demonstrated that treatment with biphasic insulin and metformin can be used to obtain significant glycemic control over triple OHA treatment. The comparative assessment of these two approaches may further be substantiated with more evidence and can be used in clinical decision-making.

5. Limitations

The results of this study should be understood based on the following limitations. The study was carried out for a limited period of one year. The study did not offer randomization of study subjects, as the patients were grouped at the physician's discretion. Moreover, hypoglycemic events were reported using patients' self-monitoring blood glucose logs only. In view of the above-mentioned limitations, further research is warranted to obtain more specific, significant and diverse outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- American Diabetes Association, 2019. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes–2019. *Diabetes Care* 42 (Suppl. 1), S90–S102.
- Bloomgarden, Z., 2017. Is insulin the preferred treatment for HbA1c >9%?. *J. Diabetes* 9 (9), 814–816. <https://doi.org/10.1111/1753-0407>.
- Buse, J.B., Wolfenbittel, B.H., Herman, W.H., et al., 2009. DURAbility of basal versus lispro mix 75/25 insulin efficacy (DURABLE) trial 24-week results: safety and efficacy of insulin lispro mix 75/25 versus insulin glargine added to oral antihyperglycemic drugs in patients with type 2 diabetes. *Diabetes Care* 32 (6), 1007–1013.
- Buse, J.B., Wolfenbittel, B.H., Herman, W.H., et al., 2011. The DURAbility of Basal versus Lispro mix 75/25 insulin Efficacy (DURABLE) trial: Comparing the durability of lispro mix 75/25 and glargine. *Diabetes Care* 34 (2), 249–255.
- Eurich, D.T., Simpson, S.H., Majumdar, S.R., et al., 2005. Secondary failure rates associated with Metformin and sulphonylurea therapy for T2DM patients. *Pharmacotherapy* 25 (6), 810–816.
- Hauber, A., Gale, E.A.M., 2006. The market in diabetes. *Diabetologia* 49 (2), 247–252.
- Hengameh, A., Fereidoun, A., Atieh, A., 2018. Insulin monotherapy versus insulin combined with other glucose-lowering agents in Type 2 diabetes: a narrative review. *Int. J. Endocrinol/Metab.* 16 (2). <https://doi.org/10.5812/ijem.65600>.
- Highlights of Prescribing Information, 2011. Novo Log[®] Mix 70/30. Novo Nordisk Inc., Princeton, NJ. September 2011. Available from: <http://www.novo-pi.com/novologmix7030.pdf> (accessed 22 November 2012).
- Janneth, B.C., Paloma, A.V., Josefa, R.P., et al., 2018. Insulin adherence in Type 2 diabetes in Mexico: behaviors and barriers. *J Diabetes Res.* 2018, 3190849. <https://doi.org/10.1155/2018/3190849>.
- Holden, S.E., Jenkins, J.S., Currie, C.J., 2016. Association between insulin monotherapy versus insulin plus metformin and the risk of all-cause

- mortality and other serious outcomes: a retrospective cohort study. *PLoS One* 11. <https://doi.org/10.1371/journal.pone.0153594>.
- Lingvay, I., Kaloyanova, P.F., Adams-Huet, B., et al., 2007. Insulin as initial therapy in type 2 diabetes: effective, safe, and well accepted. *J Investig Med* 55 (2), 62–68.
- Lingvay, I., Legendre, J.L., Kaloyanova, P.F., et al., 2009. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes. *Diabetes Care* 32 (10), 1789–1795.
- Lund, S.S., Tarnow, L., Frandsen, M., et al., 2009. Combining insulin with metformin or an insulin secretagogue in non-obese patients with type 2 diabetes: 12 month, randomised, double blind trial. *BMJ* 339. <https://doi.org/10.1136/bmj.b4324>.
- Moon, M.K., Hur, K.Y., Ko, S.H., et al., 2017. Combination therapy of oral hypoglycemic agents. *Korean J Intern Med* 32 (6), 974–983.
- Noale, M., Veronese, N., Cavallo, P.P., et al., 2016. Polypharmacy in elderly patients with type 2 diabetes receiving oral antidiabetic treatment. *Acta Diabetol* 53 (2), 323–330. <https://doi.org/10.1007/s00592-015-0790-4>.
- Ogurtsova, K., Fernandes, J.D., Huang, Y., et al., 2017. IDF Diabetes Atlas: global estimates for the prevalence of diabetes for 2015 and 2040. *Diabetes Res Clin Pract* 128, 40–50. <https://doi.org/10.1016/j.diabres.2017.03.024>.
- Qayyum, R., Bolen, S., Maruthur, N., et al., 2008. Systematic review: comparative effectiveness and safety of premixed insulin analogues in type 2 diabetes. *Ann Intern Med* 149 (8), 549–559.
- Reidel, A.A., Heien, H., Wogen, J., et al., 2007. Loss of glycaemic control in patients with T2DM who were receiving initial metformin, sulphonylurea or TZD monotherapy. *Pharmacotherapy* 27 (8), 1102–1110.
- Siraj, E.S., 2003. Is there a role for metformin or acarbose as a weight-loss agent in the absence of diabetes?. *Cleve Clin J Med* 70 (8), 702–704.
- Sirajudeen, S.A., Danapal, C.K., Abdulla, N.K., et al., 2013. Comparison of efficacy and safety of basal and premixed insulin regimens among Type II diabetes patients transiting from oral agents to insulin. *IJOOP* 6 (4), 27–32.
- Sirajudeen, S.A., Dhanapal, C.K., Khaled, M.A., et al., 2014. Benefits and pitfalls of using insulin in the management of type 2 diabetes patients: a clinical evaluation. *J. App. Pharm.* 6 (4), 416–426.
- Tri Murti, A., Mohamed, I.M.I., Ahmad, H.A., 2010. Comparison of the glycemic control of insulin and triple oral therapy in type 2 diabetes mellitus. *J. Diabetes Endocrinol.* 1 (2), 13–18.
- Wallia, A., Molitch, M.E., 2014. Insulin therapy for type 2 diabetes mellitus. *JAMA* 311 (22), 2315–2325.
- Wright, A., Burden, A.C., Paisey, R.B., et al., 2002. Sulphonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 25 (2), 330–336.
- Yunjuan, G., Xuhong, H., Lei, Z., et al., 2012. The impact of initiating biphasic human insulin 30 therapy in Type 2 diabetes patients after failure of oral antidiabetes drugs. *Diabetes Technol Ther.* 14 (3), 244–250.