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Muhammad Abdul-Ghani MD, PhD, Osama Mujahid MD, Ayman Mujahid MD, Ralph A. DeFronzo, MD, Mahmoud Zirie MD, Amin Jayyousi MD.

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Efficacy of Exenatide Plus Pioglitazone Versus Basal/Bolus Insulin in T2DM Patients With Very High HbA1c

[1,2]Muhammad Abdul-Ghani* MD, PhD, [1]Osama Mujahid* MD, [1]Ayman Mujahid MD, [2]Ralph A. DeFronzo, MD, [1]Mahmoud Zirie MD, [1]Amin Jayyousi MD.

[1]Diabetes Research, Academic Health System, Hamad General Hospital, Doha, Qatar, and [2]Division of Diabetes, University of Texas Health Science Center at San Antonio, TX.
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*These authors equally contributed to the study

Aim: To examine the efficacy and safety of combination therapy with exenatide plus pioglitazone versus basal-bolus insulin in poorly controlled type 2 diabetic patients with very high HbA1c (HbA1c>10%) on metformin plus sulfonylurea and long duration of disease.
Research Design and Methods: 101 participants in Qatar Study with very poor glycemic control (HbA1c > 10%) and long duration of diabetes (10.9 years) on maximum/near-maximum doses of sulfonylurea plus metformin were randomized to receive: (i) pioglitazone plus weekly exenatide (Combination Therapy), or (ii) basal plus prandial insulin (Insulin Therapy) to maintain HbA1c <7.0%.
Results: Baseline HbA1c was 11.5 ± 0.2% and 11.2±0.2 (P=NS) in Combination Therapy and Insulin Therapy groups, respectively. At 6 months, Combination Therapy caused a robust decrease in HbA1c to 6.7 ± 0.1% (Δ = -4.8%) compared to 7.4 ± 0.1% (Δ = -3.8%) in subjects receiving Insulin Therapy. Combination Therapy was effective in lowering the HbA1c independent of gender, ethnicity, or BMI. Subjects in the Insulin Therapy group experienced significantly greater weight gain and 2.5-fold higher rate of hypoglycemia compared to patients receiving Combination Therapy.
Conclusion: Combination exenatide/pioglitazone therapy is a very effective and safe therapeutic option in poorly controlled T2DM patients on metformin plus sulfonylurea with very high HbA1c (>10%).

PRECIS: The present study demonstrates that combination therapy of pioglitazone plus exenatide is equally effective to insulin in poorly controlled T2DM patients with very high HbA1c on multiple oral agents

INTRODUCTION

Hyperglycemia is the major factor responsible for diabetic microvascular complications, i.e. retinopathy and nephropathy (1-4). Every 1% decrease in HbA1c is associated with ~35% reduction in the incidence of retinopathy and nephropathy (1-4). Progressive beta cell failure is the principal pathophysiologic abnormality responsible for the development and progression of hyperglycemia in individuals with T2DM (5). In addition to its role in the development of diabetic microvascular complications, chronic elevation in the plasma glucose concentration exerts a deleterious effect on beta cell function, i.e. glucotoxicity (6), creating a negative feedback cycle which exacerbates the defect in insulin secretion. Studies in both experimental animals and in man have demonstrated that chronic elevation in the plasma glucose concentration impairs beta cell function (7-8). Conversely, correction of the hyperglycemia improves beta cell function in experimental animals and in patients with T2DM (9-12).

The progressive nature of diabetes, long duration of disease, markedly elevated HbA1c, and glucotoxic effect of chronic hyperglycemia on beta cell function have led to the dogma that, in subjects with a very high HbA1c, e.g. HbA1c >10%, insulin therapy is the treatment of choice (13,14). Independent of beta cell function, insulin therapy can effectively lower the plasma glucose concentration, ameliorate the glucotoxic effect of hyperglycemia on the beta cell (9-11), and reduce the HbA1c to 6.5-7.0% (10,11). Based upon this rational, the ADA (13) and AACE (14) have recommended the institution of insulin therapy in poorly controlled T2DM with high HbA1c (>9-10%), especially in type 2 diabetic individuals with clinical symptoms of hyperglycemia, e.g. polydipsia and polyuria.

GLP-1 receptor agonists (RA) improve beta cell function by enhancing beta cell responsiveness to glucose, i.e. improved beta cell glucose sensitivity (15-17); this beneficial effect on the beta cell can be observed within 8 hours of a single injection of the GLP-1 RA (17) and persists for at least 4 years (16,18,19). Thus, the GLP-1 RAs produce a rapid and durable reduction in HbA1c with low risk of hypoglycemia. Thiazolidinediones (TZDs), which were developed as insulin sensitizers, also have a potent effect to improve beta cell function (20-26) and clinical trials have demonstrated durable HbA1c reduction with low risk of hypoglycemia compared to sulfonylureas (26). Because TZDs improve both insulin action and insulin secretion via mechanisms which are distinct from the GLP-1 RAs, we hypothesized that combination therapy with pioglitazone plus exenatide would effectively lower the plasma glucose concentration in poorly controlled T2DM patients with a very high HbA1c and long standing diabetes. This combination therapy could provide a therapeutic option to insulin for the treatment of patients with very high HbA1c. To address this question, we analyzed data from participants of the QATAR Study who had a baseline HbA1c >10% and compared the decrease in HbA1c from baseline to 6 months in subjects receiving Combination Therapy with exenatide plus pioglitazone versus basal bolus insulin therapy.

Research Design and Methods

Study participants included all T2DM patients in the QATAR Study who had a baseline HbA1c >10% (range 10.0-15.1%) and manifested symptoms of hyperglycemia as evidenced by polydipsia and nocturia. The QATAR Study (27) is an open label, single center, randomized control trial (NCT 02887625) which examines the efficacy, durability and safety of Combination Therapy with exenatide plus pioglitazone versus basal/bolus Insulin Therapy in poorly controlled T2DM patients on metformin plus sulfonylurea. T2DM patients with poor glycemic control on maximal/near maximal doses of metformin plus sulfonylurea were recruited to the study. Eligible subjects were randomized to receive basal (glargine)/bolus (aspart) insulin therapy or weekly exenatide plus pioglitazone to achieve HbA1c <7.0%. The study is an ongoing study and is carried out at Hamad General Hospital, Doha, Qatar. Herein, we report the efficacy (measured as the decrease in HbA1c from baseline to 6 months) of Combination Therapy with exenatide plus pioglitazone on glycemic control compared to basal/bolus Insulin Therapy in subjects who had a starting HbA1c >10%. 101 participants fulfilled the criteria for inclusion in the present report. The study protocol was approved by the IRB of Hamad General Hospital and informed written consent was obtained from all patients prior to enrollment.

Other than diabetes, patients were in good general health as determined by medical history and physical exam. Participants had normal kidney (creatinine <1.4) and liver function (LFT < twice the upper normal level), serum chemistries, EKG, and urinalysis, and negative pregnancy test. Body weight was stable (±3 pounds) within the preceding year and no subject participated in

any excessively heavy exercise program. Exclusion criteria were hematocrit <34%, medications known to affect glucose metabolism other than sulfonylureas and metformin, evidence of diabetic proliferative retinopathy, albumin excretion > 300 mg/day, major organ system disease as determined by physical exam, medical history, and screening blood tests. All patients received maximal/near maximal therapy with metformin plus sulfonylurea.

Study Design:

Subjects were consecutively randomized to receive Combination Therapy with pioglitazone (30 mg/day) plus Bydureon (2 mg/week) (Combination Therapy) or basal (glargine)/bolus (aspart) insulin (Insulin Therapy) to maintain HbA1c <7%. Insulin therapy was started with insulin glargine before breakfast. The starting glargine dose was calculated based upon the 4T algorithm, and the dose was adjusted weekly to achieve a FPG < 110 mg/dl. After achieving the FPG goal, if the HbA1c was >7.0%, 4-6 units of insulin aspart was started before each meal and the dose was adjusted to achieve a plasma glucose concentration at 2 hour after meals <140 mg/dl. All subjects in the Insulin Therapy arm were receiving aspart insulin at 6 months. The insulin dose (both glargine and aspart) was adjusted weekly until the desired level of glycemic control was achieved or hypoglycemic events (see definition below) were encountered. The highest insulin dose after hypoglycemic events had resolved was continued as the therapeutic dose and patients continued with their monthly follow-up visits.

After randomization, patients were seen at months 1, 2, 3, 4 and 6 or more frequently based upon the plasma glucose concentration. FPG, body weight, and HbA1c were measured at each follow-up visit and medication dose was adjusted to maintain FPG <110 mg/dl, 2h postmeal plasma glucose concentration <140 mg/dl, and HbA1c <7% unless hypoglycemia was encountered. Because the subjects were markedly hyperglycemic, the sulfonylurea dose was not reduced at the time of initiation of Insulin Therapy or Combination Therapy. Rather, it was prespecified that the sulfonylurea dose should be reduced if 3 minor hypoglycemic events occurred at 2 consecutive follow up visits.

If hypoglycemia occurred (defined as >3 events on two consecutive visits), the sulfonylurea dose was reduced (by 30 mg/day for gliclazide and by 2 mg/day for glimepiride) at each follow-up visit until the hypoglycemia resolved. If, after discontinuation of sulfonylurea, patients in the Insulin Therapy group continued to experience hypoglycemia, the insulin dose was adjusted. If hypoglycemia was encountered in the Combination Therapy group (pioglitazone plus exenatide), the sulfonylurea dose was reduced as described for the Insulin Therapy group. In no subject in either the Insulin Therapy or Combination Therapy group was the metformin dose reduced. Subjects who manifested hypoglycemia were seen weekly and medication dose was adjusted (as described above) according to home measured blood glucose values until the hypoglycemia disappeared, after which they continue with their monthly follow-up visits. Hypoglycemia was defined as blood glucose concentration < 60 mg/dl with or without symptoms or hypoglycemic symptoms that subsided following glucose ingestion. Blood glucose levels were measured by home blood glucose monitoring (One Touch) and verified by the study coordinator on each follow up visit. Subjects were asked to perform once weekly a 7-point home blood glucose profile. During each follow-up visit, FPG was measured, records of home measured glucose values were reviewed, and patients were questioned about symptoms of hypoglycemia. Severe hypoglycemia was defined as hypoglycemia requiring third party assistance.

Blood pressure and lipid lowering medications were adjusted to achieve the goals recommended by the ADA: blood pressure <140/90 mmHg and LDL cholesterol < 100 mg/dl.

Data Analysis and Statistical Analysis

The change in HbA1c from baseline to 6 months was compared in subjects receiving Combination Therapy versus Insulin Therapy. Secondary end points included: (i) percentage of subjects achieving HbA1c <6.5% and <7.0%; (ii) decrease in fasting plasma glucose concentration, (iii) change in body weight, (iv) rate of hypoglycemic events. Overall frequency of hypoglycemia was calculated as total number of hypoglycemic events divided by number of patient-years of follow-up in each arm. The percentage of subjects experiencing hypoglycemia was calculated as the number of subjects experiencing at least a single event divided by number of patients in that arm.

Values are presented as mean ± SEM. Two sided t-test was used to compare mean differences between the two treatment arms. Chi square was used to test significance of discrete variables.

RESULTS

In the QATAR Study 101 patients had a baseline HbA1c >10%. Of these, 53 patients received Combination Therapy and 48 patients received Insulin Therapy. Table 1 presents the baseline characteristics of study participants. The two groups were well matched in age, gender, BMI, disease duration and baseline HbA1c. The baseline HbA1c was 11.5±0.2 and 11.2±0.2% in the Combination Therapy and Insulin Therapy groups, respectively (P=NS).

All patients were receiving background therapy with metformin plus sulfonylurea. The mean metformin dose was 1896±50 and 1978±30 mg/day in the Combination and Insulin Therapy groups, respectively (P=NS). 58% and 55% of patients were on gliclazide and 42% and 45% of patients were on glimepiride in the Combination Therapy and Insulin Therapy groups, respectively.

At 6 months all subjects in the Insulin Therapy group were receiving insulin glargine plus insulin aspart before meals. The mean insulin dose was 45±3 units of glargine (range 22 to 110 units/day, median 48) plus 48±1 units per day (range 8 to 102 units/day, median 44 units) of aspart. Thus, patients in the Insulin Therapy group received ~1.2 units/kg of insulin per day. All subjects in the Combination Therapy group were receiving 2 mg/week of Bydureon; the mean dose of pioglitazone was 33±1 mg/day. The metformin dose at 6 months was identical to the starting dose. However, the sulfonylurea dose was reduced to avoid hypoglycemia (defined as at least 3 minor events on 2 consecutive follow-up visits). In approximately 30% (n=14) of subjects receiving insulin therapy, the sulfonylurea was discontinued (9 receiving gliclazide and 5 receiving glimepiride), and the dose was reduced in the other 70% (n=34) to 82.5±6.5 and 4.1±0.4 mg/day of gliclazide and glimepiride, respectively (starting dose was 115±2 and 7.2±0.2 mg, respectively). Similarly, at 6 months, the sulfonylurea was discontinued in 11 subjects in the combination therapy arm (5 received gliclazide and 6 received glimepiride), and the dose was reduced to 101.8±3.6 and 4.6±0.6 m/day for gliclazide and glimepiride, respectively, (starting dose113±3 and 7.4±0.2, respectively).

Figure 1A depicts the change in HbA1c over 6 months. Subjects in the Insulin Therapy group experienced a reduction in HbA1c from 11.2%±0.2 at baseline to 7.4%±0.1 (ΔHbA1c=-3.8%) at 6 months. A more robust decrease in HbA1c from 11.5±0.2% to 6.7±0.1% (ΔHbA1c=-4.8%) was achieved in subjects receiving Combination Therapy (Figure 1B). At 6 months, there was a statistically significant greater HbA1c decrement (1.0%, p<0.001) in the Combination Therapy group.

More individuals receiving Combination Therapy achieved the American Diabetes Association treatment goal (HbA1c <7.0%) at 6 months versus subjects receiving Insulin Therapy (70% versus 35%, p=0.003). Similarly, more patients achieved an HbA1c <6.5 in the Combination Therapy (53% versus 13%, p<0.0001). Combination Therapy was equally effective in lowering the HbA1c in all three ethnic groups, Qatari Nationals, Arabs Non-Qatari and Indians. The efficacy of Combination Therapy in lowering HbA1c was independent of age, gender, BMI or diabetes duration.

Fasting and Postprandial Glucose

Baseline FPG was similar in the Combination Therapy and Insulin Therapy groups (258±10 vs 264±8 mg/dl, respectively, P=NS) and decreased rapidly after starting therapy (Figure 2A) in both groups. The decrease in FPG was faster in subjects receiving Insulin Therapy than in subjects receiving Combination Therapy (Figure 2A) and at month 1 the FPG concentration was significantly lower in the Insulin Therapy group (133±6 vs 162±9, mg/dl, p<0.05). However, after 1 month, the FPG was comparable in both treatment groups. The postprandial plasma glucose concentration at 6 months was significantly higher in subjects receiving Insulin Therapy than in subjects receiving Combination Therapy. The mean incremental area under the plasma glucose concentration curve during the daily glucose measurements (7-point home blood glucose profile) in insulin treated subjects was almost twice as great as in subjects receiving combination therapy (609±35 vs 312±13, p<0.01) (Figure 2B).

Body Weight

The mean body weight increased in both treatment groups. However, subjects in the Combination Therapy group experienced half as much weight gain as subjects in the Insulin Therapy group (2.7 ± 0.5 kg versus 5.3 ± 0.6 kg, p=0.002).

Adverse Events:

In general, both treatments were well tolerated and only a small number (<5%) of patients dropped out of the study because of adverse events. Approximately 90% of patients in both groups experienced at least one adverse event (Table 2); most adverse events were mild and unrelated to study treatment. With regard to adverse events related to the study treatments, hypoglycemia was the most common, being reported by 83% and 56% of participants receiving Insulin Therapy and Combination Therapy, respectively (P<0.0001). The overall frequency of hypoglycemic events was approximately 2.5-fold greater in the Insulin Therapy versus Combination Therapy group (5.8 vs 2.1 events per patient year, p<0.0001). All hypoglycemic events were mild; no severe hypoglycemia occurred in either group. Two subjects in the Combination Therapy group experienced a local reaction at the injection site. Subjects receiving Combination Therapy experienced more frequent gastrointestinal side effects and ankle edema. 37% of Combination Therapy subjects experienced nausea at the initiation of exenatide therapy; the nausea was mild and subsided after 2-3 months. Only one patient discontinued treatment due to nausea. The incidence of peripheral edema was low, 5.6% versus 13.5% in the Insulin Therapy and Combination Therapy groups, respectively. Peripheral edema was mild in all but one case and easily controlled with the addition of a distally acting diuretic. One patient discontinued Combination Therapy because of peripheral edema. There were no cases of congestive heart failure. The number of subjects who withdrew because of adverse events was small: 2 receiving Combination Therapy and none receiving Insulin Therapy.

DISCUSSION

The major new finding of this study is that Combination Therapy with pioglitazone plus exenatide is very effective and safe in lowering the HbA1c in poorly controlled, symptomatic T2DM patients with a very high HbA1c (HbA1c>10%) and long standing (mean duration >10 years) disease treated with maximal/near maximal doses of metformin plus sulfonylurea.

The American Diabetes Association, EASD (13) and AACE (14) recommend starting T2DM patients with high baseline HbA1c (>9.0%) and patients with symptoms of hyperglycemia on insulin therapy. Previous studies have demonstrated that chronic elevation of plasma glucose concentration exerts a deleterious action on beta cell function, i.e. glucotoxicity (5-7). Thus, T2DM patients with HbA1c >10.0% have a severe impairment in beta cell function and often respond poorly to the addition of other oral agents. Insulin is a powerful antihyperglycemic agent, and it rapidly lowers the plasma glucose concentration independent of beta cell function. Further, restoration of euglycemia and reversal of glucotoxicity (9-11) and lipotoxicity (28) can lead to recovery of beta cell function. No previous study has compared the efficacy of insulin therapy with other antidiabetic regimens in patients with very high HbA1c, e.g. HbA1c >10%. To the best of our knowledge, the present study is the first to compare insulin therapy with another antidiabetic regimen in patients with a very high HbA1c and symptomatic hyperglycemia including polydipsia and nocturia (mean = 2.4 voids per night).

As anticipated, insulin produced a rapid decrease in the plasma glucose concentration and the fasting plasma glucose concentration declined to the normal range at one month after the start of therapy, resulting in a marked reduction in HbA1c. With the combination of pioglitazone plus exenatide, the decline in fasting plasma glucose concentration and HbA1c was slower than with insulin therapy (Figure 2A). This is explained by the slower onset of action of pioglitazone and the time (4-6 weeks) required to reach steady state plasma exenatide levels with Bydureon. Nonetheless, subjects receiving Combination Therapy were asymptomatic after one month. At month 2 the reductions in FPG concentration and HbA1c were similar in the Combination and Insulin Therapy groups and at month 3, 4, and 6 the reduction in HbA1c was significantly greater in subjects receiving Combination Therapy (Figure 1A). At month 6 the decrease in HbA1c from baseline in subjects receiving Combination Therapy (-4.8%) was significantly greater than ($p<0.001$) that in subjects treated with Insulin (-3.8%). More subjects receiving Combination Therapy achieved the ADA treatment goal of HbA1c <7.0% (70% vs 35%, $p<0.001$) with significantly less hypoglycemia. It should be noted that, subjects in both treatment arms, despite very poor initial glycemic control (HbA1c >10%), experienced very good glycemic control at 6 months. These results demonstrate that Combination Therapy with exenatide plus pioglitazone is very effective therapeutic option for poorly controlled T2DM patients with very high HbA1c (e.g. HbA1c >10%).

Despite a significantly lower HbA1c at 6 months the Combination Therapy group experienced significantly lower rate of hypoglycemia 2.1 vs 5.8 events per patient per year ($p<0.001$). Reducing the sulfonylurea dose in the Combination Therapy group significantly decreased/eliminated the incidence of hypoglycemia. It should be noted that the sulfonylurea dose was reduced similarly in both treatment groups to avoid hypoglycemia. Nonetheless, subjects in the Insulin Therapy group experienced a 2.5-fold greater incidence of hypoglycemia which impeded further escalation of the insulin dose. It is possible that sulfonylurea has contributed to the high hypoglycemia rate in subjects receiving insulin therapy, and if sulfonylurea would have been stopped at randomization in all subjects receiving insulin therapy, lower rate of hypoglycemia was achieved. However, in such scenario, higher insulin dose would

have been required to achieve the same level of glycemic control. It should be noted that the mean FPG concentration in insulin treated subjects reached the target (110 mg/dl) at about 2 months, documenting the rigorous insulin intensification schedule. Nonetheless the glycemic goal (HbA1c<7.0%) was achieved in only one third (35%) of the patients.

Other studies (29-33) have utilized different insulin titration algorithms for initiation of insulin therapy in T2DM patients and reduced the mean HbA1c to <7.0%. However, higher rates of hypoglycemia were observed in these studies. For example, the target HbA1c for the intensive treatment arm in the ACCORD study (33) was 6.5%, and 25% of participants experienced severe hypoglycemia and 10% required medical assistance to manage the hypoglycemia. Similarly, large portion of patients in the studies by Edelman et al (31) and Bergenstal et al (32) experienced nocturnal hypoglycemia. Because the risk of hypoglycemia increases with the decrease in HbA1c, the caring physician always has to weigh risk of hypoglycemia versus the benefit of further HbA1c reduction. In the present study, we prespecified the threshold for hypoglycemia at 3 minor events on 2 consecutive visits to minimize the risk of hypoglycemia and, indeed, the incidence of hypoglycemia in both treatment arms was relatively low compared to other studies which utilized intensive insulin therapy. Nonetheless, despite a very high starting HbA1c (~11.5%) the vast majority of patients in both treatment arms achieved the ADA glycemic target (HbA1c < 7.0%) or had their HbA1c decreased close to the target at 6 months, demonstrating that both treatment regimens (intensive basal/bolus insulin) and combination therapy with exenatide plus pioglitazone safely can be utilized in symptomatic T2DM patients with a very high HbA1c (e.g. >10.0%).

In the present study, we utilized the algorithm developed by 4-T study investigators (30) to initiate insulin therapy and unlike the 4-T study, subjects in the present study injected insulin glargine in the morning. It is possible that the timing of insulin injection in the present study have contributed to the increased rate of hypoglycemia in the insulin arm compared to combination therapy arm. However, previous study (29) has demonstrated that morning dosing of glargine is associated with lower risk of hypoglycemia that bedtime.

Subjects receiving Combination Therapy experienced half as much weight gain compared to subjects receiving Insulin Therapy (2.7 vs 5.3 kg). Although pioglitazone therapy resulted in weight gain on mean, approximately one third (29%) of patients receiving Combination Therapy experienced weight loss compared to only 2% ($p<0.01$) in the Insulin Therapy group. This most likely is explained by the concomitant use of exenatide which suppresses the appetite and promotes weight loss (15, 16, 19). It also should be noted that with pioglitazone, the greater is the weight gain, the greater are the improvements in HbA1c, insulin sensitivity, and beta cell function (24). The marked improvement in glycemic control and the removal of glucosuria also could have contributed to the weight gain in both treatment groups.

Both treatments were well tolerated and few subjects (<5% in Combination Therapy; 0% in Insulin Therapy) withdrew because of adverse events. The majority of adverse events were mild and unrelated to study treatment. Hypoglycemia was the most common adverse event. Compared to other studies which have employed intensive insulin therapy in T2DM (24-26), the rate of hypoglycemia rate was relatively low (Table 2). The relatively low rate of peripheral edema (Table 2) with Combination Therapy most likely is explained by the lower dose of pioglitazone (30 mg/day) utilized in the present study and the natriuretic effect of exenatide. The majority of cases of edema were mild and the edema was easily controlled with addition of a distally acting diuretic to the treatment regimen. Only 1 subjects discontinued Combination

Therapy because of ankle edema. No cases of congestive heart failure or fractures occurred in either group.

There are several limitations to the present study. The therapies employed (weekly exenatide and multiple daily insulin injections) prohibited blinding of the study medications. The study included a relatively small number of participants, primarily of Arab origin (~70% of participants). Thus, a larger multiethnic study is warranted to examine the generalizability of this novel treatment approach in poorly controlled individuals with long standing T2DM. Further, longer follow-up is required to determine the durability of glycemic control achieved in the Combination Therapy. Nonetheless, the present results are impressive and, contrary to standard dogma, demonstrate that, even in very poorly controlled (HbA1c >10%), long standing T2DM individuals, combination therapy with a GLP-1 RA plus pioglitazone can achieve near normal/normal HbA1c levels. Therefore, this combination can provide an alternative therapeutic option in addition to insulin in very poorly controlled T2DM patients without the need of multiple daily injections and dose titration, and with lower risk of weight gain and hypoglycemia.

In summary, the present results demonstrate that Combination Therapy with pioglitazone plus exenatide is a very effective and safe therapeutic option in poorly controlled T2DM patients with clinical symptoms of hyperglycemia and long standing disease who have failed on metformin plus sulfonylurea. Continued follow up will be required to ascertain how long the beneficial effects of Combination Therapy are maintained.

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Corresponding Author: Muhammad Abdul-Ghani, Diabetes Research, Academic Health System, PO Box 3050, Hamad General Hospital, Doha, Qatar, Phone: 974-4439 1208, abdulghani@uthscsa.edu

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Contributions of Authors:

OM and AM generated the data. M.A.G designed the study, wrote the protocol, contributed to data generation and data analysis, and wrote the manuscript. R.A.D, M.Z., and A.J. reviewed and revised the manuscript.

M.A.G is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest Statement:

RAD - Advisory Board: Astra Zeneca, Novo Nordisk, Janssen, Intarcia, Boehringer-Ingelheim; Research Support: Bristol Myers Squibb, Boehringer-Ingelheim, Takeda, Astra Zeneca; Speaker's Bureau: Novo-Nordisk, Astra Zeneca. Other authors have no conflict of interest

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Figure 1: Effect of Combination Therapy and Insulin Therapy on glycemic control. **Figure 1A:** time-related change in HbA1c in subjects receiving Combination Therapy and Insulin Therapy. **Figure 1B** the change in HbA1c from baseline to 6 months in each treatment group

Figure 2: Effect of Combination Therapy and Insulin Therapy on plasma glucose concentration. Figure 2A depicts the change over time in the fasting plasma glucose concentration in both treatment arms. Figure 2B depicts the 7-point home blood glucose profile at 6 months in the Insulin Therapy and Combination Therapy groups. FBG = fasting blood glucose; AB = after breakfast; BL = before lunch; AL= after lunch; BS = before supper; AS = after supper; BT = bed time.

Figure 3: Effect of Combination Therapy and Insulin Therapy on body weight

Figure 4: Incidence of hypoglycemia in subjects receiving Combination Therapy and Insulin Therapy

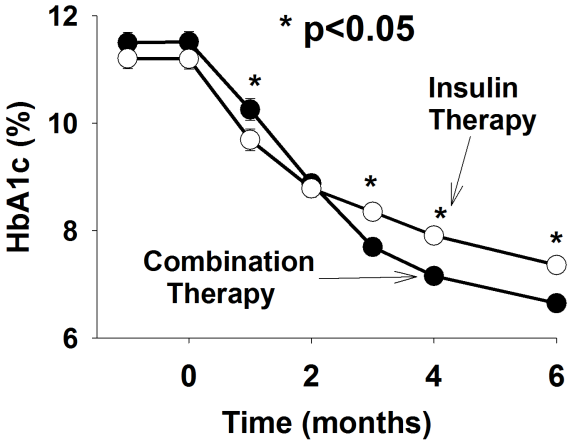
Table 1: Baseline characteristics of the study participants

	Combination Therapy	Insulin Therapy	P-Value
Number	53	48	
Age (years)	50±1	52±1	NS
Gender (% male)	40	37	NS
BMI (kg/m^2)	31.3±0.9	29.7±0.8	NS
Diabetes Duration (years)	10.6±0.7	11.4±0.8	NS
HbA1c (%)	11.5±0.2	11.2±0.2	NS
FPG (mg/dl)	258±10	264±8	NS
Blood Pressure (mmHg)	126/74	129/73	NS
LDL Cholesterol (mg/dl)	105±3____	106±3____	NS
Ethnicity (%)			
Qataris	48	39	NS
Non-Qatari Arabs	26	29	NS
Asian Indians	17	25	NS
Others	9	7	NS
Background Therapy			
Metformin, mg (% of patients)	1896±50 (100)	1978±30 (100)	NS
Gliclazide, mg (% of patients)	113±3 (58)	115±0.2 (55)	NS
Glimepiride mg (% of patients)	7.4±0.2 (42)	7.2±0.2 (45)	NS

Table 2: Adverse Events (AE)

	Combination Therapy	Insulin Therapy	P-Value
Any AE (% of patients)	87	91	NS
Therapy Related AEs			
Hypoglycemia			
% of patients	56	83	<0.0001
Incidence rate (events/patient year)	2.1	5.8	<0.0001
Severe hypoglycemia (n)	0	0	
Ankle edema (%)	13.5	5.6	<0.01
Injection site reaction (%)	2	0	
Gastrointestinal (%)	37	9	<0.0001
Discontinue Due to AE	2	0	
Serious AEs			
CV events (n)	0	1	
Cancer (n)	0	1	
Fractures (n)	0	0	
Deaths (n)	0	0	

1A



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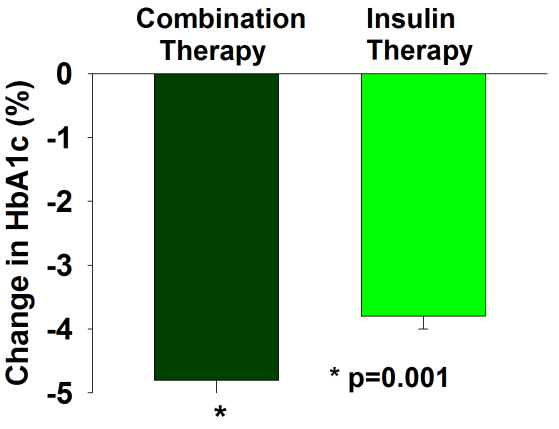

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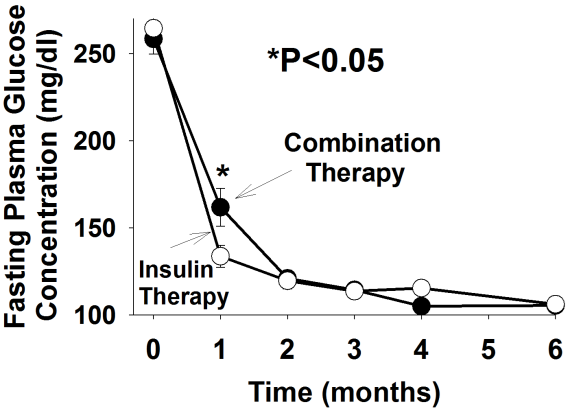

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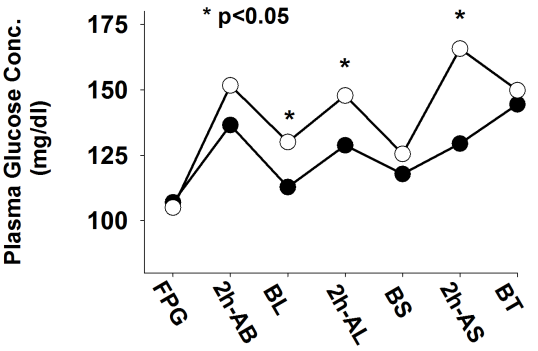

Figure 3

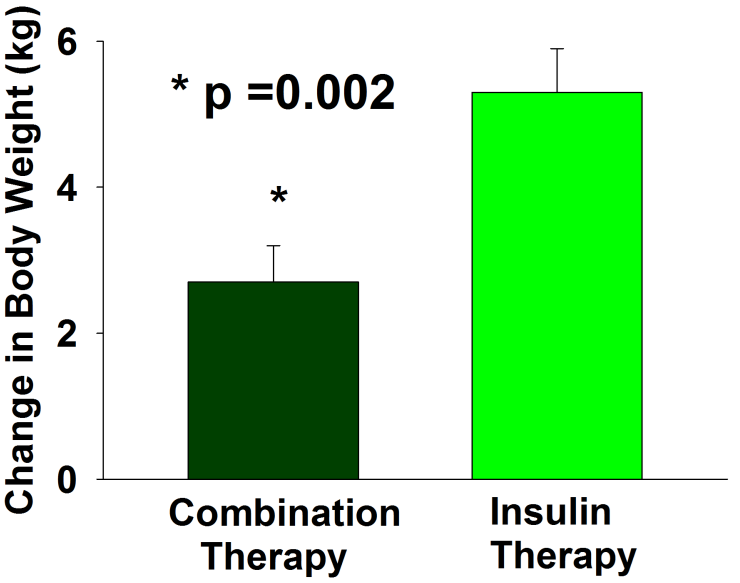

Figure 4