Implication of Insulin Therapy Initiation (Jusline®) in Type II Diabetes Mellitus Patients Who Fail to Achieve Euglycemia with Oral Antidiabetic Drugs

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Background: Diabetes mellitus is one of the biggest health catastrophes in the world. Its management depends on the patient’s lifestyle and the physician’s experience. Outcomes with oral antidiabetic drugs (OADs) alone are suboptimal. As disease progresses and cell function deteriorates, insulin initiation may be necessary for glycaemic control. Thus, the purpose of this study was to assess the Implication of Insulin Therapy Initiation (Jusline®) in Type II Diabes Mellitus Patients who fail to achieve Euglycemia with Oral Antidiabetic Drugs.

Methods: This is a prospective, open label, single arm study. Patients with type II diabetes with HbA1c > 8%, on OADs for more than 6 months, with minimum 3 months of double complementary synergistic OADs were recruited. Insulin dose was individualized to achieve glycemic control as defined by the ADA.

Results: 51 patients (20M/31F) with ages ranging from 32-80 years were enrolled. Majority (42.9%) were on Metformin HCl & Glyburide therapy before enrollment. Out of the 51 patients, 33.3% were on single night dose of average 13 ± 4.8 units of Insulin-N. HbA1c dropped significantly from 10.5 ± 2.1 to 7.9 ± 1.2 (p<0.0001); its percent change ranged between 0.8% to 65% with an average of 23.7% ± 14.0 and a median of 19.7%; after 84 days.

Conclusion: Euglycemia was achieved in 29.4% of patients with no serious side effects. Therefore, initiation of insulin therapy should not be delayed in primary care practice as it facilitates stringent glycemic control and offers promise to change the pharmacological treatment of type II diabetes mellitus.

Keywords: Type 2 diabetes mellitus; Insulin therapy; Hyperglycemia; Jusline; Middle-East.

1. INTRODUCTION

The Diabetes is rapidly emerging at an alarming rate and is considered to be one of the biggest health catastrophes in the world ¹, causing significant health and economic burdens on patients and communities ². More than 220 million people worldwide were diagnosed with diabetes; type II diabetes comprises 90% of such cases ³. These patients are getting...
older and the age of people being diagnosed is declining rapidly. The prevalence of diabetes in the Eastern Mediterranean region in year 2000 was more than 15 million and is estimated to reach more than 42 million by the year 2030 (WHO, 2011). The International Diabetes Federation estimates direct costs of diabetes of economically developed countries to be approximately 6% of the total health budget. Type II diabetes is highly inconsistent in presentation and management. Its therapy depends greatly on the patient's lifestyle and the physicians experience in identifying the right combination of pharmacological interventions and proper lifestyle. Management and treatment of type II diabetes is mainly aimed at glycaemic control and international guidelines recommend reducing glycated hemoglobin (HbA1c) to 6.5–7%. Lowering blood glucose levels is the main factor in the prevention of microvascular complications. Every percentage point decrease in HbA1c, reduces the risk of microvascular complications by 35% and every 10% reduction in HbA1c is associated with 21% reduction in cardiovascular disease. Type II diabetes patients are often maintained in poor glycaemic control for prolonged periods and are associated with an increase in the risk of microvascular complications which may be life-threatening and costly to treat.

The management of many type II diabetic patients with Oral Antidiabetic Drugs (OADs) alone is insufficient. Guidelines recommend that patients are candidates for insulin therapy if they are unable to achieve glycaemic targets with maximum doses of OADs. The traditional approach, in which insulin was an agent of last choice, is being replaced by a more progressive approach. Researchers have shown that failure to achieve glycaemic targets eventually happens in the lack of insulin initiation and this will enormously increase the number of patients who will require insulin therapy. The American Diabetes Association (ADA) algorithm for treatment of type II diabetes recommends the initiation or intensification of insulin therapy, based on effectiveness and expense, if the target HbA1c of 7% is not achieved within 3 months treatment with Metformin in combination with lifestyle interventions. The American College of Endocrinology and American Association of Clinical Endocrinologists (AACE) agreed that insulin is a surrogate initial treatment in insulin-naive patients.

Much evidence based on research in animal models and patients with diabetes indicates that insulin therapy can aid to correct insulin resistance, impaired insulin secretion, and reduce hyperglycemia. Short-term insulin therapy was found to result in a long-term improvement in blood glucose control, particularly when administered in the earliest stages of diabetes. In a retrospective, population-based study, the time between OAD treatment and the initiation of insulin therapy was investigated among Swedish patients. Many type II diabetic patients who began treatment with an OAD eventually received insulin. Age, disease severity and the type of prior treatment was found to affect the rate of the transition. With reference to these observations, diabetes experts have supported initiating intensive insulin therapy early in the course of type II diabetes, or immediately after a diet and exercise regimen failure, in the effort to protect remaining β-cell function and improve long-term glycaemic control.

The effectiveness of insulin either as monotherapy or in combination with OAD is well-established. A treatment with a combination of insulin and metformin alone proved more cost-effective than triple OAD therapy of sulfonylurea, metformin and thiazolidinedione. According to epidemiologic data in 1997 and 2002 the percentage of people with diabetes achieving glycaemic control declined from 44.5% to 35.8%. The percentage of patients using insulin injections alone decreased from 24.2% to 16.4%, and the use of insulin in conjunction with oral OADs increased from 3.1% to 11.0% (NHANES III, 1998; NHANES, 2011). The increasing use of insulin with oral agents could be a proof of a trend toward more intensive treatment, but more than two thirds of adults with type II diabetes failed to achieve glycaemic control. The extensive decrease in glycaemic control which may be an outcome of insufficient management of oral drug therapy and delayed initiation of insulin therapy is of particular concern as it is inconsistent with reductions achieved for many indicators of long-term complications, such as blood pressure and cholesterol.

Insulin initiation or replacement is normal and healthy. It is essential prior to multiple organ failures that may occur in cardiac, cerebral, renal, pancreatic, retinal, and peripheral vascular systems. Hence, the main objective of the study was to assess the ‘Implication of Insulin Therapy Initiation (Jusline®) in Type II Diabetes Mellitus Patients who fail to achieve Euglycemia with Oral Antidiabetic Drugs’.

2. METHODS

The study was conducted in coherence with the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP). The study protocol was approved by Independent Ethics Committee (IEC) and Institutional Review Board (IRB) of the American University of Beirut Medical Center (AUBMC). The IEC/IRB of the AUBMC complies with the membership requirements defined in the United States code of Federal regulation (21CFR56 and 45CFR46) of the Food and Drug Administration and operates in a manner consistent with the ICH guidelines and in compliance with the legal country regulations.

a. Study design and patients

We undertook an open label, prospective and single arm study between March 2007 and June 2008 in AUBMC. Patients between 18 to 80 years of age, with body mass index 18.50 kg/m², diagnosed with type II diabetes for more than 1 year, on oral hypoglycemic for more than 6 months, finished at least 3 months since starting double
complementary synergistic oral hypoglycemic therapy with A1c ≥ 8%; were recruited. Additionally, it was taken into consideration that all patients were medically stable for the last 3 months, able to communicate, cooperate with the investigator and were prepared to start insulin therapy with no fear of injection.

Patients with S. creatinine > 1.8 mg/dl or AST > 2.5 times above the upper normal limit, with history of narcotic or alcohol abuse, and mental incapacity; were excluded from the study. Women who were pregnant, lactating, and sexually active, not on contraceptive methods or in preconception care period were also not enrolled.

b. Study medication and treatment
Jusline® R, N and 30/70 vials from Julphar - Gulf Pharmaceutical Industries Jusline® N consists of human insulin (rDNA origin) isophane suspension, Jusline® R regular insulin human injection (rDNA origin) consists of zinc-insulin crystals and Jusline® 30/70 insulin human (rDNA) consists of 30% as soluble insulin and 70% as isophane insulin.

Jusline®’s dose R, N and 30/70 was individualized as per the physician judgment and was pursued to the maximum as recommended to achieve euglycemia defined by the ADA as: Fasting Plasma Glucose (FPG) 80-120mg/dl, 2h- Post Prandial Glucose (PPG) less than or equal to 180 mg/dl and HbA1c less than or equal to 7%. Adjustment to the dose was done if FPG is less than 80mg/dl or more than 130 mg/dl, bed time Self Monitoring Blood Glucose (SMBG) is less than 100mg/dl or more than 160mg/dl and dose adjustment did not exceed 10% of the last dose and was done on alternative days only.

Procedures
During the screening visit, patients were screened for fulfillment of the inclusion and exclusion criteria and written informed consent was obtained. After screening, a diet plan and diary sheet was provided. Following which subjects were asked to attend at the diabetic clinic before their Jusline® morning dose timing. The investigator assessed the patient’s diary sheet, educated them thoroughly about Insulin storage, dosing and regimen, gave them the first dose and supplied them with Insulin dosage according to the decided regimen plan. The diabetic educator followed-up the patient’s general condition, SMBG readings and compliance on days 1, 35, 49, 63 and 77, by telephone.

Subjects were asked to attend the diabetic clinic on days 3, 7, 14, 21, 28, 42, 56 and 70 before the Insulin morning dose timing. The investigator assessed the patients compliance to study medication, diary sheet, vital signs, FPG, PPG, recorded any adverse events, and all concomitant medications with dosage, regimen and their compliance. The investigator gave the patient Insulin injection and checked for dosage sufficiency until the next visit.

On day 84 subjects were asked to attend the diabetic clinic before Insulin morning dosage timing. The investigator assessed the patients diary sheet, compliance to study medication, and vital signs; performed the laboratory analyses (FPG, PPG, A1c, CBC, lipid profile, RFT, LFT, serum electrolytes, and urine analyses); recorded all adverse events, and concomitant medications. Morning Insulin dose was given and the study was terminated.

a. Concomitant medication and diet
Oral hypoglycemic drugs were listed with dose, frequency and daily compliance. Patients on salicylates, steroids, sulfa drugs, birth control pills, thyroid, and depression medications were carefully monitored.

Special individualized diabetic diet was prepared by the physician and patient’s adherence to it was monitored. Alcohol was prohibited throughout the study period. Patients were engaged in normal activity for the 84 days, avoiding both vigorous exertion and complete rest.

b. Parameters
Efficacy and safety parameters were measured. Efficacy measures included HbA1c % change between baseline and day 84, and number of patients (%) achieving euglycemia.

Safety measures included vital signs, CBC (Hb, RBC count, WBC count and platelet count), liver function test (total protein, albumin, bilirubin, AST, ALT, and Alk. Ph), renal function test (S. creatinine, urea, and uric acid), serum electrolyte (K, Na, and Cl), lipid profile (TC, LDL, HDL and TG), urine analysis (protein, microalbumin/ creatinine ratio, glucose, hemoglobin, urobilinogen, acetone, pH and specific gravity), and adverse events. Adverse events were evaluated as time and date of onset, intensity (mild, moderate and severe), seriousness, and relationship to the study material (related, probably related, possibly related, not related or unknown) or other factors.

The following adverse events were monitored:
- Hypoglycemic event frequency (blood glucose below 50 mg/dl with or without symptoms) and were classified into major event when patient needed assistant to get over it or minor event when patient needed no assistant and self-management was sufficient to take over it.

Event timing was specified as 6 am - 12 noon, 12 noon - 6 pm, 6 pm - 12 midnight and 12 midnight - 6 am. Symptoms recorded were tachycardia, sweating, trembling, hunger pain, anxiety, clouding of vision, loss of fine motor skills, combativeness seizure, mental confusion and loss of consciousness.

- Other adverse events were depression, anxiety, headache, trouble in concentration, increased sweating, skin rash, injection site redness, pain, itching, swelling, and insomnia.

c. Endpoints
The primary endpoint was after 12 weeks when all efficacy and safety parameters were assessed for the test medication. The secondary endpoint was after 6 weeks if the patient failed to show adequate response to reach glycaemic goals, or patient’s withdrawal due to one of the following reasons:

- Any two consecutive SMBG readings of FPG more than 300mg/dl despite aggressive dose increment.
### 3. RESULTS

Fifty-one patients (20 males and 31 females) were enrolled during the 15 months period, with ages ranging from (32-80) years and BMI average of 28.8 ± 4.2. None of the patients were hospitalized. Of the total population, majority 84.3% (n=43) were Lebanese, 72.5% (n=37) were Caucasian and 10% (n=5) were oriental. Thirty-seven patients (72.6%) had positive diabetic family history. The duration since diagnosis as type II diabetes mellitus till enrollment ranged between 18 months to 15 years with an average of 5.9 ± 2.9 years. Thirty patients (58.8%) suffered from hypertension since 5 months to 27 years with an average of 4.7 ± 4.4 and median of 3 years. The percentage of patients treated with β-adrenergic blockers, Ca-channel blockers, ACE inhibitors, Angiotensin II receptor antagonist with thiazide and ACE inhibitors with thiazide were 36.6%, 16.6%, 13.3%, 13.3% and 6.6% respectively. Fifteen patients (29.4%) suffered from dyslipidaemia. The most common oral hypoglycemic therapy used before starting Insulin was a combination of (Metformin HCl + Glyburide) in 42.9% (n=21), then (Metformin HCl + Gliclazide) and (Metformin HCl + Glyburide + Rosiglitazone maleate) in 8.2% (n=4), while the common single oral hypoglycemic therapy was Gliclazide in 61% (n=3). The most common complications among the patients were neuropathy in 39.2% (n=20), nephropathy in 21.6% (n=11), retinopathy 17.7% (n=9) and peripheral vascular disease (PVD) in 11.8% (n=6). The most common combined complication was neuropathy- PVD in 9.8% (n=5), while the solo complication was neuropathy in 19.6% (n=10). All 51 patients were on individualized special diabetic low calorie diet, and their average body weight (73 kg) remained stable throughout the study period. Compliance to Insulin ranged between 40-100%, with an individual patient average of 99.4 ± 2.3% with a range of 88-100%. Out of the 51 patients, 33.3% (n=17) were on single night dose averaging to 13 ± 4.8 units of Insulin-N and ranged between 6-28 units, 64.7% (n=33) were on fixed regimen, 19.6% (n=10) took their single formula doses at different timings, while 15.7% (n=8) were given both Insulin-N and 30/70 formulation. Insulin dosages varied with average difference of individual dose between starting and ending point of 11.6 ± 9.4 and range of 0-36 units (Table 1). The site of the injection was changed in 74.5% (n=38) patients, and it was mainly resting thigh, abdomen and arm for 62%, 31% and 7% respectively throughout the study period.

#### a. Concomitant medications:
Concomitant oral hypoglycemic were used during the study period in 88.2% (n=45) patients, as Glyburide + Metformin HCl in 51.1% (n=23), Metformin HCl in 48.9% (n=22), Gliclazide in 15.6% (n=7), and/ or Glimepiride in 13.3% (n=6). Antihyperlipidemic drugs were used by 33.3% (n=17) of patients, divided between HMG-CoA Reductase Inhibitor (n=13) and Fibric acid (n=4). Aspirin was taken by 25.5% (n=13) patients.

#### b. Safety and Efficacy Parameters:
There were no significant changes noticed in vital signs readings throughout the study assessment days (screening, 0, 3, 7, 14, 21, 28, 42, 56, 70 and 84), except for the respiratory rate that dropped per minute from average of 13.1 ± 1.7 at screening to 12.3 ± 0.7 at the study end. The blood hemoglobin, platelets, white and red blood cells count were insignificantly changed during the 84 days study period. Similarly, the liver and renal function tests including electrolytes were stable except serum chloride that increased from 100.0 ± 3.7 to 101.8 ± 3.1 mmol/L (p=0.01). Lipid profile dropped significantly during the study period as total cholesterol dropped from 5.0 ± 1.3 to 4.5 ± 0.9 mmol/L (p=0.02) as well as LDL (p=0.04) and triglyceride (p=0.006). Urine analysis showed no significant change in hemoglobin, urobilinogen, acetone, protein, pH, and microalbumin/creatinine ratio, while there was significant reduction (P<0.05) in specific gravity and number of patients with positive glucose in urine.

Six patients (11.8%) had episodes of hypoglycemia in the morning and 2 (3.9%) at night, out of which 2 and 1 patients had more than one episode respectively, throughout the study period. All episodes were classified as asymptomatic minor and self management was sufficient to get over them. The underlying cause was defined as non adherence to diet plan. Two patients showed high diastolic blood pressure (>90 mmHg) more than once during the study period with no previous history of being hypertensive, one was given medical treatment (ACE inhibitor) only, while both were
advised for exercise. No dramatic changes were noticed in patient’s hypertensive therapy regimens and dosages. Moreover, 3.9% (n=2) developed mild tremor that lasted for few minutes, one had dizziness that lasted for seconds, one had mild upper respiratory infection, and one suffered from redness and tenderness at the injection site. All recorded adverse event were determined as unrelated to the tested drug (Jusline®).

Fasting blood sugar and HbA1c dropped significantly from 211.9 ± 80 to 143 ± 54.6 and 10.5 ± 2.1 to 7.9 ± 1.2 respectively by the end of the study period (p<0.0001). The percent change of HbA1c ranged between 0.8% to 65% with average of 23.7% ± 14.0 and a median of 19.7% (Figure 1). Similarly FBS dropped significantly (p<0.0001) from 211.9 ± 80.0 to 143.0 ± 54.6 mg/dl and the 2 hours PPG from 187.5 ± 46.3 to 152.4 ± 54.0 mg/dl by the end of the study period (Figure 2). Fifteen patients (29.4%) achieved euglycemia as per the ADA definition by the end of the study.

c. Dropout and withdrawal:
During the last month of the study, 4 (7.8%) out of 51 patients were lost to follow-up and one patient was withdrawn due to recurrent hypoglycemic attacks caused by patient’s non compliance to the diet plan; nevertheless they were all included in efficacy and safety analysis.

4. DISCUSSION
Normalizing blood glucose and achieving HbA1c target levels are important for the prevention of vascular complications. Despite the variety of available antidiabetic medications and methods of assessing disease progression, most patients with type II diabetes mellitus develop these complications. Many patients will require intensive insulin regimen to achieve euglycemia. Designing an insulin regimen depends greatly on the degree of impairment in insulin secretion, the degree of insulin resistance, and the patient’s compliance to intensified insulin therapy. With the exception of insulin; all diabetes medications have limited glucose lowering capacity. Therefore, many patients with type II diabetes will eventually need insulin therapy because of progressive β-cell dysfunction. The primary objectives of insulin therapy are to achieve the best glycaemic control with the lowest rate of hypoglycaemia and the least weight gain.

Options available for treatment of type II diabetes include sulfonylureas, metformin, glinides, thiazolidinediones (glitazones), a-glucosidase inhibitors, glucagon-like peptide-1 analogues (incretin mimetics), amylin mimetics, and dipeptidyl peptidase-IV inhibitors, however, the most common OAD combination is metformin with a sulfonylurea as noted in our study. OADs are more likely to be effective as initial therapy in patients diagnosed early after diabetes onset, whereas patients diagnosed many years after onset may require the prompt addition of insulin.

In our study we evaluated the implications of insulin therapy initiation in patients who failed to achieve euglycemia with OADs for more than a year. These patients after being treated with OAD for more than 6 months, failed to achieve reduction of their HbA1c % below 8 even in a double complementary synergistic 3 months course.

We followed the current ADA guidelines in our practice for achieving glycaemic control, with emphasis on when and how insulin should be initiated and intensified and how to overcome barriers to insulin initiation.

By day 84 of the study, the HbA1c dropped significantly from 10.5 ± 2.1 to 7.9 ± 1.2 (p<0.0001), and the percent change of HbA1c ranged between 0.8% to 65% with average of 23.7% ± 14.0 and a median of 19.7%. This result is considered clinically significant success, as 29.4% (n=15) of patients achieved euglycemia as per the ADA definition by the study end with no Insulin related side effects other than minor hypoglycemia episodes defined to be due to non-adherence to the diet plan. This shows the importance of integrating improved insulin therapies into clinical practice to help more patients reach their glycaemic goals safely.

The study also demonstrated that adding Insulin to an OAD in insulin naïve patients with type II diabetes was found to reduce the incidence of nocturnal hypoglycemia as well as overall hypoglycaemia which is consistent with the findings from other clinical trials. Similar studies assessing the effectiveness of combining insulin (basal) with OADs, compared with conventional insulin therapy, for the treatment of patients with type II diabetes mellitus not adequately controlled by OADs showed similar results.

Diabetes burden on patients and communities is a growing problem that should be tackled by both early and aggressive treatment with insulin therapy to avoid excessive glycaemic exposure complications and achieve a near normal glycaemic target. Evidence from various clinical trials suggests that insulin therapy not only leads to symptomatic improvements, but also helped correct the underlying pathogenetic mechanisms responsible for type II diabetes (insulin resistance and impaired insulin secretion). Insulin therapy greatly improved insulin secretion by reducing hyperglycemia.

Research evidence has shown that insulin protects islets from apoptosis and may even augment cell regeneration. Short-term insulin therapy appears to result in long-term improvement in blood-glucose control, especially when administered in the earliest stages of diabetes. A review article proved that continuing metformin and/or sulphonylurea at the start of therapy with a long-acting insulin results in better glycaemic control with less insulin requirements, less weight gain and less hypoglycaemic events. And it seems evident that the start of insulin therapy should not mean the discontinuation of at least metformin.

In a survey conducted to investigate 505 Primary Care Physicians (PCPs), practicing in USA, beliefs about insulin initiation in patients with type II diabetes, showed that most
PCPs agreed that patients felt much better after they started insulin therapy and that patients were able to handle the demands of insulin. They also agreed that patients were satisfied and adherent to insulin therapy. Nearly all PCPs agreed education is the key to insulin initiation and that can be applied to patients in the Middle Eastern countries. Certainly, one of the largest obstacles concerning the initiation of insulin is to conquer patients’ fears and misconceptions regarding insulin use. Preconceived patient perceptions regarding injection pain, weight gain, regimen complexity and its impact on quality of life, and the risks and consequences of hypoglycemia often hinder successful initiation of therapy. For patients with type II diabetes mellitus every effort should be made to overcome these obstacles to continue achieving the targeted HbA1c% goals.

Table 1: Jusline dose (n=51)

<table>
<thead>
<tr>
<th>Formula</th>
<th>Regimen</th>
<th>N</th>
<th>%</th>
<th>Dose mean ±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>N - Jusline</td>
<td>Single night</td>
<td>17</td>
<td>33.3</td>
<td>13 ±4.8</td>
<td>6-28</td>
</tr>
<tr>
<td></td>
<td>Single day</td>
<td>8</td>
<td>15.7</td>
<td>14 ±5.7</td>
<td>8-30</td>
</tr>
<tr>
<td></td>
<td>Dual (day + night)</td>
<td>1</td>
<td>2</td>
<td>Day: 18 ±7.6</td>
<td>10-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Night: 19 ±7.4</td>
<td>10-35</td>
</tr>
<tr>
<td>30/70 Jusline</td>
<td>Dual (day + night)</td>
<td>7</td>
<td>13.7</td>
<td>Day: 30 ±13.2</td>
<td>10-50</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Night: 25 ±10.2</td>
<td>6-40</td>
</tr>
<tr>
<td>N - Jusline</td>
<td>Single day to Dual</td>
<td>4</td>
<td>7.8</td>
<td>-</td>
<td>4-25</td>
</tr>
<tr>
<td>N to 30/70 Jusline</td>
<td>Single night</td>
<td>3</td>
<td>5.9</td>
<td>-</td>
<td>7-13</td>
</tr>
<tr>
<td>N to 30/70 Jusline</td>
<td>Dual</td>
<td>2</td>
<td>3.9</td>
<td>-</td>
<td>8-38</td>
</tr>
<tr>
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<td>Single day to night</td>
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<td>3.9</td>
<td>-</td>
<td>5-34</td>
</tr>
<tr>
<td>N - Jusline</td>
<td>Others</td>
<td>4</td>
<td>7.8</td>
<td>-</td>
<td>4-20</td>
</tr>
<tr>
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<td>Others</td>
<td>3</td>
<td>5.9</td>
<td>-</td>
<td>8-50</td>
</tr>
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</table>

5. CONCLUSION

Our study showed that Insulin proved its efficacy by significantly reducing HbA1c from 10.5 ± 2.1 to 7.9 ± 1.2 (P < 0.0001). Euglycemia as per the ADA definition was achieved by 29.4% of the patients. Thus, initiation of insulin therapy should not be delayed in primary care practice. Jusline®, generic insulin of today, facilitates stringent glycaemic control and offers promise to essentially change the pharmacological treatment of type II diabetes mellitus.

6. REFERENCES


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