ORIGINAL ARTICLE

Early Intensified Insulin Therapy in Newly Diagnosed Type 2 Diabetes Leads to Sustained Improvement in Glycemic Control and Improved Beta Cell Function

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Abstract

Aim: Type 2 diabetes (T2D) is a progressive disease characterized by relentless deterioration of pancreatic β-cell function. Traditionally, insulin is used in later stages of T2DM. This study looks at use of insulin at time of diagnosis of T2DM and its effect on glycemic control and beta cell function.

Methods: This is a prospective observational study conducted in symptomatic newly diagnosed type 2 diabetes adults (>18 years) who presented with glycated hemoglobin (A1C) levels > 9%. For the initial 8 weeks, patients were treated with pre-mix insulin after which they were changed over to oral agents, and followed up for next three years.

Results: Amongst 122 study participants, who completed the study, 50% were female and 90% were from rural areas. Average age of participants was 51.4 ± 9.6 years. Baseline mean fasting plasma glucose (FPG), post prandial plasma glucose (PPPG) and A1C were 267 ± 76 mg/dl, 408 ± 101 mg/dl and 11.5 ± 1.4% respectively. At the end of insulin therapy (8 weeks), the mean FPG, PPG and A1C reduced to 107 ± 10 mg/dl, 145 ± 24 mg/dl and 7.3 ± 0.8% respectively all of which were highly significant. The mean post-prandial C-peptide significantly increased from 1.8± 0.6 to 2.8± 0.9 ng/dl. An average of 1.7 kg weight gain and 0.97 episodes of mild to moderate hypoglycemia were observed. At the end of study (156 weeks), the mean FPG, PPG and A1C were 99 ± 14 mg/dl, 152 ± 12 mg/dl and 6.7 ± 0.4%.

Conclusion: Early insulin therapy in treatment naïve patients with type 2 diabetes results in rapid improvement of glycaemia thus helps to maintain long term normoglycemia and improves β-cell function.

Introduction

Diabetes mellitus currently affects 69 million people in India and this number is expected to rise to 109 million by 2030.[1] Moreover, the age at onset of T2D is decreasing. The shift of age at onset of diabetes at younger ages means that their chances of developing complications at middle age are substantially higher.

The primary objective of treatment of type 2 diabetes (T2DM) is to achieve and maintain good glycemic control in order to minimize the long-term micro- and macro vascular complications.[2] Current clinical guidelines recommend a stepwise approach to glycemic management in newly diagnosed T2D, starting with life style changes followed by sequential use of one, and then several, oral hypoglycemic agents (OHAs) and finally insulin treatment when all OHAs fail.[3] Although insulin is effective in all stages of the natural course of T2D and is ultimately necessary to achieve glycemic control, it is currently the most underused anti-diabetic agent as a mere 12% of patients with type 2 diabetes use insulin alone while another 14% use insulin along with OHAs.[4] As stated above, typically, insulin is recommended; when dual or triple OHA therapy does not achieve the targeted glycemic goals.[3] Unfortunately, research has shown that by this time, many patients have lived 5 years with A1C levels greater than 8%, and 10 years with A1C levels greater than 7%.[5]

Extreme hyperglycemia creates "glucose toxicity"- a state of very high and sustained glucose levels that paradoxically worsens both insulin secretion and insulin resistance.[6] Therefore at the time of diagnosis, if there is marked hyperglycemia and glucotoxicity, temporary insulin therapy may help restore physiologic function and this help conversion to non-insulin treatment later for sustained period of time.[6] Unfortunately, there is very little data on early insulin therapy in T2DM for India. Herein, we describe the initiation of insulin in T2D 33 patients with marked hyperglycemia at the time of diagnosis for a period of eight weeks followed by sustained maintenance of targeted glycemic target for next 36 months on oral hypoglycemic agents.

Material and Methods

Study design and study setting

We conducted this study in newly diagnosed type 2 diabetes (treatment naïve) adult (>18 years) patients who presented to the outpatient internal medicine clinic of Indira Gandhi Medical College and Hospital (IGMC), Shimla from January 2012 through June 2016. Patients enrolled in the study fulfilled the inclusion criteria: Age > 18 years, newly diagnosed type 2 diabetes patients with A1C levels higher than10% and /or A1C levels higher than 9% with

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Received: 09.05.2017; Revised:14.02.2018 ; Accepted: 11.04.2018

symptoms of hyperglycemia.[7] This study complies with WHO diagnostic criteria for diabetes mellitus, i.e., a random or casual plasma glucose concentration ≥ 200mg/dl or fasting plasma glucose ≥ 126 mg/dl or 2-hour plasma glucose ≥ 200 mg/dl during standard 75g oral glucose tolerance test. Patients were excluded if they had: type 1 diabetes, acute complications (hyperglycemic hyperosmolar state or / diabetic ketoacidosis), renal or hepatic dysfunction, acute infection, congestive heart failure, acute coronary syndrome, age < 18 years *or* > 80 years or if they were pregnant. At baseline, the patient's history was recorded and a thorough physical examination conducted. Anthropometric measurements: weight, height, waist (at the level of anterior superior iliac spine in standing position) and body mass index (weight in kilogram divided by height in meter square) were recorded. Fasting plasma glucose, post prandial plasma glucose, A1C and blood pressure were recorded. Post-prandial C-peptide was measured at base line and at the end of two-month. Plasma glucose levels were measured by using glucose oxidase and A1C and C-peptide was measured by radioimmunoassay. All patients underwent routine blood tests i.e. complete heamogram, liver and kidney functions and lipid profile at base line. X-ray chest and thyroid function functions were done where clinically indicated. Patient's telephone number and address were recorded and they were advised to follow at 2-month intervals. At base line, patients were educated regarding the symptoms of hypoglycemia and about the corrective measure if hypoglycemia occurs. Patients were advised to contact the treating physician in case of emergency i.e. unconsciousness.

Study duration and follow up

Patients were enrolled from January 2012 through June 2013 and were followed up for 3 years from the month of enrollment. Due to difficult geographical terrain, patients were advised to come for follow up between 3 to 6 months at their convenience.

Study participants were followed up at 2 month, 6 month, 12 month, 18 month, 24 month, 30 month and 36 month; respectively. Patients were reminded telephonically for their follow up visits. At each follow up visits, fasting plasma glucose, post-prandial plasma glucose and A1C were measured. Symptoms of hypoglycemia (minor as well as major included hospitalization) and subjective feeling of well being were recorded.

Hypoglycemia:[8] "Any abnormally low plasma glucose concentration that exposes the subject to potential harm" and defined as:

Biochemically: Based on documented blood glucose levels < 70 mg/dl.

Overall hypoglycemia: any event classified by study investigators as such (from history: patient had one or other symptom of hypoglycemia and symptom resolved on taking sugar without knowing the blood glucose level).

Hypoglycemia was classified:[8]

Mild: An event associated with symptoms (autonomic symptoms) and individuals are able to self-treat.

Moderate: An event associated with symptoms (both autonomic and neuroglycopenic) and the individual is able to self-treat.

Severe: An event requiring assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions and unconsciousness may occur.

Treatment protocol and follow up

We obtained a written informed consent from each participant before subjecting to clinical examination and treatment. All participants who gave their consent to participate in the study were treated with pre-mix human insulin (30:70) at dose 0.5 IU/Kg twice daily and metformin 500 mg twice daily and increased to 1000 mg twice daily after one week.[12] We preferred pre-mix insulin to basal insulin because twice-daily pre-mix insulin provided lower A1C level compared with once daily and post-prandial glucose level is better controlled with twice-daily pre-mix insulin.[9] All participants were advised to adopt healthy life style. The treating physician taught insulin injection technique to each study participant before prescribing insulin to remove injection phobia and to build patient's confidence. For co-morbidities (hypertension and dyslipidemia) patients were treated as per the standard guidelines.

At the end of two months (first follow-up) insulin was discontinued and patients were switched over to oral anti-diabetic drugs. The choice of oral antidiabetic agents (metformin, Pioglitazone, and secretagogue and DPP-4 inhibitor in single and / or in combination) was at the discretion of treating physician. At subsequent follow up (6, 12, 18, 24, 30 and 36 month) visits, the oral agents were modified (dose increased or decreased; and new oral agent and/ or insulin added) depending on the A1C level and at the discretion of the treating physician.

Statistical analysis

Discrete values were expressed as percentage and continuous variables as mean± SD. Student t test was applied to assess the significance of difference in mean values and chi-square test applied for assessing the significance of the difference between groups. 'P' value < 0.05 was considered significant.

Results

One hundred and eighty three (183) patients fulfilled the eligibility criteria and were enrolled the study, of whom 41 patients agreed for the insulin therapy while 142 patients refused for insulin therapy at the first contact (Figure 1). Fear of habituation was the commonest reason for refusal of insulin therapy in 84 patients followed by fear of injection and not confident in injecting insulin seen in the other 43 patients. In addition, 15 patients voiced their concerns about inconvenience of insulin therapy (particularly while traveling) as they believed that insulin needed to be refrigerated and said that a refrigerator was not available in villages. All the 142 patients who initially refused insulin were briefly educated about insulin. They were specifically told that insulin would be given for the initial 2 months to control the very high blood glucose and were assured that after 2 months they will be switched to oral drugs. After this brief insulin education period, 105 (73.9%) patients agreed for insulin therapy but 37 (26.1%) patients still refused. Then, 37 patients were excluded from the study, and were treated with oral agents. Insulin injection technique was demonstrated to all patients who accepted insulin therapy. In virtually, patient's injection phobia went away after the first injection. The most common response after insulin demonstration was, "Oh it is

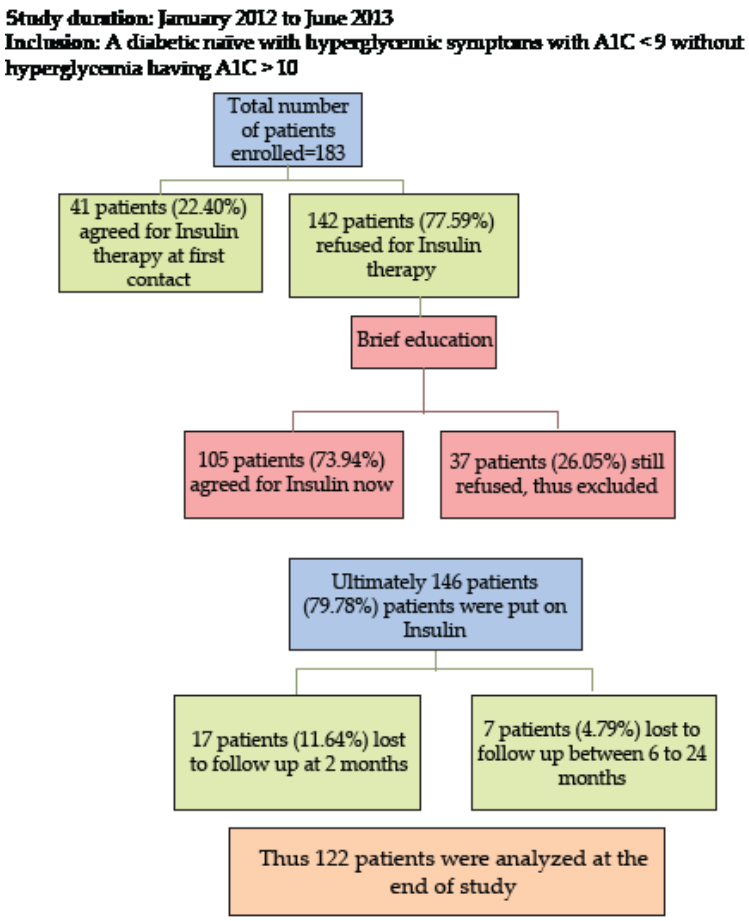

Fig. 1: Flow chart of the patients participated in the study

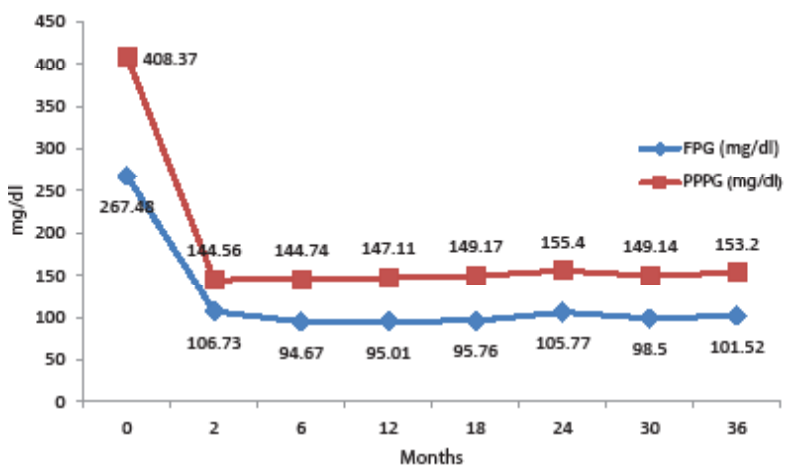

Fig. 2: Change in level of FPG and PPPG from baseline to 36 months

so simple and it does not hurt". It took an average of 5 minutes to educate and demonstration of insulin technique in the busy OPD. Thus, final the number of patients who accepted the insulin therapy was 146 (79.8%) (Figure 1).

Of 146 patients who accepted insulin therapy, 17 (11.6%) patients were lost to follow up at first visit at 2-month and seven (4.79%) patients left treatment between 6 month and 24 months and were excluded from the study. Thus, finally, 122 subjects completed the three year study period and were included in the study for the final analysis (Figure 1).

The demographic profile of 122 study participants who completed the study is shown in Table 1. Ninety-one (74.6%) patients had history of osmotic symptoms. Sixteen (13.11%) patients were diagnosed during routine laboratory work up, 10 (8.2%) patients were diagnosed before undergoing preoperative check up prior to various different surgeries.

Table 1: Demographic profile at baseline (n = 122)

Variables		Mean (± SD)	p value
Age(years)	Male	53.7 (± 9.6)	0.012
	Female	49.0 (± 9.1)	
Sex	Male	61 (50%)	NA
	Female	61 (50%)	
Height(cm)	Male	168.5 (± 5.3)	0.000
	Female	155.5 (± 4.8)	
Weight(kg)	Male	70.6 (± 9.1)	0.000
	Female	64.7 (± 10.1)	
Waist(cm)	Male	93.7 (± 6.2)	0.04
	Female	91.5 (± 7.2)	
BMI(kg/m^2)	Male	24.9 (± 2.6)	0.003
	Female	26.6 (± 3.5)	
SBP (mmHg)	Male	139 (±15)	0.50
	Female	137 (± 14)	
DBP (mmHg)	Male	84 (± 7)	0.71
	Female	84 (± 9)	

NA- Not Applicable; Number of patients with BP ≥140/90 mmHg are 28

At baseline, FPG of study subjects ranged between 160 - 525 mg/dl with a mean of 267 ± 76 mg/dl, the PPPG ranged between 229-750 mg/dl with a mean of 408 ± 101 mg/dl and A1C ranged from 9.4 - 15.5% with a mean of 11.4%. The post –prandial C-peptide levels could only be measured in 39 study subjects due to financial reasons and it ranged between 0.8 ng/dl – 2.7 ng/dl with mean of 1.8± 0.6 ng/dl. The systolic blood pressure ranged between 110 - 192 mmHg with a mean of 137 ± 15 mmHg (male: 138 ± 16 mmHg; women: 136 ± 14 mmHg). Diastolic pressure ranged between 60 - 110 mm Hg with a mean of 83 ± 8 mm Hg (male: 83 ± 7 mm Hg; women: 83 ± 9 mm Hg) and 28% were found to be hypertensive at base line (Table 1).

First follow-up visit at 2-months

The fasting plasma glucose levels of study participants at 2-month follow up ranged from 76 - 178 mg/dl with a mean of 106 ± 10 mg/dl. The postprandial plasma levels ranged from 102 - 238 mg/dl with a mean of 144 ± 24 mg/dl (Figure 2). The A1C at the end of two-month insulin treatment ranged from 5.5 – 9% with a mean A1C of 7.3% (Figure 3). The reduction in the mean FPG, PPPG and A1C was highly significant at 2-months ($p < 0.001$). The post-prandial C-peptide levels measured in 39 study subjects at 0 month was 1.81 ± 1.0 ng/dl which increased to 2.78 ng/dl at the

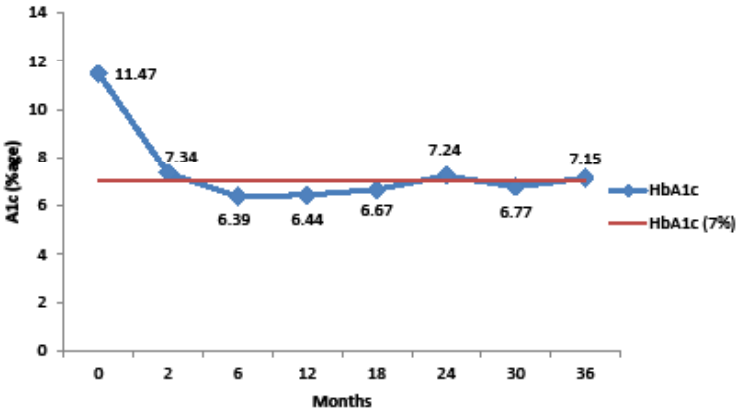

Fig. 3: Change in level of A1C (%) from baseline to 36 months

end of 2-months (p = 0.01). There was an average 1.7 kg increase in the weight of study participants from 67.7 kg to 69.4 kg. Overall, there were 0.97 episode/ patient of hypoglycemia. However, all episodes of hypoglycemia were minor except for seven, which were of moderate intensity. 113 patients (92.62%) were satisfied with the treatment and reported improvement in the quality of life after insulin treatment. The 'feel good phenomenon' was attributed to relieving of osmotic symptoms and feeling more energetic.

Treatment changes at 2-month follow-up

At two-month, the insulin injection was discontinued and participants were treated with oral antidiabetic agents. Twelve (9.8%) patients were treated with the combination of metformin (2000 mg) and pioglitazone (15 mg), 36 (29.5%) patients were treated with the combination of Sitagliptin (50 or 100 mg) and metformin (2000 mg) and 74 (60.7%) patients were treated with combination of glimepiride (1 or 2 mg) and metformin (2000 mg). Subsequent follow up was planned at 6, 12,18,24,30 and 36 month.

Follow-up at 6, 12, 18, 24 and 30 months

The mean FPG of study subjects ranged from 95 ± 12 mg/dl to 102 ± 12 mg/dl), the mean postprandial plasma glucose ranged from 145 ± 19 mg/dl to 153 ± 10 mg/dl and the mean A1C ranged from 6.3 to 7.3% at 6, 12, 18, 24 and 30 month respectively (Fig. 2 and 3). The reduction in mean FPG, PPG and A1C at 6, 12, 18, 24 and 30 months were highly significant ($p < 0.001$). In four patients (2 in sitagliptin and 2 in glimepiride arm) another short course of insulin was required at 12, 18 and 24 months respectively, for deteriorating plasma glucose and rising A1C (> 9%) despite maximum dose of oral agents. In all four patients, plasma glucose was normalized in 4 to 6 weeks, and was later reverted to oral agents, and subsequently their plasma glucose remained well controlled on oral agents.

Follow up results at 36 months

At 36 month, the fasting plasma glucose ranged from 70 - 153 mg/ dl with a mean of 99 ± 13 mg/dl and post-prandial plasma glucose ranged from 124 - 178 mg/dl with a mean of 152 ± 12 mg/dl and the A1C ranged from 5.2 – 9.9% with a mean of 6.6% (Figures 2 and 3). The reduction in all three parameters (FPG, PPG and A1C) remained significantly lower at 36 months compared to the base line levels. At the end of 36 month, 93 (76.2%) had A1C 7%. The baseline A1C and reduction in A1C after treatment was similar in male and female participants.

At the end of 36 months, the majority of patients were on two drug OHA regimens while few needed three drug regimens.

Discussion

In the natural course of type 2 diabetes, early, intensive and strict glycemic control is clinically important because it limits exposure to high glucose level and consequently its toxic effects with substantial reduction in risk of development both microvascular and macrovascular complications in long term. This phenomenon of long term protective effects on micro vascular and macrovascular complications with short burst of intensive therapy soon after the diagnosis is termed as "metabolic memory".[10]

The natural history of diabetes reflects two abnormalities: a gradual increase in the insulin resistance and a progressive decline in insulin secretary response, over a decade or more, to a point that 50-80% of β-cell functions is lost by the time diabetes is diagnosed.[10] Prolonged exposure to hyperglycemia results in glucotoxicty and oxidative stress of β-cells, culminating in β-cell destruction.[11] Early level of insulin secretion (first-phase) is key determinant of pancreatic β-cell function[12] and loss of first phase insulin secretion is crucial defects in the pathogenesis of type 2 diabetes.[12] The rapid acquisition of glycemic control with transient intensive insulin therapy (TIIT) has been demonstrated to have beneficial effect on β-cell function in a number of studies[11] and this has been confirmed by a meta-analysis.[13] The statistically significant increase in the level of C-peptide after short course of insulin therapy suggests improvement of β-cell function in our study subjects and extends support to these previous studies. The probable underlying mechanism in the improvement of β-cells function with insulin therapy is that insulin therapy keeps the pancreatic β-cells in a resting state and thereby eases the burden of the pancreatic β cells and also possibly accelerates β cell repair by suppressing glucotoxicity and lipotoxicity.[14] Further, by directly enhancing the insulin sensitivity in the peripheral tissues (free fatty acid antagonizes the action of insulin on peripheral cells and Insulin reduces free fatty acid production), insulin therapy has demonstrated improvement in the insulin resistance in number of studies.[13]

Significant reduction in glycemic levels (FPG, PPG and A1C) at the end of insulin therapy in this study is suggestive of effectiveness of early use of insulin in the treatment of newly diagnosed type 2 diabetes with marked hyperglycemia and extends support to a number of previous studies.[13] The rapid acquisition of glycemic control with short intensive insulin therapy helps in maintaining long-term glycemic control has been demonstrated in a number of studies.[13] Sustained glycemic control after use of early insulin therapy was seen in this study, as 73.7% of patients had A1C 7% at the end of 3 years compared to 33% of patients treated with oral agents from the time of diagnosis in

United Kingdom Prospective Diabetes Study. Guidelines recommended glycemic control (<7%) early in the natural course of diabetes has been demonstrated to have a beneficial effect on cardiovascular events compared to strict glycemic control in the later part of natural course of diabetes.[15]

Hypoglycemia and weight gain are two commonly associated adverse effects of insulin therapy.[16] However, since insulin is used only for 2 months, these are not an issue compared to late addition of insulin in the usual treatment paradigm.[16]

In this study, 77.6% of patients initially refused to have insulin therapy; this confers the patient's resistance in starting insulin therapy and supports the findings of previous studies.[17] However, identifying these barriers and addressing the patient's fears crucially important for the timely initiation of insulin therapy.[17] We are pleased that 73.9% of patients ultimately accepted the insulin therapy after a brief education session of only about 5 minutes. This is feasible even a busy outpatient clinic. Furthermore, patients with a positive attitude about insulin therapy are more likely to achieve higher remission rates. However, in some patients preconceived fears and beliefs are stronger than their health care provider's advice and may have difficulty in changing their opinion.[17] This is shown by the 26.1% of our patients; who did not agree for insulin therapy despite their health care provider's advice.

The treatment satisfaction and improvement in the quality of life seen after insulin therapy in this study extend support to the results of previous studies[18] and serve as encouragement for an introduction of insulin therapy at an earlier stage in the natural course of type 2 diabetes. Education as well as increased level of support from medical personnel during treatment initiation to patient, positively influences the patients perception and reduces their fear of treatment leading to acceptance of insulin therapy.

The U.K. Prospective Diabetes Study (UKPDS) and Diabetes Control and Cardiovascular Trial (DCCT) and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) studies provide rational that aggressive glycemic control early in the natural course of diabetes (at time of diagnosis) will dramatically lessen the burden of cardiovascular disease many years down the road.[2] However, tight glycemic control late in the natural course of diabetes with long standing T2D with established cardiovascular disease may actually increase mortality rates.[19] It has been reported that less than one third of physicians in India prescribe insulin compared to OADs.[20] Based on our experience, we suggest that patients with newly diagnosed T2DM and A1C > 9% (with symptoms) could be given short time intensive insulin therapy to rapidly obtain normoglycemia. This insulin treatment can be stopped as soon as stable glycemic control is achieved and they can then be moved into standard care according to a patient-centered treatment approach. This also makes it easier to restart the insulin treatment in the natural course of disease when insulin is needed as shown by four of our patients who readily accepted insulin when their glycemic control deteriorated later. Finally, education about the initiation of insulin treatment at first contact influences the patients' psychological condition positively and reduces the fear of insulin therapy.

In summary, a more proactive approach in the management of severe uncontrolled diabetes early in the natural course of diabetes with transient use of intensive insulin therapy has the potential of achieving and maintaining effective glycemic control and improving beta cell function. This could also potentially reduce the risk of long-term complications compared with later addition of insulin in the treatment paradigm of diabetes, although admittedly long term follow up studies are needed in this aspect as currently we do not have the data to support prevention of diabetes complications based on early and aggressive treatment with insulin in T2 patients.

Acknowledgement

Authors are thankful to Principal, Indira Gandhi Medical College, Shimla for providing basic facilities to carry out the study. Authors gratefully acknowledge the participation of all the patients in the study.

References

1. International Diabetes Federation. IDF Diabetes Atlas Seventh Edition 2015, Brussels, Belgium, 2015. Available at URL: http://www.diabetesatlas.org/[Accessed on 13th December 2016].
2. Holman RR, Paul SK, Bethel MA, Mathews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *NEJM* 2008; 359:1577-1589.
3. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycaemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193-203.
4. National Diabetes Information Clearinghouse. National Diabetes Statistics 2011. http://diabetes.niddk.nih.gov/dm/pubs/statistics/. Accessed April 25, 2014.
5. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. *Diabetes Care* 2004; 27:1535-1540.
6. Garvey WT, Olefsky JM, Griffin J, Hamman RF, Kolteman OG. The effect of insulin treatment on insulin secretion and insulin action in type 11 diabetes mellitus. *Diabetes* 1985; 34:222-234.
7. International Diabetes Federation Clinical Guidelines Task Force. Global Guidelines for type 2 diabetes. Brussels, Belgium: International Diabetes Federation Clinical Guidelines Task Force; 2012. http://www.idf.org.
8. American Diabetes Association Workgroup on hypoglycaemia. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association workgroup on hypoglycemia. *Diabetes Care* 2005; 28:1245-49.
9. Shah S, Sharma SK, Singh P, Murugnathan A, Das AK; Diabetes Consensus Group. Consensus evidence based guidelines for insulin initiation, optimization and continuation in type 2 diabetes mellitus. *J Assoc Physicians India* 2014; 62(Suppl7):49-54.
10. Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes* 2009; 58:773-795.
11. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycaemic control and β-cell function in newly diagnosed type 2 diabetes with severe hyperglycaemia after short-term intensive insulin therapy. *Diabètes Care* 2008; 31:1927-1932.
12. Brunzell JD, Robertson RP, Lerner RL, Hazzard WR, Ensinck JW, Bierman EL, Porte D Jr. Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. *J Clin Endocrinol Metab* 1976; 42:222-229.
13. Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2013; 1:28-34.
14. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. *JAMA* 1999; 281:2005-2012.
15. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352:854- 865.
16. Fonseca V, McDuffie R, Calles J, Cohen RM, FeencyP, Feinglos M et al. Determination of weight gain on the action to control cardiovascular risk in diabetes trial. *Diabetes Care* 2013; 36:2162-8.
17. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, et al. Resistance to insulin therapy among patients and providers: results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. *Diabetes Care* 2005; 28:2673–9.
18. Hajos TR, Pouwer F, deGrooth R et al. Initiation of insulin glargine in patients with Type 2 diabetes in suboptimal glycaemic control positively impacts health-related quality of life. A prospective cohort study in primary care. *Diabet Med* 2011; 28:1096–1102.
19. Action to Control cardiovascular Risk in Diabetes Study Group. Gerstein HC, Miller ME, Byington RP, Golf Jr DC, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358:2545-59.
20. Joshi SR, Das AK, Vijay VJ, Mohan V. Challenges in diabetes care in India: Sheer numbers, lack of awareness and inadequate control. *J Assoc Physicians India* 2008; 56:443-50.