Introduction Of Biphasic Insulin Therapy For The Poorly Controlled Type 2 Diabetics Can Help In Achieving Recommended Glycemic Targets

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Abstract:

Introduction: Insulin therapy in type 2 diabetes is either delayed or is suboptimal. Achieving intensive glycemic control will have the greatest benefits in patients with less advanced disease. OBJECTIVES: To demonstrate that introduction of biphasic insulin therapy can help in achieving stringent recommended glycemic control in poorly controlled diabetics.

Methods: Six months prospective study on introduction of biphasic insulin instead of variable treatment modalities was carried out on 71 poorly controlled type 2 diabetics. Patients were interviewed three times, at the begining, after three and six months each time they were examined physically and investigated thoroughly.

Results: Glycemic control parameters, glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) were investigated at the baseline , after three and six months. The parameters had shown a statistical significant reduction to meet the recommended glycemic control targets of the American Diabetes Association (ADA) and very close to the International Diabetes Federation, European Diabetes Policy Group (IDF). Lipid profiles were investigated at the beginning and after three months of the study. Total cholesterol, LDL-C and non-HDL-C were achieved statistical significant reduction. The triglyceride, VLDL-C, HDL-C and atherogenic index (TC/ HDL-C ratio) were reduced but the achievements were statistically insignificant.

Conclusion: Biphasic insulin aspart progressively enable the poorly controlled type 2 diabetics to achieve the recommended glycemic targets. Achievements of the recommended targets reduce and/or normalize the lipid profile elements. Excellent results obtained can break down the patients and physicians barriers against use of insulin in type2 diabetes.

Key Words: type 2 diabetes mellitus, biphasic insulin, glycemic control, lipid profile.

Introduction

The prevalence of type 2 diabetes is rising in parallel with the rise in obesity and has reached epidemic proportions. In the United States, between 2000 and 2001, the prevalence of obesity rose from 19.8% to 20.9%, and that of diabetes rose from 7.3% to 7.9%. [1] An additional 47 million Americans are estimated to have the metabolic syndrome which is a cluster of metabolic disorders that has been linked to an increased risk for type 2 diabetes and coronary artery disease. It is well established that insulin resistance underlies the metabolic syndrome which is one of the two major defects in type 2 diabetes. [2] The other important underlying defect in type 2 diabetes is insulin deficiency resulting from the progressive decline in pancreatic beta-cell function. Because of these forwarded underlying defects, it can be anticipated that most patients will eventually require insulin therapy to achieve and maintain glycemic control.[3,4]

Intensive glycemic control significantly reduces diabetic microvascular complications, and mounting data support the role of glycosylated hemoglobin (HbA1C) reduction in decreasing cardiovascular disease risk.[5, 6, 7] Such data have led the American Diabetes Association (ADA) to reduce the target HbA1C value to $\leq$ 7.0% and to consider even lower targets for higher risk patients. [4] The American Association of Clinical Endocrinologists currently advocates an HbA1C goal of < 6.5% for all patients, noting that achieving intensive glycemic control will have the greatest benefits in patients with less advanced disease; [8] such stringent levels of glucose control cannot generally be maintained with oral antidiabetic drugs (OADs) alone.[9]

Reasons for the under use of insulin in type 2 diabetes have been well defined. [10, 11] Delays in initiating insulin may stem from both physician and patient barriers. Negative patient perceptions regarding insulin include fear of injections and hypoglycemia. In some cases, patients may perceive insulin as a sign of their personal failure to control the disease.[10] Clinician concerns include hypoglycemia, weight gain, and the misconception that elevated insulin increases cardiovascular risks.[5, 11, 12] In addition, both clinicians and patients may consider insulin therapy to be complicated and labor-intensive.[11] The risk for hypoglycemia in type 2 diabetes is low, and newer insulin analogues have demonstrated even lower rates of hypoglycemia than older insulin products.[13, 14] The introduction of newer insulin analogues may help to address many of the physician and patient barriers to insulin use.

Objectives

To demonstrate that introduction of biphasic insulin therapy can help to achieve stringent glycemic control which is often necessary for

achieving the recommended diabetes treatment targets in poorly controlled type 2 diabetics.

Patients & Method:

Six months period (Nov. 2004 – Apr. 2005) prospective study on introduction of biphasic insulin instead of variable treatment modalities (OADs with or without insulin) was carried out on a total of seventy one, poorly controlled (HbA1c > 7.0% and<12.0%) type 2 diabetics, registered in the National Diabetes Center (NDC) / Al-Mustansiriya University, after obtaining their agreements according to the medical research and ethical regulations.

Patients selected to participate in the study, 28 male and 43 female (M/F ratio =1/1.5), had mean ±SD of age 50.77 ± 10.65 years, diabetes duration 12.38 ± 8.77 years, BMI 26.54 ± 4.9 kg/m^2, HbA1c 9.46 ± 1.78 %. All patients were interviewed three times, at the begining, after three months and after six months at the end of the study; each time they were asked about any associated disease, side effect,complications and coexistant treatment; then examined physically (height, weight and BMI) and blood were taken for the following laboratory investigations FPG, PPG, HbA1c, serum total cholesterol (TC), serum triglycerides, LDL-C, VLDL-C, non HDL-C, HDL-C and atherogenic index (TC/HDL ratio).

Biphasic insulin used in the study was the premixed insulin analogue, NovoMix® 30, consist of soluble insulin aspart 30% and protamine-bound insulin aspart 70%; b.i.d (morning and evening dose).

All the statistical work and regesteration of obtained data were carried out by using Microsoft Excel - Windows XP professional program. Differences considered of significance according to the t-test at 0.05 level of P-value.

Results

A total of seventy one diabetic patients had been complete the six months trial successfully without problems.

The glycemic control parameters, HbA1c, FPG and PPG were founded at the baseline investigations 9.46±1.78%, 220.8±64.6 mg/dl and 312.1±90.6 mg/dl respectively; later on shown a statistical significant reduction after three months from the baseline findings and founded to be 8.1±1.2 %, 160.4±34.8 mg/dl and 214.1±53.7 mg/dl respectively (table 1).

After six months the HbA1c, FPG and PPG persisting to show the same pattern of a statistical significant reduction, founded as 7.07±0.7 %, 125.1±23.08 mg/dl and 169.0±24.0 mg/dl respectively, to the limit reaching the recommended glycemic control targets of the ADA and very close to the IDF stringent recommendations (table 1).

Table-1: The glycemic control parameters, HbA1c, FPG and PPG, at the baseline, three and six months with the recommended targets.

Findings	Baseline	After 3 months	After 6 months	IDF *	ADA **	P-value
HbA1c (%)	9.46±1.78	8.1±1.2	7.07±0.7	≤ 6.5	< 7.0	<0.005
FPG (mmol/l)	12.2±3.58	8.8±1.9	6.9±1.2	≤ 5.5	5.0 – 7.2	<0.005
(mg/dl)	220.8±64.6	160.4±34.8	125.1±23.08	≤ 99	90 - 130	
PPG **(mmol/l)**	17.2±5.02	11.8±2.9	9.3±1.3	< 7.5	< 10.0	<0.005
(mg/dl)	312.1±90.6	214.1±53.7	169.0±24.0	< 135	< 180	

* International Diabetes Federation, European Diabetes Policy Group. ( )
** American Diabetes Association. ( )

The glycemic control parameters HbA1c, FPG and PPG reduced gradually during the period of study shown percent of reduction or achievements after three months were 13.8%, 13.8% and 31.4% respectively; and after six months the percents of

reduction or achievements were 24.4%, 43.3% and 45.8% respectively (table 2).

All the participants were investigated for the lipid profile at the beginning and after three months of the study. The total cholesterol, LDL cholesterol and non-HDL cholesterol were 197.9±46.2 mg/dl, 123.6±35.5 mg/dl and 151.0±45.8 mg/dl respectively at the baseline finding; patients achieved significant reduction after three months of introduction of biphasic insulin therapy, findings were 175.0±34.7 mg/dl, 109.1±22.6 mg/dl and 110.4±56.0 mg/dl respectively (table 3).

Although the participants achieved similar achievements in the VLDL-c, HDL-c and atherogenic index (total cholesterol / HDL cholesterol ratio) as 22.6±10.6, 48.0±11.6 and 3.8±1.1 respectively; but the achievements founded to be statistically insignificant (table 3).

Table-2: The glycemic control parameters, HbA1c, FPG and PPG, amount and percent of achievement after three and six months.

Achievments	After 3 months	After 6 months	P-value
(%)	8.1±1.2	7.07±0.7	
HbA1c points	1.35±1.3	2.3 ±1.5	<0.005
(% of achievement)	13.8	24.4	
(mmol/l)	8.8±1.9	6.9±1.2	
FPG (Mg/dl)	160.4±34.8	125.1±23.08	<0.005
(% of achievement)	27.3	43.3	
(mmol/l)	11.8±2.9	9.3±1.3	
PPG **(Mg/dl)**	214.1±53.7	169.0±24.0	<0.005
(% of achievement)	31.4	45.8	

Table-3: The lipid profile findings at baseline, after three months of the study and the recommended targets.

	Findings (mean±SD)			NCEP *
	Baseline	After 3 months	Achievement	
Total cholesterol (mg/dl)	197.9±46.2	175.0±34.7	11.5 % †	<200
Triglycerides (mg/dl)	151.7±98.3	131.5±73.0	13.3 % ‡	<150
LDL-C (mg/dl)	123.6±35.5	109.1±22.6	11.7 % ††	<100
VLDL-C (mg/dl)	26.4±13.0	22.6±10.6	14.4 % ‡	<30
HDL-C (mg/dl)	46.6±13.5	48.0±11.6	2.9 % ‡	>40
Non HDL-C (mg/dl)	151.0±45.8	110.4±56.0	26.8 % †	<160
Atherogenic index	4.7±2.4	3.8±1.1	19.1 % ‡	<5

*National Cholesterol Education Program/Adult Treatment Panel III (ATP III) Guidelines
† = P-value <0.01, †† = P-value <0.05, ‡ = P-value >0.05

Biphasic insulin aspart analogue, NovoMix® 30, requirement to obtain the glycemic control were used in two doses, b.i.d, morning and evening doses were 35.0±8.4 iu, 26.2±8.1 iu respectively, and the total doses were 61.7±16.4 iu/day; when taking the body weight in consideration the morning and evening doses requirements were 0.52±0.25 iu/kg/day, 0.39±0.20 iu/kg/day respectively and the total dose per day 0.92±0.46 iu/kg/day (table 4).

Fifteen patients required metformin, 1500 mg/day in three divided doses, to be added to their course of treatment to achieve the recommended glycemic targets.

Nine patients experienced bouts of moderate hypoglycemia during the course of the study which were managed by the patients themselves without further complication.

The patients BMI, mean±SD, at the baseline evaluation were 26.5±4.9 kg/m^2; participants gain some weight after three and six months, when their BMI were 27.0±4.1 and 27.0±4.0 kg/m^2 respectively.

Table-4: Biphasic insulin aspart analogue requirement.

Insulin requirment			
	IU	**IU/kg**	**% of dose**
Morning dose	35.0±8.4	0.52±0.25	~57 %
Evening dose	26.2±8.1	0.39±0.20	~43 %
Total	61.7±16.4	0.92±0.46	~100 %

Discussion

The preliminary report, 1998-2000, of glycemic control among United States adults type 2 diabetics shown that overall rates of insulin use for type 2 diabetes in the United States are very low; Approximately 11% of patients were treated with a combination of insulin plus OADs and another 16% received insulin monotherapy.[15] The IDF at 1999 intentionally undertakes the targets published by the European Diabetes Policy Group for the stringent type 2 diabetes glycemic control and considered as recommended targets, HbA1C ≤ 6.5%;[16] However, An HbA1C < 7.0% is only achieved in 36% of patients. [13] Higher rates of glycemic control have been reported among patients with type 2 diabetes who are receiving care from endocrinology practices (61%) and may in part be due to higher rates of insulin use. [17] Later on, 2004, the ADA undertakes lesser, for instance, tight recommendations as recommended targets, as an HbA1C ≤ 7.0%, for good glycemic control.[18]Our data obtained after, three and six months, of introduction of biphasic insulin (table 1, 2) shown clearly how Iraqi patients had achieved the recommended glycemic targets, percentages of achievements ranged between 13.8% and 45.8%, by using biphasic insulin in spite of the educational, cultural, economical and technical obstacles; so, confidently speaking, in better patient's situation, longer and wider study more solid and trusted results could be obtained.

Emerging data from the Epidemiology of Diabetes Interventions and Complications (EDIC) study, and the long-term follow-up of the Diabetes Control and Complications Trial (DCCT), also support the benefits of glycemic control for cardiovascular risk reduction. The EDIC study demonstrated that patients who initially received intensive insulin therapy have reduced incidence of cardiovascular disease events. [19, 20]

The Framingham Heart Study, [21] the Multiple Risk Factor Intervention Trial (MRFIT), [22] and the Lipid Research Clinics (LRC) trial [23, 24] found a direct relationship between levels of LDL cholesterol or total cholesterol and the rate of new-onset of Coronary Heart Disease (CHD) in men and women who were initially free of CHD. The same way, results of lipid profile elements from the present study for diabetics showed an achievements ranging between 2.9% and 26.8% (table- 3). The pattern of lipid profile showed statistical significant achievements for the reduction of total cholesterol, LDL-C and non HDL-C toward the recommended targets (table- 3).

Although the achievements in the triglycerides, VLDL-C, HDL-C and atherogenic index were of no statistical significance but the changes after three months were obvious and noticeable toward the recommended targets. [25, 26]

The present study shown that injection of small morning and evening doses of biphasic insulin 0.52 and 0.39 iu/kg body weight respectively (table- 4)

were relatively more than that required by the Danish study group who required 0.04-0.08 iu/kg body weight to be given 30 minutes before meals in order to achieve significant reduction in postprandial plasma glucose (PPG) to the non-diabetic levels. [27]

Also, fifteen patients (21% of study group) required metformin to be added to their course of treatment to get optimal glycemic control. [27]Adding insulin to oral agents is simple to implement, well tolerated, and highly effective; particularly for patients with HbA1c levels between 7.0% and 10.0% .[13, 14, 28, 29]

Although weight gain can be expected with insulin therapy, the benefits of glycemic control clearly exceed the small increases in body weight. [29] The participants of present study shown an increase of 0.5 kg/m^2 in the BMI mean, after six months of treatment, which is easily manageable and accepted as far as they were within acceptable limits.

Conclusions

Biphasic insulin aspart progressively enable the poor glycenic controlled type 2 diabetics to achieve the recommended glycemic targets of the IDF and the ADA.

Achievement of the recommended targets by introduction of biphasic insulin normalize the lipid profile which may reduce or prevent the cardiovascular risk and other complications of type 2 diabetics after few months.

Excellent results obtained by introduction of biphasic insulin can break down the patient and physician barriers against use of insulin in type2 diabetes.

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