THE EFFECT OF BIPHASIC INSULIN ASPART 30 ON BODY WEIGHT AND A1c LEVELS ON PATIENTS PREVIOUSLY TREATED WITH ORAL ANTIDIABETIC DRUGS OR BIPHASIC HUMAN INSULIN 30

(Oral Antidiyabetik veya Bifazik İnsan İnsülini 30 ile Tedavi Edilmekte Olan Hastalarda Bifazik İnsülin Aspart 30'un Vücut Ağırlığı ve A1c Düzeyleri Üzerine Etkisi)

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Summary

It is crutial and necessary to initiate insulin therapy when it is a failure to provide adequate glycemic control with oral antidiabetic agents in type 2 diabetic patients' clinical care [(1,2)]. It is unnecessary to recommend intensified insulin treatment since most of type 2 diabetic patients have partial endogenous insulin secretion capacity, yet it is not possible to provide postprandial glycemic control using once or twice daily NPH insulin injections. Biphasic insulin premixes provide the opportunity to regulate both the basal and prandial glucose concentrations [(3)]. In our study we aimed to compare the efficacy of a widely used biphasic human insulin (BHI 30) and recently developed biphasic insulin aspart (BIAsp 30), on glycemic control and body weight. A total of 68 type 2 diabetic patients who had inadequate glycemic control (A_{1c} >7.5%) under current therapies for ≥ 4 months were enrolled into the study in two groups. The patients in group 1 (n:38; mean age: 54.58±6.55 years, mean weight: 82.79±15.22 kg; mean BMI: 32.76±5.34 kg/m_2; A_{1c} : 9.07±1.26 %) were on BHI 30 treatment. Group 2 consisted of patients (n:30; mean age: 55.07±7.63; mean weight: 76.93±11.92 kg; mean BMI:30.50±4.5 kg/m_2, A_{1c}: 10.28±1.36 %) receiving OHA's (combination of sulphonylurea and metformin) treatment. The patients were switched to BIAsp 30 therapy and followed for 4 months. At the end of the determined period, A_{1c} levels and body weights were measured. The results were compared using paired t-test and independent samples t-test. A_{1c} levels were lowered by 0.6% and 1.96% in patients receiving BHI 30 and BIAsp 30 respectively. The result was significantly low in group 2 compared to baseline A_{1c} levels. The change in body weight was 1.03±2.11 kg in group 1 and 3.10±3.35 kg in group 2. Weight gain was significantly high in group 2 compared to group 1. In our trial BIAsp 30 was found to be more effective in lowering A_{1c} levels in both groups compared to BHI 30 and OHA treatment but it was associated with a significant weight gain. Given the fact that weight gain may be the result of undetected minor hypoglycemic episodes, this result should be furtherly evaluated through new trials.

Key words: *Type 2 diabetes; weight gain; biphasic human insulin 30; biphasic insulin aspart 30*

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There are not enough number of studies comparing the metabolic effects of premixed biphasic human insulin (BHI 30) and premixed insulin analogue biphasic insulin aspart (BIAsp 30) in patients with type 2 diabetes. We aimed to compare their effects regarding A_{1c} levels and change in weight in our study.

Type 2 diabetes is a chronical disease which results from a progressive insulin secretory defect on the background of insulin resistance. It has been shown that the intensive management of type 2 diabetes reduces the risks for chronic complications [4]. When life style changes and oral hypoglycemic agents (OHAs) fail to correct persistant hyperglycemia, insulin is often required [5,6,7]. Approximately 20-30% of people with type 2 diabetes require insulin to correct persistant hyperglycemia [3].

Generally insulin is prescribed as once or twice NPH insulin injections for these patients in order to provide basal insulin requirements. But postprandial glycemic levels are yet to be corrected [3]. Since postprandial glycemic control is necessary for delaying incidence and progression of late diabetic complications, biphasic insulin premixes offer the opportunity to achieve prandial and basal aspects of glucose regulation [3]. One of the widely used biphasic insulin premixes is biphasic human insulin (BHI 30) which consists of 30% soluble insulin and 70% of NPH insulin. The subcutaneous absorption of soluble human insulin takes 20-30 minutes so it is recommended that patients arrange their mealtime accordingly [8]. However it has been supported by some studies that nearly two thirds of diabetic patients tend to have their meals immediately after injecting insulin [9,2]. Therefore it may be difficult to cover the postprandial insulin requirements adequately in patients with such insulin mixtures.

Insulin aspart (Iasp) is a new rapid acting insulin analog which is similar to human insulin except the replacement of proline with aspartic acid at position 28 of the B chain [10]. Due to intermolecular charge repulsion and lower self-association tendency to hexamers, this replacement results with a faster onset and shorter duration of action [10]. This feature enables the patient have the injection immediately before the meal. Some studies have shown that Iasp improves postprandial and long-term glycemic control compared to regular human insulin [10,11,12]. Combination of protamine retarded formulate of insulin aspart in a stable 30/70 mixture (30% insulin aspart and 70% protamine-retarded formulation) provides the patients with an alternative to BHI 30. The compliance of the patients to injection-meal time interval may result with better glucose control and less complications.

In this study we investigated the change on A1c levels and body weight under treatment of BIAsp 30 for twelve weeks in type 2 diabetic patients.

MATERIALS and METHODS

A total of sixty eight patients regularly attending to outpatient clinic of Diabetes, Endocrinology and Metabolism Department of Haseki Research and Training Hospital were included into the study. Enrolled patients were men or women, 40 years or older, with type 2 diabetes mellitus [8] and had inadequate metabolic control (A_{1c} $\geq$7.5%). The patients were not included in case of serious late diabetic complications or other serious disease. Thirty patients were insulin naive and on oral antidiabetic drug (sulphonylureas and/or metformin) therapy. Thirty eight patients were having a regimen of twice-daily BHI 30 injections already. All of the patients had been receiving their therapeutic regimens for at least four months. The study was approved by local ethics committee and pretrial written informed consent was obtained from the participants.

Following a screening period patients were randomized to a 12-weeks' treatment period and informed for attendance at 2,4,8,12 weeks after randomization. The patients receiving BHI 30 and OHA's were defined as group 1 and group 2 respectively. Baseline metabolic characteristics of both groups were recorded. The dosage of BHI 30 was not changed in group 1 and the patients were planned to inject the same doses of BIAsp 30 as before. The patients in group 2 were recommended to discontinue OHA's and have subcutaneous BIAsp 30 injections of totally 0,2-0,4 IU/kg twice a day within 10 minutes before breakfast and dinner. The 2/3 of total BIAsp 30 dose was prescribed in the morning and 1/3 was

prescribed before dinner. All of the patients were given private education on insulin formulations and insulin injection techniques. Re-education on principles of medical nutritional therapy was provided for each patient. Insulin doses were adjusted according to patients' self blood glucose measurements. Patients were allowed to use metformin if prescribed before or considered to profit according to SBGM. Body weight and A_{1c} levels were measured before and after twelve weeks. HbA_{1c} was assayed by central hospital laboratory using immuntribudumetric method (Olympus AU2700, Roche) normal range 4.2-6.2%. Patients recorded hypoglyceamic episodes or other adverse events. The groups were compared with independent t-test and the values before and after the study were analysed by paired samples t-test. Statistical analyses were performed using SPSS 11.0 version. All statistical tests were performed using a of significance.

RESULTS

BMI, age and diabetes of duration were similar in both groups before BIAsp 30 therapy. Body weight was slightly increased in group 1 than in group 2, however the difference was not significant (mean body weight in group 1: 82.79±15.22 kg; mean body weight in group 2: 76.93±11.92 kg; p=0.08). Both groups had poor glycemic control before BIAsp 30 therapy and A1c levels in group 1 were significantly lower than in group 2 (mean A_{1c} in group 1: 9.07±1.26 %, mean A_{1c} level in grup 2 : 10.28± 1.36 %; p<0.001) (Table 1)

After BIAsp 30 therapy for four months, A_{1c} levels were significantly decreased compared to baseline levels in both groups. In group 1 mean A_{1c} level was 8.40±1.41 % and the mean difference in A_{1c} levels was 0.67±1.21 (p=0.002) in group 1. In group 2, mean A_{1c} level after BIAsp 30 therapy was 8.18±1.46 and the mean difference before and after therapy was 1.98±1.34. The decrease in A_{1c} levels was more prominent in group 2 compared to group 1 (p<0.01). Body weight was significantly increased in both groups compared to baseline. The mean difference in body weight was 1.03±2.11 kg in group 1 (p=0.005) and 2.91±3.33 kg (p<0.001) in group 2. The body weight in group 2 was significantly higher than group 1 (p<0.001) (Table 2).

Table 1. Demographic and baseline characteristics of the study population

	OHA±metformin (Group 1)	BHI30±metformin (Group 2)	p value
Number	38	30	
Age (years)	54.58± 6.55	55.07± 7.63	p>0.05
Sex (M/F)	10/28	6/24	
Body weight	82.79±15.22	76.93±11.92	p>0.05
BMI (kg/m2)	32.76± 5.34	30.50± 4.65	p>0.05
Years diabetes	12.37±5.56	13.33± 5.70	p>0.05
A_{1c} (%)	10.28±1.36	10.28 ±1.36	p<0.001

Table 2. Treatment comparisons of changes in A1c and body weight after 12 weeks

	Group 1	Group 2	p value
A_{1c} (%Hb)	8.40±1.41 (p=0.002)	8.32±1.47 (p<0.001)	p=0.826
Body weight (kg)	83.81±15.05 (p=0.005)	80.031±1.66 (p<0.001)	p>0.05

DISCUSSION

There are several studies confirming the improvement in glycemic control of type 2 diabetic patients following development of insulin analogues [10,11,12,13]. In our study A_{1c} levels of the patients under OAD and BHI 30 treatment were significantly lower after 12-weeks' period of BIAsp 30 treatment. These findings are compatible with literature findings.

It has been demonstrated that the pharmacokinetics of BIAsp 30 showed a rapid onset of metabolic effect. Its effect is potentiated during the first 4 hours which is considered to be the important reason why BIAsp 30 was more effective in regulating postprandial glycemic levels than BHI 30. This finding is supported by a hyperinsulinemic euglycemic clamp study carried out on twenty-four healthy male volunteers [10].

In our study the reason of the difference in weight gain in group 2 may be explained by the first anabolic effect of insulin since they were insulin naive patients. With the patients in group 2, although they were switched to the same BHI 30 doses they had been receiving previously, weight gain was also recorded but less than in group 1. The weight gain following 12 weeks of BIAsp 30 therapy with the same doses of BHI 30 in group 1 may be due to rapid onset metabolic effect of BIAsp 30 during the first four hours of injection compared to BHI 30 as mentioned by Weyer et al. before (1997). But considering the SBGMs, although no serious hypoglycemic episode was reported, the blood glucose levels before lunch were lower than expected. Since glycemic control was better and weight gain was prominent, it is probable that the patients tend to consume different kinds of food planned other than in their meal plans because of relatively low glycemic levels. According to Boehm et al [14] body weight was not changed in patients receiving BIAsp 30 compared to those receiving BHI 30 therapy. However in our study, body weight was significantly increased after BIAsp 30 therapy in both groups and the increase was significantly prominent in group 2 compared to group 1. But considering that the patients in group 1 had encountered with the anabolizan effect of insulin, therefore they might have already lived through the period of rapid weight gain. There are scarce data in the literatue concerning body weight change in patients receiving BIAsp 30 therapy as far as we could achieve. Thus we concluded that to have a healthy opinion about the difference between weight gain in patients receiving BIAsp 30 and BHI 30, a new study on insulin naive patients should be carried on concerning both insulins.

In another study, Boehm et al [15] randomized patients receiving biphasic insulin therapy as BIAsp 30 and BHI 30 group. After therapy for 12 weeks, A_{1c} levels were reported to be similar in BIAsp 30 and BHI 30 groups. However, in our study, in group1 which consisted of patients receiving BHI 30 therapy had significantly lower A_{1c} levels after switching to BIAsp 30 therapy (table 2). Boehm et al. did not find a significant difference in A_{1c} levels between BHI 30 and BIAsp30 groups, but they reported that daily glycemic profile/glucose levels in BIAsp 30 group were significantly better than in BHI 30 group. They explained the lack of difference in A_{1c} levels between BIAsp 30 and BHI 30 groups by a possible reflection of hypo and hyperglycemic episodes.

In conclusion, we found out that following BIAsp 30 therapy, both groups had significantly better glycemic control indicated by A_{1c} levels and significantly increased body weight. There are few data in the literature concerning the insulin analogues, therefore further studies are needed to find out if these molecules are more effective than biphasic human insulin in diabetic patients.

REFERENCES

1. Boehm BO, Home PD, Behrend C. Kamp, N.M. (2002) Premixed insulin aspart 30 vs. premixed human insulin 30 twice daily: a randomized trial in type 1 and type 2 diabetic patients. ***Diabet. Med.,*** 19, 393-399.

2. Jacobsen LV, Sogaard B, Riis A.(2000) Pharmacokinetics and pharmacodynamics of a premixed formulation of soluble and protamine-retarded insulin aspart. ***Eur J Clin Pharmacol.,*** 56, 399-403.

3. Christiansen JS, Vaz JA, Metelko Z, Bogoev M, Dedov I, (2003) Twice daily biphasic insulin aspart improves postprandial glycaemic control more effectively than twice daily NPH insulin. With low risk of hypoglycaemia in patients with type 2 diabetes. ***Diabetes, Obes. Metab.,*** 5, 446-454.

4. UK Prospective Diabetes Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). ***Lancet,*** 352, 837-853.

5. Flier JS, Underhill LH. (1996) Non-insulin dependent diabetes mellitus: A genetically programmed failure of the beta cell to compansate for insulin resistance. ***N Engl J Med.,*** 334, 777-783.

6. Rachman J, Turner RC. (1995) Drugs on the horizon for treatment of type 2 diabetes. ***Diabetic Med.,*** 12, 467-468.

7. DeFronzo, R.A. (1997) Pharmacologic therapy for type 2 diabetes mellitus. ***Ann Intern Med.,*** 17, 281-303.

8. American Diabetes Association. Insulin administration (1997) ***Diabetes Care,*** 20, 46-49.

9. Lean MEJ, Ng LL. (1985) Tennison B.R. Interval between insulin injection and eating relation to blood glucose control in adult diabetics. ***Br Med J.,*** 290, 105-108.

10. Weyer C, Heise T, Heinemann L. (1997) Insulin Aspart in a 70/30 premixed formulation. Pharmacodynamic properties of a rapid acting insulin analog in stable mixture. ***Diabetes care,*** 20, 1612-1614.

11. Kilo C, Mezitis N, Jain R, Mersey J, McGill J, Raskin P. (2003) Starting patients with type 2 diabetes on insulin therapy using once-daily injections of biphasic insulin aspart, biphasic insulin 70/30 or NPH insulin in combination with metformin. ***Diabetes complications,*** 17, 307-313.

12. Lindholm A, Jensen LB, Home PD, Raskin P, Boehm BO, Rostam J. (2002) Immun responses to insulin aspart and biphasic insulin aspart in people with type 1 and type 2 diabetes. ***Diabetes care,*** 25, 876-882.

13. Hermansen K, Vaaler S, Madsbad S, Dalgaard M, Zander M, Begtrup K, Soendergaard K. (2002) Postprandial glycaemic control with biphasic insulin aspart in patients with type 1 diabetes. ***Metabolism,*** 51, 896-900.

14. Boehm BO, Vaz JA, Brondsted L, Home PD. (2004) Longterm efficacy and safety of biphasic insulin aspart in patients with type 2 diabetes. ***Eur J Intern Med.,*** 15, 496-502.

15. Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. (2002) Premixed insulin aspart 30 vs. premixed insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients. ***Diabet Med.,*** 19, 393-9.