Medeniyet Medical Journal 2019;34(1):15-19
doi:10.5222/MMJ.2019.26790

Original Article/Orijinal Makale
Internal Medicine / İç Hastalıkları

Downward Insulin Therapy in Type 2 Diabetes

Tip 2 Diyabette İnsülin Tedavisinde Doz Azaltma

Banu Mesci, Murat Tekin, Aytekin Oğuz, Damla Çoksert Kılıç, Gonca Tamer Burcu Doğan, Arzu Akalın

Ethics Committee Approval: Received from Istanbul Goztepe Training and Research Hospital Clinical Research Ethics Committee (27.04.2009/56/P)
Conflict of interest: No competing financial interests exist.

Cite as: Mesci B, Tekin M, Oğuz A, Çoksert Kılıç D, Tamer G, Doğan B, Akalın A. Downward insulin therapy in type 2 diabetes. Med Med J. 2019;34(1):15-19.

ABSTRACT

Aim: *Despite increasing insulin doses, glycemic regulation fails in many obese patients with type 2 diabetes, The purpose of the present study was to compare the effects of increasing and decreasing insulin doses adjustments in obese type 2 diabetic patients with poor glycemic control.*
Methods: *Sixty type 2 diabetic patients with poor glycemic control under insulin treatment and had gained at least five kilograms in the last year were randomized into either conventional (increasing insulin doses) and downward insulin dosage groups. All patients had been given education on healthy eating and exercise in all visits. Patients' obesity parameters (as waist circumference and weight) and glycemic controls evaluated at the end of sixth months, respectively) in downward dose adjustment group and increased (from 110.7 to 115.6 cm and 83.2 to 84.6 kg, respectively) in conventional insulin dose adjustments. Both groups had significant reduction in HbA1C levels (from 9.64 to 9.12, and from 10.05 to 8.86; p=0.024, p=0.003; respectively). Changes in HbA1C levels were similar in the groups (p=0.12).*
Conclusion: *Downward insulin dose adjustment with intensified life style modifications provided weight loss and reduction in waist circumference similar to the levels achieved with glycemic control with conventional insulin dose adjustments.*

Keywords: *Downward dose adjustment, conventional insulin dose adjustments, type 2 diabetes, insulin therapy*

ÖZ

Amaç: *Pek çok obez tip 2 diyabetli hastada, arttırılan insülin dozlarına rağmen glisemik kontrol başarılı değildir. Çalışmamızın amacı, obez, kötü glisemik kontrollü tip 2 diyabetik hastalarda insülin doz arttırma ve azaltma yaklaşımlarının etkisini karşılaştırmaktır.*
Yöntem: *İnsülin tedavisi altında, kötü kontrollü ve son bir yıl içerisinde en az beş kilo almış olan 60 tip 2 diyabetli hasta konvansiyonel (insülin dozu arttırma) ve azaltma gruplarına randomize edildi. Tüm hastalara, her vizitte sağlıklı beslenme ve egzersiz eğitimi verildi. Altıncı ayın sonunda hastalara ait obezite parametreleri (bel çevresi ve kilo) ve glisemik kontrolleri değerlendirildi.*
Bulgular: *Bel çevresi ve kilo insülin dozu azaltılan grupta azalırken (sırasıyla 113 cm'den 109,4 cm'e ve 88,2 kg'dan 86,8 kg'a), insülin dozu arttırılan grupta (sırasıyla 110,7 cm'den 115,6 cm'e ve 83,2 kg'dan 84,6 kg'a) arttı. Her 2 grupta da HbA1C gruplarında anlamlı azalma vardı. (%9,64'ten 9,12'ye, %10,05'ten 8,86'ya; p=0,024, p=0,003) Grupların HbA1C seviyelerindeki değişiklikler benzerdi (p=0,12).*
Sonuç: *Yoğunlaştırılmış yaşam tarzı değişiklikleri eşliğinde insülin dozu azaltma stratejisi ile kilo kaybı ve bel çevresinde azalma ve aynı zamanda konvansiyonel tedaviye benzer düzeyde HbA1C değişikliği sağlanmıştır.*

Anahtar kelimeler: *Doz azaltma, doz arttırma, tip 2 diyabet, insülin tedavisi*

Received: 04.11.2018
Accepted: 30.01.2019
Publication date: 30.03.2019

Banu Mesci
Istanbul Medeniyet University, Göztepe Training and Research Hospital Department of Internal Medicine, Istanbul, Turkey
banualpaslan@gmail.com
ORCİD: 0000-0002-1524-2809

M. Tekin 0000-0001-6841-3045
Istanbul Medeniyet University, Göztepe Training and Research Hospital Department of Family Medicine, Istanbul, Turkey

A. Oğuz 0000-0002-2595-5167
D. Çoksert Kılıç 0000-0002-3194-9994
G. Tamer 0000-0001-9503-4497
Istanbul Medeniyet University, Göztepe Training and Research Hospital Department of Internal Medicine, Istanbul, Turkey

B. Doğan 0000-0002-3817-7560
A. Akalın 0000-0001-6384-2035
Istanbul Medeniyet University, Göztepe Training and Research Hospital Department of Family Medicine, Istanbul, Turkey

INTRODUCTION

Weight gain is one of the inevitable side effects of insulin treatment[1-3]. Insulin treatment in type 2 diabetes may cause increase in body fat. Thus insulin resistance get worse and eventually higher insulin doses is needed for glycemic control[4]. However, Higher insulin doses frequently leads to only a minimal

decrease in hyperglycemia. In our daily clinical practice, we observed that the blood glucose levels did not increase with the reduction of insulin doses in type 2 diabetic patients. As such, we wonder whether decreasing rather than increasing insulin doses, with an emphasis on dieting, could be a method to achieve optimal glycemic control. The aim of this study was to compare the effects of conventional (upward) and downward dose adjustment aproaches in insulin treatment in type 2 diabetic patients.

MATERIAL and METHODS

Sixty type 2 diabetic patients with poor glycemic control under insulin treatment who had gained at least five kilograms during the previous year were included in the study. Patients with cardiac, renal or hepatic insufficiency, smokers, and those receiving corticosteroids or drugs affecting weight (any other antidiabetic drug-except fixed dose metformin-, antipsychotic drugs like colazepin, lithium, haloperidol, antidepressant drugs like amitriptyline, sertraline, paroxetine, drugs for epilepsy like carbamezine, valproate and beta blockers as antihypertensive drug) within the last 6 months were excluded from the study. The study protocol was designed in accordance with Helsinki Criteria and approved by local ethics committee (Local Ethics Committee of Istanbul Goztepe Training and Research Hospital Drug Investigations, 27.04.2009 and Decision No: 56/P). Written informed consent was obtained. Patients were randomized into two groups. Insulin dosage in the first group (Group A) was rearranged as 0.3 U/kg/day. In the second group (Group B), the initial insulin doses were set according to fasting plasma glucose levels of patients (FPG < 110 mg/dl: no change, FPG=110-139 mg/dl: +2 U, FPG=140-179 mg/dl: +4 U, FPG≥180 mg/dl: +6 U). After initial arrangement, insulin doses increased or decreased 2 units according to their lowest blood glucose levels in both groups, because strict life style modifications patients were introduced into a refined carbohydrate restricted diet. The characteristic of this diet was total exclusion of flours and sugar. Allowed amount of daily bread consumption was 60 gram (3 thin slices of bread. No other foods containing refined carbohydrates were allowed except bread. Besides, 30 minutes of walking a day was emphasized) were recommended fror both groups. All patients continued to receive metyformin therapy at tolerated maximal doses. The progress of both groups were tracked every two months during six months. At the end of six months, demographic and clinic data were reevaluated.

Statistical analyses:

Statistical analyses were performed by using the software SPSS for Windows V13.0. Normality of variables' distribution was tested with Shapiro-Wilk and Kolmogorov-Smirnov tests. Subjects were compared with two-tailed Mann-Whitney U or Student's t test. Data were expressed as mean ± SD. A p-value below 0.05 (two tailed) was considered as statistically significant.

RESULTS

The study was completed with 56 patients (11 M, 45 F). Four patients were withdrawn from the study because they lost to follow-up. Mean duration of insulin treatment was 4.7 years for both groups. In Group A, 13 patients were treated with intensive insulin therapy, 13 patients with premix, and 2 patients with basal insulins.

Demographic and clinical characteristics of the patients did not differ between the two groups, as listed in Table 1. Patients were tracked beginning with 39.2 units of insulin (- 18.6 unit) in Group A and 59.2 units (+ 6.9 unit) in Group B. Finally, mean insulin doses were reduced to 18 U in Group A and increased to 21 U in Group B (Table 2). Metformin doses were similar in two groups. (1969.2±205.7 mg in Group A, 1953.9±112.7 mg in Group B; p=0.96). At the end of 6 months, the patients achieved lower HbA1C levels (67.8% in Group A and 71.4% in Group B (Table 3). Both groups had significant decreases in HbA1C levels (p=0.024,and p=0.003; respectively). Changes in HbA1C were similar (p=0.12). Unlike Group B, Group A had lost weight (p<0.0001). Waist circumference decreased in Group A (p=0.002); however there was

a clinically important but statistically nonsignificant increase in Group B (p=0.055). Other biochemical parameters were not different in either groups (Table 4). No major hypoglycemic event was reported in any group throughout the study.

Table 1. Demographic and clinical data.

	Group A (5 Male, 23 Female)	Group B (6 Male, 22 Female)	P
Age (years)	59.2±9.2	56.8±8.0	0.3
Duration of diabetes (years)	13.5±7.2	10.8 ±6.2	0.14
Weight (kg)	87.8±14.6	83.3±16.9	0.26
BMI (kg/m^2)	34.4±4.4	33.3±6.1	0.44
Waist circumference (cm)	112.6±9.4	112.0±12.9	0.84
FPG (mg/dl)	216.0±87.1	239.6±71.4	0.07
HbA1C (%)	9.6±1.4	10.0±1.2	0.26
C peptid (ng/ml)	3.4±1.7	2.4±2.3	0.14
Insulin dose (U)	57.8±13.6	52.2±11.9	0.14

Group A. Downward dose adjustment group
Group B. Upward dose adjustment group
BMI: Body Mass Index, FPG: Fasting Plasma Glucose

Table 2. Mean insulin doses throughout the study.

Insulin doses (U)	Group A	Group B
First dose (U)	57.8±13.6	52.2±11.9
Initial dose (U)	39.2±13.2	59.2±8.5
Final dose (U)	39.4±13.2	73.6±15.1

Group A. Downward dose adjustment group
Group B. Upward dose adjustment group

Table 3.

		Group A	Group B
Increase in HbA1C	N	8	7
	%	28.6	25.0
No change in HbA1C	N	1	1
	%	3.57	3.57
Decrease in HbA1C	N	19	20
	%	67.8	71.4

Group A. Downward dose adjustment group
Group B. Upward dose adjustment group

DISCUSSION

This study evaluated two opposing approaches in type 2 diabetic patients who were not succesful in achieving good glycemic control with insulin therapy. HbA1C levels were reduced similarly in both groups. Although advice on life style modifications were given to all patients, only the downward dose adjustment resulted in weight loss. It has been commonly accepted that better glycemic control requires higher insulin doses and more intensive therapy[5,6]. Also in a short-term study investigating five subcutaneous doses of insulin glargine (0, 0.5, 1.0, and 2.0 U/kg), it was found that greater doses of glargine reduce plasma glucose levels better than lower doses[7]. However, in a recent study comparing the effect of basal bolus insulin with only basal insulin in type 2 diabetic patients, any difference between basal-bolus insulin and basal insulin was not found in hyperglycemia, but

Table 4. Comparison of the efficacy of both treatment modalities.

	Group A			Group B			
	First	Last	p	First	Last	p	p*
Weight (kg)	88.2±14.7	86.8±14.4	0,004	83.2±17.3	84.6±15.0	0.138	‹0.0001
WC (cm)	113.0±9.6	109.4±11.9	0.002	110.7±11.4	115.6±12.3	0.055	0.178
FPG (mg/dl)	216±87.1	203±78.7	0.15	239.6±71.4	206.2±81.9	0.08	0.32
HbA1C (mmol/mol)	81±8	76±6	0.024	86±10	73±8	0.003	0.12
Total Cholesterol (mg/dl)	211.9±58.3	193.3±39.3	0.041	205.4±38.6	203.4±43.6	0.83	0.18
HDL (mg/dl)	47.1±8.5	48.0±9.7	0.37	48.0±9.4	48.4±11.8	0.59	0.77
LDL (mg/dl)	140.5 ±45.7	128.9±37.4	0.15	131.7±31.9	122.5±31.4	0.42	0.87
Triglyceride (mg/dl)	243 ±189.6	208.7±110.7	0.15	190.1±93.0	181.4±71.7	0.53	0.46

**Comparison of the changes in both groups during follow up.*
Group A. Downward dose adjustment group
Group B. Upward dose adjustment group
WC: Waist circumference, FPG: Fasting Plasma Glucose

nocturnal hypoglycemia was more frequently seen with basal bolus insulin[8].

Meanwhile, two recent and large randomized trials, Veterans Administration Diabetes Trial (VADT) and Action to Control Cardiovascular Risk in Diabetes (ACCORD), conveyed that tight glycemic control unexpectedly increases mortality and morbidity[9,10]. One of the most obvious differences in the intensive approach group with high mortality was that these patients had gained more weight than the other group. Therefore, we tested glycemic control by emphasising life style modification and reducing insulin doses instead of giving more insulin to every uncontrolled diabetic patient. Our results showed that such an approach could be successful.

The Finnish Multicenter Insulin Therapy Study that was conducted on type 2 diabetic patients showed that body mass index was the most important parameter of deterioration in glycemic control[11]. Insulin-associated weight gain is also highly dependent on where increased body fat is located. Central adiposity is associated with increased risk of cardiovascular disease[12,13]. Recently, Gin at al.[14] have investigated the outcomes of body weight and body composition in type 2 diabetic patients who were on insulin therapy and the consequences on muscle strength and increase in free fat. This study showed that body weight gain was related exclusively of fat mass with no improvement in muscle strength. In the present study, there was an increase in waist circumference in the conventional dose adjustment group; however, the downward dose adjustment group showed a significant reduction in waist circumference. Success of the testing approach also depends on the patients' compliance to both diet and exercise. Our patients' levels of compliance can be considered limitations to our study results or that only standard recommendations were made instead of placing the patients in an intensive life style management programme. Moreover, such an approach should be evaluated not only with glycemic results; we also require more comprehensive, and long-term studies that will show the effect of this approach on mortality and complications. Because the design does not allow a double blind trial, the open label design in our study can be considered as another limitation.

CONCLUSION

Type 2 diabetes is an inevitable consequence of obesity. Insulin resistance is the major problem rather than insulin deficiency in type 2 diabetes unlike in type 1 diabetes. non metabolic Moreover, there are several concerns related to hyperinsulinemia in the presence of insulin resistance. Increasing insulin doses in type 2 diabetics with poor glycemic control who are on insulin treatment is not the only solution. In our study, type 2 diabetics under insulin treatment, obese and poorly controlled patients, a downward dose adjustment with intensified life style changes provided glycemic control as effective as conventional dose adjustment and led weight loss and decreased waist circumference. Thus, high doses of insulin stimulating metabolic and non metabolic pathways in the presence of insulin resistance might be avoided, in addition to the economic benefits of using less insulin.

The authors have declared that they have no significant relationships with or financial interests in any commercial company that pertains to this educational activity.

REFERENCES

1. Philippe J. How to minimize weight gain associated with insulin treatment. Rev Med Suisse. 2010;6:1199-1200.
2. Daly A. Use of insulin and weight gain: optimizing diabetes nutrition therapy. J Am Diet Assoc. 2007;107:1386-93. https://doi.org/10.1016/j.jada.2007.05.004
3. Davies MJ, D'Alessio DA, Fradkin J et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and theEuropeanAssociation for the Study of Diabetes (EASD). Diabetes Care Publish Ahead of Print, published online October 4, 2018. https://doi.org/10.2337/dci18-0033
4. Hermansen K, Davies M. Does insulin detemir have a role in reducing risk of insulin associated weight gain? Diabetes, Obesity and Metabolism. 2007;9:209-217. https://doi.org/10.1111/j.1463-1326.2006.00665.x
5. Garber AJ, Wahlen J, Wahl T, et al. Attainment of glycaemic goals in type 2 diabetes with once-, twice-, or thrice-daily

dosing with biphasic insulin aspart 70/30 (The 1-2-3 study). Diabetes Obes Metab. 2006;8:58-66.
https://doi.org/10.1111/j.1463-1326.2005.00563.x
6. Raskin P, Allen E, Hollander P, et al. INITIATE Study Group. Initiating insulin therapy in type 2 Diabetes: a comparison of biphasic and basal insulin analogs. Diabetes Care. 2005;28:260-5.
https://doi.org/10.2337/diacare.28.2.260
7. Wang Z, Hedrington MS, Joy NG, et al. Dose-response Effects of Insulin Glargine in Type 2 Diabetes. Diabetes Care. 2010;33:1555-60.
https://doi.org/10.2337/dc09-2011
8. Esposito K, Chiodini P, Capuano A, et al. Basal supplementation of insulin lispro protamine suspension versus insulin glargine and detemir for type 2 diabetes: meta-analysis of randomized controlled trials. Diabetes Care. 2012;35:2698.3
9. Duckworth W, Abraira C, Moritz T, et al. VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med. 2009;360:129-39.
https://doi.org/10.1056/NEJMoa0808431
10. Calles-Escandón J, Lovato LC, Simons-Morton DG, et al. Effect of intensive compared with standard glycemia treatment strategies on mortality by baseline subgroup characteristics: the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care. 2010;33:721-7.
https://doi.org/10.2337/dc09-1471
11. Yki-Järvinen H, Ryysy L, Kauppila M, et al. Effect of obesity on the response to insulin therapy in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1997;82:4037-43.
https://doi.org/10.1210/jcem.82.12.4460
12. Meneghini L, Koenen C, Weng W, et al. The usage of a simplified self-titration dosing guideline (303 Algorithm) for insulin detemir in patients with type 2 diabetes--results of the randomized, controlled PREDICTIVE 303 study. Diabetes Obes Metab. 2007;9:902-13.
https://doi.org/10.1111/j.1463-1326.2007.00804.x
13. Kazempour-Ardebili, Ramezankhani, Eslami et al. Metabolic mediators of the impact of general and central adiposity measures on cardiovascular disease and mortality risks in older adults: Tehran Lipid and Glucose Study. Geriatr Gerontol Int. 2017 Nov;17(11):2017-24.
https://doi.org/10.1111/ggi.13015. Epub 2017 Mar 28.
14. Gin H, Rigalleau V, Perlemoine C. Insulin therapy and body weight, body composition and muscular strength in patients with type 2 diabetes mellitus. J Nutr Metab. 2010; 2010. pii: 340570. Epub 2009 Oct 21.