CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2638149

Available online at: http://www.iajps.com Research Article

COMPARISON OF HYPOGLYCEMIA BETWEEN COMBINATION OF INSULIN DETEMIR AND ASPART WITH COMBINATION OF NPH (NEUTRAL PROTAMINE HAGEDORN) AND REGULAR INSULIN IN PATIENTS OF TYPE 1 DIABETES MELLITUS

Dr. Ibrar Hussain, Dr. Soud Ul Javed, Dr. Ali Farhan Abid
Medical Officer DHQ Hospital Faisalabad

Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:
Introduction: *Insulin analogues were developed to improve treatment of insulin-treated diabetes with respect to glycemic control and avoidance of hypoglycemic episodes. Short-acting insulin analogues (aspart, lispro and glulisine) were designed to mimic the fast-physiological postprandial insulin release and long-acting insulin analogues (detemir and glargine) were designed to mimic the basal continuous insulin release with minimal peak action, thereby leading to a presumed decreased risk of hypoglycemia.*
Objectives: *To compare the frequency of hypoglycemia between combination of insulin detemir and aspart with combination of NPH and regular insulin in patients of type 1 diabetes mellitus.*
Study Design: *Randomized controlled trial.****Settings***: *Department of Pediatric Medicine, DHQ Hospital Faisalabad.*
Study Duration: *26th October 2016 to 25th April 2016.* ***Materials & Methods***: *A total of 90 patients of age between 1 and 15 years of both genders with type 1 diabetes were included. Patients with renal impairment, hepatic dysfunction, obese and cushing syndrome were excluded. In group A, patients received insulin detemir once daily with insulin aspart 3 times daily and in group B, patients received twice-daily NPH insulin accompanied by twice-daily Regular Insulin approximately 30 minutes before meals. There was follow up of each patient after 2 weeks and was checked with signs and symptoms of hypoglycemia.* ***Results***: *Mean age was 10.23 ± 11.58 years. Out of 90 patients, 47 (52.22%) were males and 43 (47.78%) were females with male to female ratio of 1:1. Hypoglycemia in Group A (combination of insulin detemir and aspart) was seen in 02 (4.44%) patients while in Group B (combination of NPH and regular insulin) was seen in 10 (22.22%) patients (p-value = 0.013).Conclusion: This study concluded that combination of insulin detemir and aspart is better than combination of NPH and regular insulin in patients of type 1 diabetes in terms of hypoglycemia.*
Keywords: *Type 1 diabetes mellitus, insulin detemir, NPH, hypoglycemia.*

Corresponding author:
Ibrar Hussain,
Medical Officer DHQ Hospital Faisalabad

QR code

Please cite this article in press Ibrar Hussain et al., ***Comparison of Hypoglycemia Between Combination of Insulin Detemir And Aspart With Combination Of NPH (Neutral Protamine Hagedorn) And Regular Insulin In Patients Of Type 1 Diabetes Mellitus.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Diabetes mellitus (DM) is regarded as single disease entity. It is a heterogeneous group of diseases characterized by chronic hyperglycemia resulting from diverse group of etiology such as environmental and genetic factors acting simultaneously or jointly.1 There are three main types of diabetes mellitus (DM): (i) Type I or insulin dependent DM or juvenile diabetes, (ii) Type II or non-insulin dependent DM or adult-onset diabetes, (iii) gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes develop a high blood glucose level. Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.2

Type 1 diabetes mellitus (T1DM), also known as insulin- dependent diabetes mellitus (IDDM) or juvenile diabetes, is a form of diabetes resulting from autoimmune destruction of insulin-producing pancreatic β- cells leading to insulin deficiency. The incidence of type 1 diabetes mellitus has increased rapidly over recent decades, particularly in young children.3 Evidence from the Diabetes Control and Complications Trial (DCCT) and other landmark studies, have shown that tight glycemic control in adults and adolescents with T1DM is of crucial importance in reducing the premature onset of micro- and macro-vascular complications. However, in these studies, intensive insulin therapy was associated with an increased risk of hypoglycemia and increased body weight.4

MATERIALS & METHODS:

STUDY DESIGN: Randomized control trial.
SETTING: Department of Pediatric Medicine, DHQ Hospital Faisalabad.
DURATION OF STUDY: 26th October 2016 to 25th April 2016.
SAMPLE SIZE: By using WHO sample size calculator for two proportions
P1 = 25%3
P2 = 6%9
Level of significance = 5%
Power of study = 80%,
Sample size = 90 (45 in each group)

SAMPLE TECHNIQUE:

Non-probability, consecutive sampling.

SAMPLE SELECTION:

a. Inclusion Criteria:

- Patients of age between 1 and 15 years of both genders with type 1 diabetes (as per operational definition).
- Body mass index less than 90th percentile.

b. Exclusion Criteria:

Patients with

- Impaired renal disease (serum creatinine ≥1.7 mg/dL).
- Hepatic function impairment (transaminases >2.5 fold the upper limit of normal range).
- Obese patients with acanthosis nigricans.
- An autosomal dominant family history of diabetes.
- Patients with secondary diabetes i.e. cystic fibrosis related diabetes (CFRD) and Cushing syndrome.
- Patients with lipoatrophy and lipohypertrophy at the injection sites.

DATA COLLECTION PROCEDURE:

After taking approval from Ethical Review committee, Punjab Medical College/ Attached Hospitals, patients coming through OPD of the department meeting the inclusion criteria were enrolled and informed consent will be taken. All the patients were randomly divided into two groups by using computer generated random number table. In group A, patients received insulin detemir once daily with insulin aspart 3 times daily with main meals and in group B, patients received twice-daily NPH insulin accompanied by twice-daily Regular Insulin approximately 30 minutes before meals. There was follow up of each patient after 2 weeks. Home record of blood glucose monitoring i.e. 4 times a day before insulin injections were checked along with signs and symptoms of hypoglycemia. All the information on Performa was collected by me.

DATA ANALYSIS PROCEDURE:

All the data was entered and analyzed by using SPSS V-20. Descriptive statistics were calculated for all the variables. Mean and standard deviation were calculated for all the quantitative variables like age, duration of diabetes mellitus, BMI and weight. Frequency and percentage were calculated for all qualitative variables like gender and hypoglycemia. Chi-square test was applied to compare hypoglycemia in both groups. Effect modifiers like age, weight, duration of diabetes mellitus, BMI and gender were controlled by stratification. Post-stratification chi-square test was applied. P-value ≤ 0.05 was taken as

significant.

RESULTS:

Age range in this study was from 1-15 years with mean age of 10.23 ± 11.58 years. The mean age of patients in group A was 8.98 ± 4.06 years and in group B was 11.49 ± 15.86 years. Majority of the patients 40 (44.44%) were between 11 to 15 years of age as shown in Table IV. Out of 90 patients, 47 (52.22%) were males and 43 (47.78%) were females with male to female ratio of 1:1 as shown in figure IX. Mean duration of disease was 3.85 ± 1.17 years (Table V). Mean weight was 17.39 ± 7.30 kg (Table VI). Mean BMI was 22.56 ± 3.24 kg/m2 (Table VII). Hypoglycemia in Group A (combination of insulin detemir and aspart) was seen in 02 (4.44%) patients while in Group B (combination of NPH and regular insulin) was seen in 10 (22.22%) patients as shown in Figure X (p-value = 0.013).

Stratification of hypoglycemia with respect to age groups and gender has shown in Table VIII & IX respectively. Stratification of hypoglycemia with respect to duration of disease has shown in Table X while Table XI & XII have shown the stratification of hypoglycemia with respect to weight and BMI.

Table-IV: Age distribution for both groups (n=90).

	Group A (n=45)		**Group B (n=45)**		**Total (n=90)**	
Age (years)	No. of patients	%age	No. of patients	%age	No. of patients	%age
1-5	11	24.44	10	22.22	21	23.33
6-10	15	33.33	14	31.11	29	32.22
11-15	19	42.22	21	46.67	40	44.44
Mean ± SD	**8.98 ± 4.06**		**11.49 ± 15.86**		**10.23 ± 11.58**	

Figure IX: Distribution of patients according to Gender.

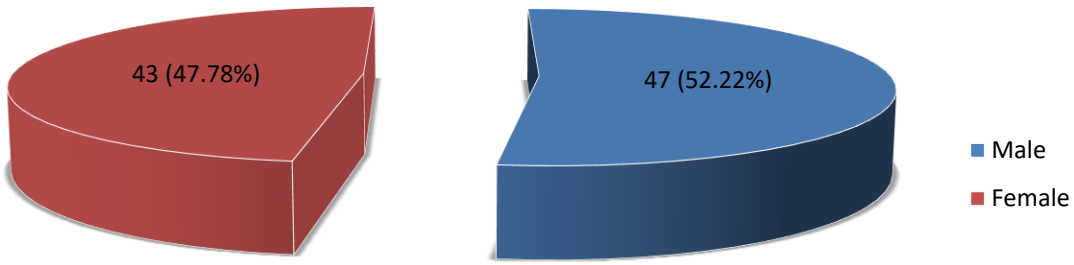


Table-V: Percentage of patients according to duration of DM (n=90).

Duration of disease (years)	**Group A (n=45)**		**Group B (n=45)**		**Total (n=90)**	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
0-1 year	19	42.22	20	44.44	39	43.33
>1 year	26	57.78	25	55.56	51	56.67
Mean ± SD	**3.84 ± 1.26**		**3.94 ± 1.11**		**3.85 ± 1.17**	

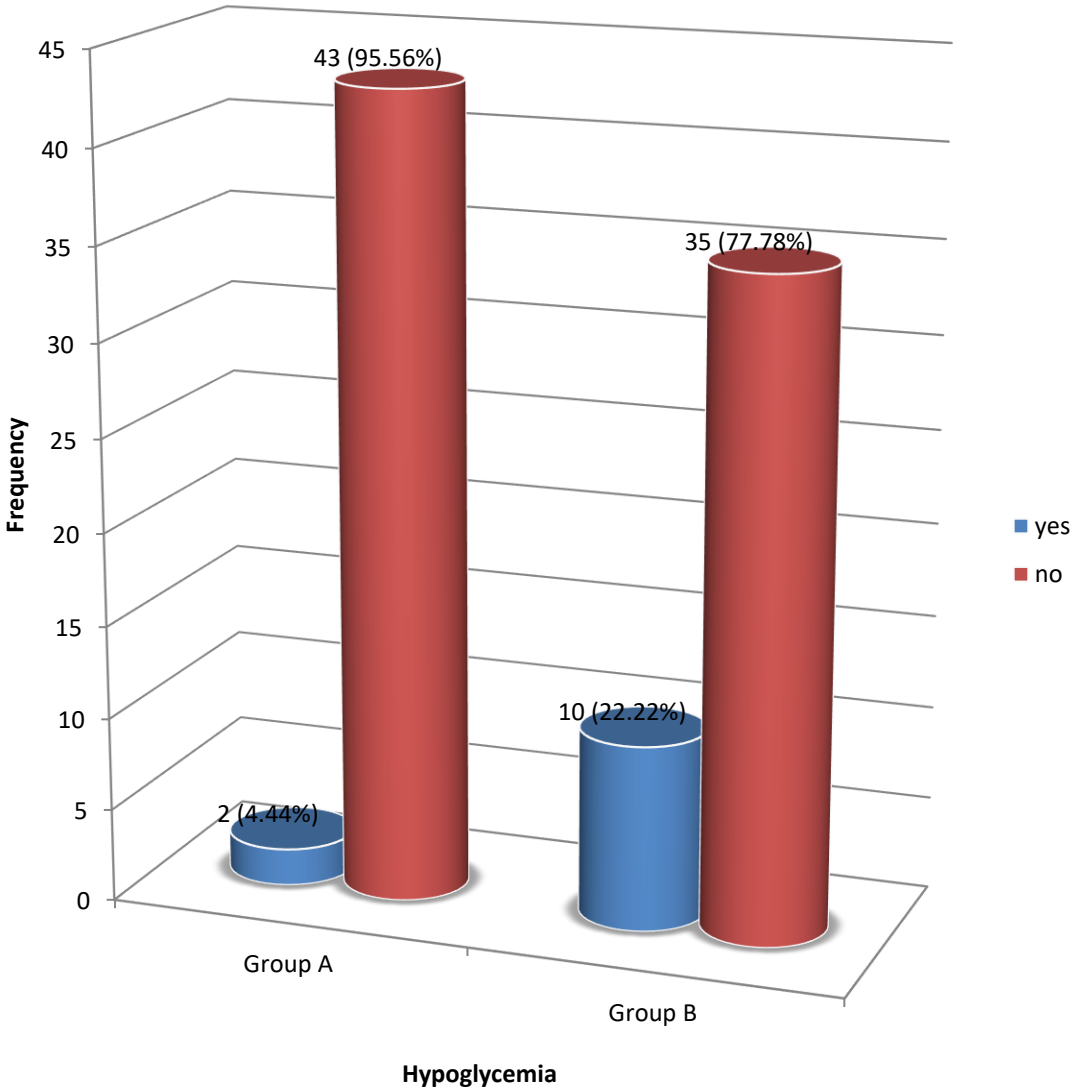
Table-VI: Percentage of patients according to weight (n=90).

Weight (kg)	Group A (n=45)		Group B (n=45)		Total (n=90)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
≤20	29	64.44	27	60.0	56	62.22
>20	16	35.56	18	40.0	34	37.78
Mean ± SD	**17.47 ± 7.50**		**17.62 ± 7.19**		**17.39 ± 7.30**	

Table-VII: Percentage of patients according to BMI (n=90).

BMI (kg/m2)	Group A (n=45)		Group B (n=45)		Total (n=90)	
	No. of patients	%age	No. of patients	%age	No. of patients	%age
≤15	17	37.78	18	40.0	35	38.89
>15	28	62.22	27	60.0	55	61.11
Mean ± SD	**22.39 ± 3.31**		**22.78 ± 3.19**		**22.56 ± 3.24**	

Figure X: Comparison of frequency of hypoglycemia in both groups



- **P-value = 0.013 which is statistically significant.**

Table VIII: Stratification of hypoglycemia with respect to age groups.

Age of patients (years)	Group A (n=45) Hypoglycemia		Group B (n=45) Hypoglycemia		P-value
	yes	no	yes	no	
1-5	00 (0.0%)	11 (100.0%)	03 (30.0%)	07 (70.0%)	**0.050**
6-10	01 (6.67%)	14 (93.33%)	02 (14.29%)	12 (85.71%)	**0.501**
11-15	01 (5.26%)	18 (94.74%)	05 (23.81%)	16 (76.19%)	**0.101**

Table IX: Stratification of hypoglycemia with respect to gender.

Gender	Group A (n=45) Hypoglycemia		Group B (n=45) Hypoglycemia		P-value
	yes	no	yes	no	
Male	01 (4.0%)	24 (96.0%)	04 (18.18%)	18 (81.82%)	**0.116**
Female	01 (5.0%)	19 (95.0%)	06 (26.09%)	17 (73.91%)	**0.062**

Table X: Stratification of hypoglycemia with respect to duration of disease.

Duration	Group A (n=45) Hypoglycemia		Group B (n=45) Hypoglycemia		P-value
	yes	no	yes	no	
0-1 year	02 (10.53%)	17 (89.47%)	04 (20.0%)	16 (80.0%)	**0.412**
>1 year	00 (0.0%)	26 (100.0%)	06 (24.0%)	19 (76.0%)	**0.008**

Table XI: Stratification of hypoglycemia with respect to weight.

Weight	Group A (n=45) Hypoglycemia		Group B (n=45) Hypoglycemia		P-value
	yes	no	yes	no	
≤20 kg	02 (6.90%)	27 (93.10%)	07 (25.93%)	20 (74.07%)	**0.053**
>20 kg	00 (0.0%)	16 (100.0%)	03 (16.67%)	15 (83.33%)	**0.087**

Table XII: Stratification of hypoglycemia with respect to BMI.

BMI (kg/m2)	Group A (n=45) Hypoglycemia		Group B (n=45) Hypoglycemia		P-value
	yes	no	yes	no	
≤15	01 (5.88%)	16 (94.12%)	04 (22.22%)	14 (77.78%)	**0.256**
>15	01 (3.57%)	27 (96.43%)	06 (22.22%)	21 (77.78%)	**0.038**

DISCUSSION:

Insulin formulations are classified into three main categories: short acting, intermediate acting, and long acting. Short-acting insulins include regular human insulin, glulisine, aspart, and lispro. The latter three are often referred to as rapid-acting insulins because their onset of activity and time to peak concentration are more rapid than those of regular human insulin. The rapid-acting insulins also have a shorter duration of activity and a time to peak action that is independent of the insulin dose, whereas regular insulin shows an increased time to peak action with increasing doses.81

Basal insulin formulations, such as the newer intermediate- or long-acting synthetic insulin analogs (e.g., insulin detemir, glargine), are effective basal insulin options for children with DM. Their primary use, particularly in type 1 DM, is to mimic the body's natural basal insulin secretion to limit gluconeogenesis and lipolysis, thereby reducing the potential for ketosis. Insulin detemir contains a 14-carbon fatty acid moiety that is acylated to lysine on the B chain of insulin. This fatty acid moiety allows insulin detemir to bind reversibly to albumin and other proteins, extending its duration of activity.81,82 The duration of action of insulin detemir appears to be dose-dependent and variable between subjects. With smaller daily doses (less than 0.4 units/kg/day), a shorter duration of action may be expected and will often require twice-daily dosing. Unlike neutral protamine Hagedorn (NPH) and insulin glargine, insulin detemir is soluble at a neutral pH. Insulin glargine is administered while soluble in its acidic formulation; when

exposed to a higher pH by subcutaneous injection, it forms a precipitate, which permits an extended duration of activity and no pronounced peak concentration compared with NPH. Both insulin detemir and glargine have been studied in children as young as 6 years, and both insulins are available in either vial or injectable pen devices.83

In my study, I have compared the frequency of hypoglycemia between combination of insulin detemir and aspart with combination of NPH and regular insulin in patients of type 1 diabetes mellitus. Age range in my study was from 1-15 years with mean age of 10.23 ± 11.58 years. The mean age of patients in group A was 8.98 ± 4.06 years and in group B was 11.49 ± 15.86 years. Majority of the patients 40 (44.44%) were between 11 to 15 years of age. Out of 90 patients, 47 (52.22%) were males and 43 (47.78%) were females with male to female ratio of 1:1. Hypoglycemia in Group A (combination of insulin detemir and aspart) was seen in 02 (4.44%) patients while in Group B (combination of NPH and regular insulin) was seen in 10 (22.22%) patients (p-value = 0.013). Hypoglycemia was found to be in 6% patients taking insulin detemir and aspart9 and in 25% patients taking Neutral protamine hagedorn and regular insulin in type 1 diabetes.3

Recent evaluation of the time action profiles of both analog insulins reveals very similar response curves.84 In an open-label, parallel-group comparison of subjects with type 1 diabetes, patients received either insulin detemir twice daily or insulin glargine once daily in combination with premeal insulin aspart.85 The overall risk of hypoglycemia was similar between the 2 groups; however, the risk of severe hypoglycemia was 73% lower and the risk of nighttime hypoglycemia was 32% lower with insulin detemir. The clinical significance of these findings needs to be evaluated.85

The PREDICTIVE (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation) trial is a multinational observational study designed to evaluate the safety and efficacy of insulin detemir. This is one of the largest diabetes trials to date, evaluating approximately 35,000 patients in multiple countries. Both type 1 and type 2 patients were enrolled, including newly diagnosed patients. The German arm of this trial (N=10,276) is the first to be published, and results were presented at the 2006 American Diabetes Association Scientific Sessions.86 The German subgroup analysis included patients who were poorly controlled on other insulins or were insulin naive, and the major intervention was adding insulin detemir to existing OAD therapy or changing to insulin detemir if patients were on another basal insulin.

Overall improvement in A1C of 0.89% in type 2 patients was seen (P < .001). In type 1 patients, major hypoglycemic events were reduced from 106 per 100 patient-years to 12 events per 100 patient years after changing basal insulin to insulin detemir. In type 2 patients, major hypoglycemic events dropped from 30 to 6 events per 100 patient-years. Subset analysis revealed an absolute A1C reduction of 1.29% in those diabetics who had been on OADs only. In the groups in which insulin detemir was substituted for insulin glargine or NPH, an absolute A1C reduction of 0.59% was seen in both sets. Despite improved control, and even adding insulin to insulin-naive groups, major hypoglycemic events were less frequent than they had been prior to the intervention.86

Current management of type 1 DM focuses on the use of basal/bolus (basal/prandial) insulin regimens to more closely mimic natural insulin secretion. The basal insulin provides background insulin release to regulate homeostatic glucose concentrations and increased nocturnal glucose release from the liver (known as the dawn phenomenon). Bolus insulin doses are designed to match new carbohydrate intake and correct for postprandial hyperglycemic excursions. Several combination insulin regimens can be chosen. The choice of insulin regimen depends on the patient's lifestyle, ability to adhere to the regimen, and physiologic limitations.87

Insulin regimens are based on the time-action curve of the particular insulin used. A traditional combination regimen consists of NPH plus a short-acting insulin. Although NPH is not a basal insulin by the strict interpretation of the definition, it is still widely used. The most common regimens use NPH with short-acting insulin in the morning and NPH administered again at dinner with the short-acting insulin or given separately at bedtime. The short-acting insulin is used to lower the postprandial glucose concentration to target concentrations by matching the carbohydrate intake at breakfast and dinner. The NPH

administered in the morning is used to cover for carbohydrate intake at lunch and offer some basal coverage during the day. Evening or bedtime administration offers basal coverage throughout the night. This NPH insulin plus short-acting insulin regimen requires a fairly strict adherence to prescribed mealtimes and carbohydrate intakes (especially at lunch) because NPH given at breakfast will not reach its peak effect for 4–6 hours.88

Newer regimens using insulin glargine or detemir for basal insulin coverage can provide a closer approximation to true physiologic secretion. Basal insulin is given once or divided twice daily, and all meals and corrections for hyperglycemia are covered with a short-acting insulin. The time-action profiles of a basal/bolus regimen make it easier to adapt to patient-specific needs. These regimens tend to be more injection intensive (often four or five injections daily) because most meal and correction boluses are given separately from the basal injection.89 However, patients have much more flexibility in the timing of meals and the ability to decrease elevated glucose concentrations to target goals. There is less risk of hypoglycemia and cyclic hyper- and hypoglycemia because of the basal insulin's flatter timeaction profile. In addition, carbohydrates in the meal can be varied with a corresponding change in the insulin bolus dose. This may make it easier to achieve tight glycemic control and reduce the hemoglobin A1C to goal; however, injection frequency and cost may be increased. Overall, a true basal/bolus regimen may be less challenging than an NPH insulin regimen.90,91

In one multicenter, open-label, randomized, six-month study, 349 type 1 diabetes mellitus patients aged five to 16 years received insulin glargine once daily or NPH insulin either once or twice daily.92 Fasting blood glucose (FBG) levels decreased significantly more in the insulin glargine group (-1.29 mmol/L) than in the NPH insulin group (-0.68 mmol/L, p=0.02). The percentage of symptomatic hypoglycemic events was similar between groups; however, fewer patients in the insulin glargine group reported severe hypoglycemia (23 versus 29 percent, respectively) and severe nocturnal hypoglycemia (13 versus 18 percent, respectively), although these differences were not statistically significant. Fewer serious adverse events occurred in the insulin glargine group than in the NPH insulin group (p<0.02).92

A trial aimed to compare insulin analogues (insulin detemir, insulin aspart) versus traditional human insulins (insulin NPH, insulin regular) in type 1 diabetic patients with basal bolus therapy showed interesting results in term of hypoglycemic events, numbers of overall hypoglycemia episodes per person-year were 37.1 and 48.2 for the insulin detemir and insulin NPH, respectively, while corresponding numbers of nocturnal hypoglycemia episodes per person-year were 4.0 and 9.2, respectively.93

A six-month, prospective, randomized, open-label, controlled, parallel-group trial conducted at 92 sites included 749 men and women with type 1 diabetes with HbA1c < 12 percent who were already taking daily intermediate- or long-acting insulin and a fast-acting human insulin or insulin analogue as bolus insulin.94 Patients were randomized to insulin detemir or NPH at bedtime in combination with human insulin with main meals. Main outcome measures included HbA1c, FPG, and hypoglycemia. After six months, FPG was lower with insulin detemir than with NPH (-1.16 mmol/L difference; p=0.001), whereas HbA1c did not differ significantly between treatments (-0.12 percent; p=NS). Day-to-day variability in self-measured fasting blood glucose was lower with insulin detemir (2.82 versus 3.60 mmol/L; p<0.001). Lower glucose levels were seen before breakfast with insulin detemir compared to NPH (p<0.001). There was a 26 percent reduction in the relative risk of nocturnal hypoglycemia with insulin detemir compared with NPH (p=0.003). The adverse effect profiles were similar between treatment groups.94

In the 18-week, randomized, open-label, parallel trial, 595 patients with type 1 diabetes received insulin detemir or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart or regular human insulin, respectively.95 Glycemic control with insulin detemir/insulin aspart was improved in comparison with NPH insulin/regular human insulin (HbA1c: 7.88 versus 8.11 percent; p<0.001). Lower postprandial plasma glucose levels were seen in the insulin detemir/insulin aspart group (p<0.001), as well as lower within-person day-today variation in plasma glucose (SD: 2.88 versus 3.12 mmol/L; p<0.001). Risk of overall and nocturnal hypoglycemia was 21 percent (p=0.036) and 55 percent (p<0.001) lower in the insulin detemir/insulin aspart

group than in the NPH insulin/regular human insulin group, respectively.95

A 22-week, multinational, open-label, randomized, parallel-group trial enrolled 395 patients with type 2 diabetes. Patients were randomized to treatment with either insulin detemir in combination with insulin aspart at meals or insulin NPH in combination with regular human insulin at meals.96 Basal insulins were administered either once or twice daily. At 22 weeks, HbA1c was comparable between treatments (insulin detemir group: 7.46 percent, NPH group: 7.52 percent, p=0.515) with decreases from baseline of 0.65 and 0.58 percent, respectively. The insulin detemir group was associated with a significantly lower within-person variation in self-measured FPG (SD: 1.20 versus 1.54 mmol/L, p<0.001), as well as a lower body weight gain (0.51 versus 1.13 kg, p=0.038) than with the NPH group. The risk of nocturnal hypoglycemia was 38 percent lower with the insulin detemir group compared to the NPH group (p=0.14). The overall safety profile was similar between the two treatments.96

CONCLUSION:

This study concluded that combination of insulin detemir and aspart is better than combination of NPH and regular insulin in patients of type 1 diabetes in terms of hypoglycemia. So, we recommend that combination of insulin detemir and aspart should be used as a primary treatment in patients of type 1 diabetes in order to reduce the hypoglycemia in these particular patients.

REFERENCES:

1. Yadav SC, Saldhana A, Majumdar B. Status of thyroid profile in type-2 diabetes mellitus. J Nobel Med Coll. 2012;1(2):64-71.
2. Mayfield J. Diagnosis and classification of Diabetes Mellitus: new criteria. Am Fam Physician. 1998;58(6):1355-62.
3. Rostami P , Setoodeh A , Rabbani A , Nakhaei-Moghadam M , Najmi-Varzaneh F , Rezaei N . A randomized clinical trial of insulin glargine and aspart, compared to NPH and regular insulin in children with type 1 diabetes mellitus. Iran J Pediatr. 2014;24:173-8.
4. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Insulin analogues in children with Type 1 diabetes: a 52-week randomized clinical trial. Diabet Med. 2013;30:216-25.
5. Kristensen PL, Pedersen-Bjergaard U, Beck-Nielsen H, Norgaard K, Perrild H, Christiansen JS, et al. A prospective randomised cross-over study of the effect of insulin analogues and human insulin on the frequency of severe hypoglycaemia in patients with type 1 diabetes and recurrent hypoglycaemia (the HypoAna trial): study rationale and design. BMC Endocr Disord. 2012;12:10.
6. Laubner K, Molz K, Kerner W, Karges W, Lang W, Dapp A, et al. Daily insulin doses and injection frequencies of neutral protamine hagedorn (NPH) insulin, insulin detemir and insulin glargine I type 1 and type 2 diabetes: a multicenter analysis of 51964 patients from the German/Austrian DPV-wiss database. Diabetes Metab Res Rev. 2014;30:395-404.
7. Morales C, de Luis D, de Arellano AR, Ferrario MG, Lizan L. Cost-effectiveness analysis of insulin detemir compared to neutral protamine hagedorn (NPH) in patients with type 1 and type 2 diabetes mellitus in Spain. Diabetes Ther. 2015;6:593-610.
8. Katz ML, Volkening LK, Anderson BJ, Laffel LM. Contemporary rates of severe hypoglycaemia in youth with type 1 diabetes: variability by insulin regimen. Diabet Med. 2012;29:926-32
9. Dündar BN, Dündar N, Eren E. Comparison of the efficacy and safety of insulin glargine and insulin detemir with NPH insulin in children and adolescents with type 1 diabetes mellitus receiving intensive insulin therapy. J Clin Res Pediatr Endocrinol. 2009;1:181-7. (for sample size calculation)
10. Emerging Risk Factors Collaboration. "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies". The Lancet. 2010;375(9733):2215–22.
11. Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassaï B, et al. "Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials". BMJ. 2011;343:4169.
12. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20:1183–97.

13. Rother KI. Diabetes treatment—bridging the divide. The New England J of Med. 2007;356(15):1499–501.
14. "Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Merck Manual Professional". Merck Publishing. April 2010.
15. Dorner M, Pinget M, Brogard JM. Essential labile diabetes (in German). Munch Med Wochenschr. 1977;119(19):671–4.
16. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. Diabetes Care. 2008;31(5):899–904.
17. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047–53.
18. Tarin SMA, Khan MI: Pattern of diabetic admissions in medical ward Pakistan. J Med Res. 2004;43(4):27-30.
19. Ichinose K, Kawasaki E, Eguchi K. Recent advancement of understanding pathogenesis of type 1 diabetes and potential relevance to diabetic nephropathy. Am J Nephrol. 2007;27(6):554–64.
20. Ahmed AM. History of diabetes mellitus. Saudi Med J. 2002;23:373-8.
21. Nathan DM, Cleary PA, Backlund JY. "Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes". The New Eng J of Med. 2005;353(25):2643–53.
22. Guthrie, Richard A. Pathophysiology of diabetes mellitus. Critical Care Nursing Quarterly. 2004;27(2):113-25.
23. Rossetti L. Glucose toxicity: the implications of hyperglycemia in the pathophysiology of diabetes mellitus. Clinic & Invest Med. 1995;18(4):255-60.
24. Cooke DW, Plotnick L. Type 1 diabetes mellitus in pediatrics. Pediatr Rev. 2008;29(11):374–84.
25. Saydah SH, Miret M, Sung J, Varas C, Gause D, Brancati FL. Post challenge hyperglycemia and mortality in a national sample of U.S. adults. Diabetes Care. 2001;24(8):1397–402.
26. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation. World Health Organization. 2006; p. 21.
27. Santaguida PL, Balion C, Hunt D, Morrison K, Gerstein H, Raina P, et al. Diagnosis, Prognosis, and Treatment of Impaired Glucose Tolerance and Impaired Fasting Glucose. Summary of Evidence Report/Technology Assessment. 2011;128.
28. McCance DR, Hanson RL, Charles MA, Jacobsson LT, Pettitt DJ, Bennett PH, et al. Which test for diagnosing diabetes? Diabetes Care. 1995;18:1042–4.
29. Davidson MB, Peters AL, Schriger DL. An alternative approach to the diagnosis of diabetes with a review of the literature. Diabetes Care. 1995;8:1065–71.
30. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med. 2010;362(9):800–11.
31. Chiang JL, Kirkman MS, Laffel LM, Peters AL. Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care. 2014 Jun 16.
32. Tucker M. First-Ever ADA Guidance Specifically for Type 1 Diabetes. Medscape Medical news. Available athttp://www.medscape.com/viewarticle/826854. Accessed: June 20, 2014.
33. Kielgast U, Holst JJ, Madsbad S. Antidiabetic actions of endogenous and exogenous GLP-1 in type 1 diabetic patients with and without residual ß-cell function. Diabetes. 2011 May. 60(5):1599-607.
34. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993 Sep 30. 329(14):977-86.
35. Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med. 2005 Dec 22. 353(25):2643-53.
36. Genuth S. Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. Endocr Pract. 2006 Jan-Feb. 12 Suppl 1:34-41.
37. Lind M, Bounias I, Olsson M, et al. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet. 2011 Jul 9. 378(9786):140-6.
38. Tomlin A, Dovey S, Tilyard M. Health outcomes for diabetes patients returning for three annual general practice checks. N Z Med J. 2007 Apr 13. 120(1252):U2493.

39. acobson AM, Ryan CM, Cleary PA, Waberski BH, Weinger K, Musen G, et al. Biomedical risk factors for decreased cognitive functioning in type 1 diabetes: an 18 year follow-up of the Diabetes Control and Complications Trial (DCCT) cohort. Diabetologia. 2011 Feb. 54(2):245-55.
40. Asvold BO, Sand T, Hestad K, Bjørgaas MR. Cognitive function in type 1 diabetic adults with early exposure to severe hypoglycemia: a 16-year follow-up study. Diabetes Care. 2010 Sep. 33(9):1945-7.
41. Garg SK, Voelmle MK, Beatson CR, Miller HA, Crew LB, Freson BJ, et al. Use of Continuous Glucose Monitoring in Subjects With Type 1 Diabetes on Multiple Daily Injections Versus Continuous Subcutaneous Insulin Infusion Therapy: A prospective 6-month study. Diabetes Care. 2011 Mar. 34(3):574-9.
42. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011 Apr. 34(4):795-800.
43. Klonoff DC, Buckingham B, Christiansen JS, et al. Continuous glucose monitoring: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011 Oct. 96(10):2968-79.
44. Medtronic, Inc. Medtronic gains approval of first artificial pancreas device system with threshold suspend automation [press release]. September 27, 2013. Available athttp://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=1859361&highlight. Accessed: October 7, 2013.
45. Tucker ME. FDA OKs insulin pump with low-glucose suspend feature. Medscape Medical News. September 27, 2013.
46. Tucker M. FDA Approves Inhaled Insulin Afrezza for Diabetes. Medscape Medical News. Available athttp://www.medscape.com/viewarticle/827539.. Accessed: July 14, 2014.
47. Afrezza (insulin inhaled) prescribing information [package insert]. Valencia CA, United States: MannKind Corporation. June, 2014. Available at
48. US Food and Drug Administration. Mixups between Insulin U-100 and U-500 (April 2008). FDA Patient Safety News. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=79. Accessed: January 28, 2012.
49. de la Pena A, Riddle M, Morrow LA, et al. Pharmacokinetics and pharmacodynamics of high-dose human regular u-500 insulin versus human regular u-100 insulin in healthy obese subjects. Diabetes Care. 2011 Dec. 34(12):2496-501.
50. Garg S, Ampudia-Blasco FJ, Pfohl M. Rapid-acting insulin analogues in Basal-bolus regimens in type 1 diabetes mellitus. Endocr Pract. 2010 May-Jun. 16(3):486-505.
51. Birkeland KI, Home PD, Wendisch U, Ratner RE, Johansen T, Endahl LA, et al. Insulin Degludec in Type 1 Diabetes: A randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care. 2011 Mar. 34(3):661-5.
52. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. Diabetes Obes Metab. 2007 Sep. 9(5):648-59.
53. Suissa S, Azoulay L, Dell'aniello S, et al. Long-term effects of insulin glargine on the risk of breast cancer.Diabetologia. 2011 Sep. 54(9):2254-62.
54. Johnson JA, Bowker SL, Richardson K, Marra CA. Time-varying incidence of cancer after the onset of type 2 diabetes: evidence of potential detection bias. Diabetologia. 2011 Sep. 54(9):2263-71.
55. Bao J, Gilbertson HR, Gray R, et al. Improving the Estimation of Mealtime Insulin Dose in Adults With Type 1 Diabetes: The Normal Insulin Demand for Dose Adjustment (NIDDA) study. Diabetes Care. 2011 Oct. 34(10):2146-51.
56. Bergenstal RM, Tamborlane WV, Ahmann A, Buse JB, Dailey G, Davis SN, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. N Engl J Med. 2010 Jul 22. 363(4):311-20.
57. Busko M. Insulin pump therapy bests injection therapy in large study. Medscape Medical News. August 19, 2013. [Full Text].
58. Johnson SR, Cooper MN, Jones TW, Davis EA. Long-term outcome of insulin pump therapy in children with type 1 diabetes assessed in a large population-based case-control study. Diabetologia. 2013 Aug 21.
59. King BR, Goss PW, Paterson MA, Crock PA, Anderson DG. Changes in Altitude Cause Unintended Insulin Delivery From Insulin Pumps: Mechanisms and implications. Diabetes Care. 2011 Sep. 34(9):1932-3.

60. Grunberger G, Abelseth JM, Bailey TS, Bode BW, Handelsman Y, Hellman R. Consensus statement by the american association of clinical endocrinologists/american college of endocrinology insulin pump management task force. Endocr Pract. 2014 May 1. 20(5):463-89.
61. Babiker A, Datta V. Lipoatrophy with insulin analogues in type I diabetes. Arch Dis Child. 2011 Jan. 96(1):101-2.
62. Giménez M, Gilabert R, Monteagudo J, Alonso A, Casamitjana R, Paré C, et al. Repeated episodes of hypoglycemia as a potential aggravating factor for preclinical atherosclerosis in subjects with type 1 diabetes.Diabetes Care. 2011 Jan. 34(1):198-203.
63. Asvold BO, Sand T, Hestad KA, Bjorgaas MR. Quantitative EEG in type 1 diabetic adults with childhood exposure to severe hypoglycaemia: a 16 year follow-up study. Diabetologia. 2011 Sep. 54(9):2404-8.
64. Kacerovsky M, Jones J, Schmid AI, et al. Postprandial and fasting hepatic glucose fluxes in long-standing type 1 diabetes. Diabetes. 2011 Jun. 60(6):1752-8.
65. Ahmedani MY, Haque MS, Basit A, Fawwad A, Alvi SF. Ramadan Prospective Diabetes Study: the role of drug dosage and timing alteration, active glucose monitoring and patient education. Diabet Med. 2012 Jun. 29(6):709-15.
66. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA. 2006 Jun 21. 295(23):2765-79.
67. Salardi S, Balsamo C, Zucchini S, Maltoni G, Scipione M, Rollo A, et al. High rate of regression from micro-macroalbuminuria to normoalbuminuria in children and adolescents with type 1 diabetes treated or not with enalapril: the influence of HDL cholesterol. Diabetes Care. 2011 Feb. 34(2):424-9.
68. de Boer IH, Rue TC, Cleary PA, et al. Long-term Renal Outcomes of Patients With Type 1 Diabetes Mellitus and Microalbuminuria: An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort. Arch Intern Med. 2011 Mar 14. 171(5):412-420.
69. Strippoli GF, Bonifati C, Craig M, Navaneethan SD, Craig JC. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. Cochrane Database Syst Rev. 2006 Oct 18. CD006257.
70. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. Circulation. 2007 Jan 23. 115(3):387-97.
71. Lipsky BA, Berendt AR, Deery HG, Embil JM, Joseph WS, Karchmer AW, et al. Diagnosis and treatment of diabetic foot infections. Clin Infect Dis. 2004 Oct 1. 39(7):885-910.
72. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005 Jan 12. 293(2):217-28.
73. Buse JB, Ginsberg HN, Bakris GL, Clark NG, Costa F, Eckel R, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Diabetes Care. 2007 Jan. 30(1):162-72.
74. Margeirsdottir HD, Stensaeth KH, Larsen JR, Brunborg C, Dahl-Jørgensen K. Early signs of atherosclerosis in diabetic children on intensive insulin treatment: a population-based study. Diabetes Care. 2010 Sep. 33(9):2043-8.
75. van Dieren S, Nöthlings U, van der Schouw YT, Spijkerman AM, Rutten GE, van der A DL, et al. Non-fasting lipids and risk of cardiovascular disease in patients with diabetes mellitus. Diabetologia. 2011 Jan. 54(1):73-7.
76. Lee SH, Kim JH, Kang MJ, et al. Implications of nocturnal hypertension in children and adolescents with type 1 diabetes. Diabetes Care. 2011 Oct. 34(10):2180-5.
77. Leiter LA, Lundman P, da Silva PM, et al. Persistent lipid abnormalities in statin-treated patients with diabetes mellitus in Europe and Canada: results of the Dyslipidaemia International Study. Diabet Med. 2011 Nov. 28(11):1343-1351.
78. Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, et al. Effect of adjunct metformin treatment on levels of plasma lipids in patients with type 1 diabetes. Diabetes Obes Metab. 2009 Oct. 11(10):966-77.
79. Tucker ME. ACC/AHA statin guidelines, with caveats. WebMD. Available athttp://www.medscape.com/viewarticle/837138. Accessed: Dec 24, 2014.
80. Marks JB. Perioperative management of diabetes. Am Fam Physician. 2003 Jan 1. 67(1):93-100.
81. Chapman T, Perry C. Insulin detemir: a review of its use in the management of type 1 and 2 diabetes mellitus. Drugs. 2004;64:2577–95.
82. Chapman T, Perry C. Spotlight on insulin detemir in type 1 and 2 diabetes mellitus. BioDrugs. 2005;19:67–9.

83. Danne T, Lupke K, Walte K, et al. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. Diabetes Care. 2003;26:3087–92.
84. Klein O, Lynge J, Endahl L, et al. Insulin detemir and insulin glargine: similar time-action profiles in subjects with type 2 diabetes. Diabetes. 2006;55(suppl 1):A76.
85. Pieber TR, Treichel H-C, Hompesch B, et al. Comparison of insulin detemir and insulin glargine in subjects with Type 1 diabetes using intensive insulin therapy. Diabetic Med. 2007;24:635-642.
86. Luddeke HJ, Hansen JB, Nauck M. PREDICTIVE[TM]: A global, prospective, observational study to evaluate insulin detemir treatment in type 1 and type 2 diabetes: German cohort data. Program and abstracts of the American Diabetes Association 66th Annual Scientific Sessions; June 9-13, 2006; Washington, DC. Poster 511-P.
87. DeWitt D, Hirsch B. Outpatient insulin therapy in type 1 and type 2 diabetes mellitus: scientific review. JAMA. 2003;289:2254–64. [PubMed]
88. Fritsche A, Haring H. At last, a weight neutral insulin? Int J Obesity Relat Metab Disord. 2004;28(Suppl 2):S41–6.
89. Haak T, Tiengo A, Waldhausl W. Treatment with insulin detemir is associated with predictable fasting glucose levels and favourable weight development in subjects with type 2 diabetes. Diabetologia. 2003;46(Suppl 2):A120.
90. Havelund S, Plum A, Ribel U. The mechanism of protraction of insulin detemir, a long-acting, acylated analog of human insulin. Pharm Res. 2004;8:1498–504.
91. Heinemann L, Linkeschova R, Rave K. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care. 2000;23:644–9.
92. Schober E, Schoenle E, Van Dyk J. Comparative trial between insulin glargine and NPH insulin in children and adolescents with type 1 diabetes mellitus. J Pediatr Endocrinol Metab. 2002; 15(4):369-376.
93. Hermansen K, Fontaine P, Kukolja K. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia. 2004b;47:622–9.
94. Russell-Jones D, Simpson R, Hylleberg B. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal-bolus regimen. Clin Ther. 2004; 26(5):724-736.
95. Hermansen K, Fontaine P, Kukolja KK. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal-bolus therapy for patients with type 1 diabetes. Diabetologia. 2004;47(4):622-629.
96. Raslova K, Bogoev M, Raz I. Insulin detemir and insulin aspart: a promising basal-bolus regimen for type 2 diabetes. Diabetes Res Clin Pract. 2004; 66(2):193-201.