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EFFICACY AND SAFETY OF INSULIN DEGLUDEC VERSUS INSULIN GLARGINE: A SYSTEMATIC REVIEW AND META-ANALYSIS OF TWENTY CLINICAL TRIALS

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Keywords:

Insulin degludec, Insulin glargine, Type 2 diabetes Mellitus, Meta-analysis, Fasting plasma glucose, HbA1c

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ABSTRACT: Introduction: This study aimed to compare the efficacy and safety of insulin degludec with insulin glargine in patients with type 1 and type 2 diabetes. **Methods:** We systematically searched PubMed, Embase, Web of Science, and Cochrane Library databases for randomized controlled trials published prior to July 2019 (no language restrictions) which compared insulin degludec with insulin glargine. Our main endpoints were glycemic control, and hypoglycemic events. We assessed pooled data using random-effects models. **Results:** A total of 20 studies that included 22706 patients, 11929 in the insulin degludec arm of the studies and 10777 patients in the insulin glargine arm were identified and subsequently assessed. Our analysis showed that compared with insulin glargine, insulin degludec yielded an improved mean reduction in fasting plasma glucose (FPG) (MD - 6.747, 95% CI - (1.702 to 11.79), p = 0.013), improved mean reduction in glycosylated hemoglobin (HbA1c) (MD 0.095, 95% CI –(-0.155 to -0.035), p = 0.867) and a lower ratio of participants experiencing the severe hypoglycemic event and nocturnal hypoglycemia (95% CI – 1.67 to 0.37, p = 0.004).Results showed insulin degludec to produce a statistically significant decrease in FPG level. **Conclusions:** Insulin degludec and insulin glargine provide more or less similar glycemic control, but the risk of hypoglycemia with insulin degludec is lower than with Insulin glargine. Insulin degludec may be an alternative treatment for managing patients with diabetes who are prone to hypoglycemia with insulin glargine.

INTRODUCTION: Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia caused either due to inadequate insulin release or resistance to insulin action. Poorly controlled Diabetes mellitus leads to various microvascular as well as macrovascular complications [1]. Glycemic control can be achieved either by oral antidiabetic drugs or insulin. Tight glycemic control prevents and delays the development of microvascular as well as macrovascular complications.

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Achieving glycemic control is associated with the risk of hypoglycemia [2]. Insulin preparations are the mainstay of management in the treatment of type 1 diabetes and type 2 diabetes. Long-acting insulin analogues insulin glargine and insulin degludec have been developed. These produce more physiological basal insulin action and are associated with a lower risk of hypoglycemia compared to older human insulin preparations while achieving glycemic control [3].

Insulin degludec is a new ultra-long-acting basal insulin analogue. It is a novel acylated basal insulin with a unique mechanism of protracted absorption which forms soluble multi-hexamers in subcutaneous tissues leading to the slow release of insulin monomers [4].

MATERIAL AND METHODS:

Search Strategy: The PubMed, web of sciences, EMBASE, and Cochrane Library electronic databases were searched for studies published up to July 15, 2019, to identify all publications that compare the effects of the Insulin degludec and that of Insulin glargine administration in patients with DM.

The following terms were used in combination with appropriate logical connectors: "degludec," "Insulin degludec," "glargine," "Insulin glargine," "diabetes," "insulin," "randomized," and "diabetes mellitus." Further, a manual search was performed by scanning the references of the identified articles to find studies that were potentially missed by the electronic searches.

Study Selection and Data Collection: The inclusion criteria of the present systematic review and meta-analysis were studies that compared the effects of the administration of Insulin degludec once a day with those of Insulin glargine treatment, RCTs with more than 26weeks follow-up, patients diagnosed with type 1 DM (T1DM) or type 2 DM (T2DM).

The exclusion criteria were Insulin degludec injected three times a week, Insulin degludec co-formulated with other hypoglycemic agents, trials lasting less than 12 weeks, short reports, and letters to editors, abstracts, or proceedings of scientific meetings. The study selection was strictly in compliance with the inclusion and exclusion criteria.

The selection process was carried out by crude screening to exclude a majority of the irrelevant studies at the level of title and abstract, and the remaining studies were double-examined by perusing the full text to reach the final decision. A consensus was reached on all eligible studies between the three screening authors. Any discrepancies were resolved by discussion.

Quality and Publication Bias of the Included Studies: The included studies' quality was quantitatively assessed using the Jadad scale. Sixteen out of the 20 included studies were carried out in multiple countries. As all the included studies had Jadad scores of 3 points or more therefore, all the included studies can be considered to be of high-quality **Table 1.**

TABLE 1: JADAD SCORE

Author Name		Descriptions of randomization	Double blinding	Dropouts and withdrawals	JADAD Score*
Tibaldi *et al*	Multicenter, parallel group trial	2	0	1	3
Rosenstock *et al*	Multicenter, parallel group trial	2	0	1	3
Wysham *et al*	Multicenter, parallel group trial	2	2	1	5
Aso *et al*	Multicenter, parallel group trial	2	0	1	3
Lane *et al*	Multicenter, parallel group trial	2	2	1	5
Iga *et al*	Multicenter, parallel group trial	2	0	1	3
Marso *et al*	Multicenter, parallel group trial	2	0	1	3
Warren *et al*	Multicenter, parallel group trial	2	0	1	3
Pan *et al*	Multicenter, parallel group trial	2	0	1	3
Hollander *et al*	Multicenter, parallel group trial	2	0	1	3
Gough *et al*	Multicenter, parallel group trial	2	0	1	3
Onishi *et al*	Multicenter, parallel group trial	2	0	1	3
Mathieu *et al*	Multicenter, parallel group trial	2	0	1	3
Zinman *et al*	Multicenter, parallel group trial	2	0	1	3
Rodbard *et a*l	Multicenter, parallel group trial	2	0	1	3
Meneghini *et al*	Multicenter, parallel group trial	2	0	1	3
Hellar *et al*	Multicenter, parallel group trial	2	0	1	3
Zinman *et al*	Multicenter, parallel group trial	2	0	1	3
Garber *et al*	Multicenter, parallel group trial	2	0	1	3
Birkland *et al*	Multicenter, parallel group trial	2	0	1	3

Three authors (AS, RM and TG) independently extracted all the relevant information from the eligible studies.

A pre-specified table that contained the relevant items was used to help with the data collection.

RESULTS: We identified 872 studies in our search of the databases, of which 20 (with data for 22,706 participants) were included in our analysis. These 20 RCTs were all published between 2012 and 2019.

The flow diagram of the search procedure is shown in **Fig. 1**, and the characteristics of the included studies 5-24 are described in **Table 2.**

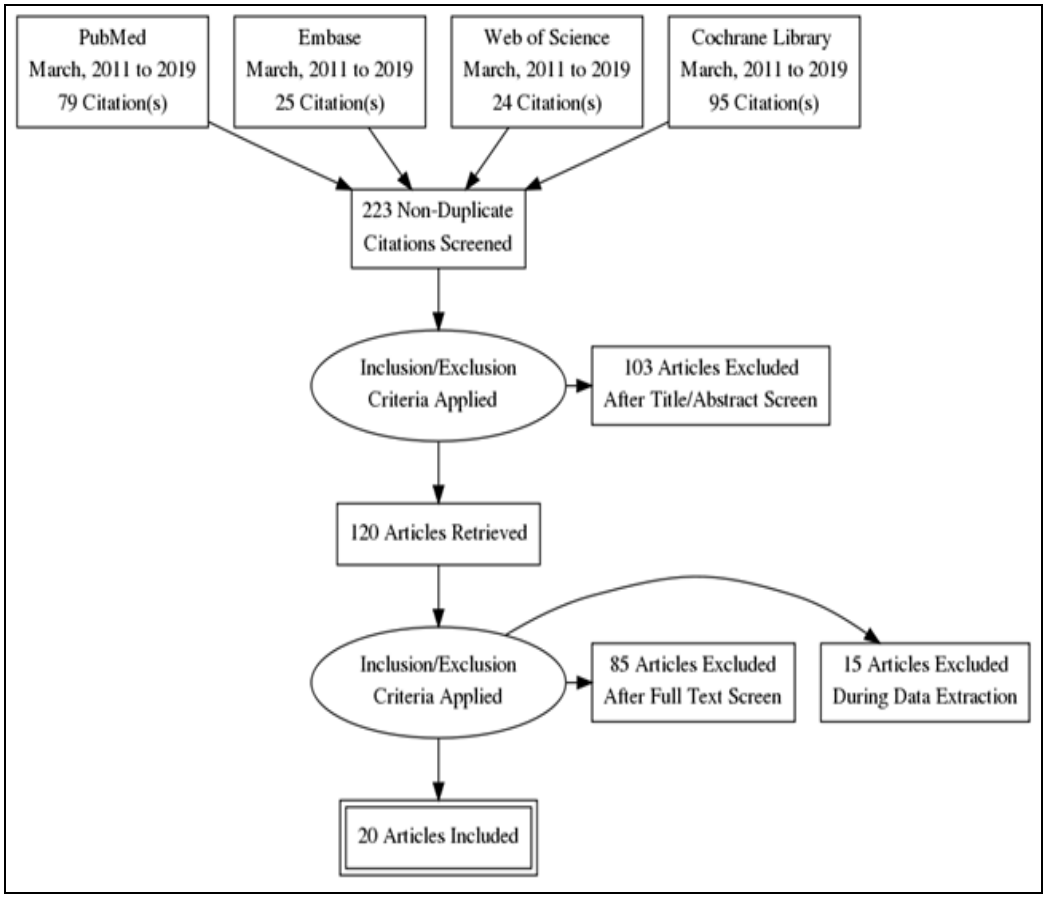

FIG. 1: FLOW DIAGRAM FOR IDENTIFYING ELIGIBLE STUDIES

The mean trial duration was 39.4 (range 12-104) weeks. Patients had a mean baseline HbA1c of 8.25% (range 7.4-9.55%), mean baseline FPG of 163.7 (range 127.4-186) mg/dL, mean baseline BMI of 30.7 (range 24-36.2) kg/ m^2, mean baseline weight of 86.7 (range 61.3-105.3) kg and mean duration of diabetes of 12.56 (range 4.8-23.3) years. Of the 20 RCTs, 16 were carried out in multiple countries [6, 9-11, 13-24], three in the USA [5, 7, 12], and one in Japan [8]. In the four crossover trials, participants were switched directly to the other intervention without a washout period [7, 9, 10, 12]. Therefore, only the first treatment phases were chosen in the meta-analysis, and we performed a pre-specified sensitivity analysis for possible bias. Ten trials compared insulin degludec with insulin glargine on a background of insulin naivety [6, 8, 13, 15-20, 22], leading us to perform a subgroup analysis based on the background treatment (insulin naivety or insulin treatment).

TABLE 2: DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF THE INCLUDED STUDIES

First author	Year	Location	Design	Background treatment	Differential interventions	Duration of intervention (weeks)	No of participants	No of participants Deg	No of participants Gla	No of male participants n(%)	Mean age	Mean baseline HbA1c	Mean baseline FPG mg/dl	Mean baseline BMI(kg/m^2)	Mean baseline body weight	Mean duration of diabetes (years)
Tibaldi *et al*	2019	USA	RCT	T2DM	IDeg100 OD vs IGlar 300 OD	26	4056			2107 (51.9)	57.8	9.55		34.35	100.3	4.8
Rosenstock *et al.*	2018	158 sites in 16 countries	RCT	insulin naive T2DM	IDeg100 OD vs IGlar 300 OD	24	929	463	466	502 (54)	60.5	8.64	186	31.5	89.7	10.6

Wysham *et al.*	2017	USA	Cross over RCT	Basal insulin +_ OADs T2DM	IDeg100 OD vs IGlar 100 OD	32	720	721	721	382 (53)	61.4	7.6	137	32.2	91.7	14.1
Aso *et al.*	2017	Japan	RCT	insulin naive T2DM	IDeg OD vs IGlar OD	24	45	33	12	20 (45)	64.4	8.86	162.5	24.6	61.3	11.5
Lane *et al.*	2017	90 sites in 2 countries	Cross over RCT	Basal insulin +_ OADs T1DM	IDeg100 OD vs IGlar 300 OD	32	720	501	501	382 (53)	61.4	7.6	137			23.3
Iga *et al.*	2017	Multicentre	cross over RCT	Basal insulin +_ OADs T1DM	IDeg100 OD vs IGlar 300 OD	12	40	20	20	25 (62.5)	54	7.4	127.4	24	62	15.2
Marso *et al.*	2017	438 sites in 20 countries	RCT	Basal insulin +_ OADs T2DM	IDeg100 OD vs IGlar 100 OD	96	7637			4778 (62.5)	65	8.4	171.7	33.6	96.1	16.4
Warren *et al.*	2017	USA	Cross over RCT	Basal insulin +_ OADs T2DM	IDeg100 OD vs IGlar 300 OD	32	290	145	145	90 (62)	55.3	8.15	144.5	36.2	105.2	12.1
Pan *et al.*	2016	68 sites in 6 countries	RCT	insulin naive T2DM	IDeg100 OD vs IGlar 300 OD	26	833	555	278	433 (52)	56	8.3	169.2	27.2	74.65	8
Hollander *et al*	2015	123 sites in 12 countries	RCT	Basal insulin +_ OADs T2DM	**I**Deg100 OD vs IGlar 300 OD	78	757			410 (54.2)	58.7	8.25	165.6	32.15	92.2	13.55
Gough *et al.*	2013	multinational	RCT	insulin naive T2DM	IDeg 200 units/mL	26	457	229	228	243 (53)	57.8	8.3	172	32.2	92.2	8.4
Onishi *et al.*	2013	52 sites in 6 countries	RCT	insulin naive T2DM	IDeg 200 units/mL	26	435	289	146	233 (53)	58.6	8.3				
Mathieu *et al*	2013	Multi-centeric	RCT	Insulin-naive T1DM	IDeg flex vs IDeg OD vs IGlar OD	26	493	329	164	284	43.7	7.7	175.8		80.5	18.4
Zinman *et al.*	2013	94 cities in 7 countries	RCT	insulin naive T2DM	**I**Deg 3TWAM vs IGlar OD	26	459			261 (56.9)	58.2	8.25	170.4	32.45	93.3	8.85
Rodbard *et al.*	2013	94 cities in 7 countries	RCT	insulin naive T2DM	**I**Deg OD vs IGlar OD	104	1030			648(63)	59	8.2	173.7	31.25	90.6	9
Meneghini *et al.*	2013	69 cities in 14 countries	RCT	insulin naive T2DM	**I**Deg OD vs IGlar OD	26	687	457	230	370(54)	56.4	8.4	160.2	29.6	81.8	10.6
Hellar *et al.*	2012	79 cities in 64countries	RCT	Basal insulin +_ OADs T1DM	**I**Deg100 OD vs IGlar 300 OD	52	629	472	157	364 (58)	43.2	7.7				
Zinman *et al.*	2012	166 cities in 12 countries	RCT	insulin naive T2DM	**I**Deg-100 OD vs IGlar-100 OD	52	1030	773	257	638(61.9)	59	8.2	173.7	31.25	90.7	9
Garber *et al.*	2012	123 cities in 12 countries	RCT	Basal insulinT2DM	**I**Deg-100 OD vs IGlar-100 OD	52	992	744	248	538 (54)	58.9	8.3	165.6	32.1	92.4	13.5
Birkeland *et al.*	2011	28 cities in 5 countries	RCT			16	178	119	59	106(59)	46	8.4	175	27	79.7	20.8
							22706				53.56	8.25	163.7	30.7	86.7	12.56

In all, 22706 patients were included in the present study. Four studies recruited patients with T1DM, [9, 10, 17, 21] and the other 16 studies enrolled patients with T2DM [5-8, 11-16, 18-20, 22-24].

In all the included studies, the authors used an intention-to-treat analysis. Withdrawals and dropouts were described adequately in all these studies, and the rates of completed treatment varied from 80% to 100%.

The clinical characteristics of each trial are summarized in **Tables 3** and **4.**

TABLE 3: CHANGES IN HBA1C AND FPG LEVELS

Author Name	HbA1c				Fasting Plasma Glucose			
	DEG (% Change)	GLA (% Change)	ETD	95% CI	DEG (% Change)	GLA (% Change)	ETD	95% CI
Tibaldi *et al*	1.48	1.22	-0.27	(-0.51, -0.03)				
Rosenstock *et al*	1.59	1.64	-0.05	(-0.15, 0.05)	63.47	71.16	7.68	(2.71, 12.65)
Wysham *et a*l.	1.07	1.03	0.09	(-0.04, 0.23)	31.9	27.9		
Aso *et al.*	1.6	1.7						
Lane *et al.*	0.8	0.92	0.03	(-0.1, 0.15)	30.8	28.1	-17	(-25.5, -8.41)
Marso *et al.*			0.01	(-0.05, 0.07)	39.9	34.9	-7.2	(-10.3, -4.1)
Warren *et al*	0.12	0.06	0.06	(-0.21, 0.09)	14.76	0.9	0.77	(-1.39, -0.15)
Pan *et al.*	1.3	1.2	-0.05	(-0.18, 0.08)	60.3	56.52	-0.26	(-0.53, 0.02)
Hollander *et al*	1	1.2	0.16	(0.02, 0.3)	43	40	-0.19	(-0.59, 0.21)
Gough *et al.*	1.3	1.3	0.04	(-0.11, 0.19)	66.7	60.9	-0.42	(-0.78, -0.06)
Onishi *et al.*	1.24	1.35	0.11	(-0.03, 0.24)	51.84	53.46	-0.09	(-0.41, 0.23)
Mathieu *et al*	0.4	0.58	0.17	(0.04, 0.3)	23.04	23.94	-1.07	(-1.82, 0.32)
Zinman *et al*	1.1	1.4	0.34	(0.18, 0.51)				
Rodbard *et al*	1.1	1.3	0.07	(-0.07, 0.22)	75.06	64.08	-0.36	(-0.67, -0.05)
Meneghini *et al*	1.28	1.26	0.04	(-0.12, 0.2)			-0.42	(-0.82, -0.02)
Hellar *et al*	0.4	0.39	-0.01	(-0.14, 0.11)				
Zinman *et al*	1.06	1.19	0.09	(-0.04, 0.22)	68.4	59.4	-0.43	(-0.74, -0.13)
Garber *et al*	1.1	1.2	0.08	(-0.05, 0.21)				
Birkeland *et al*	0.57	0.62	0.1	(-0.14, 0.34)	28.8	9.72	-0.56	(-1.84, 0.73)

ETD (Estimated treatment difference)

TABLE 4: OBSERVED OVERALL AND NOCTURNAL HYPOGLYCEMIA IN THE META-ANALYSIS

First author	Hypoglycemia (%)				Events (Per patient year)				Nocturnal Hypoglycemia (%)				Events (Per patient year)			
	Deg	Gla	ERR	95% CI	Deg	Gla	ERR	95% CI	Deg	Gla	ERR	95% CI	Deg	Gla	ERR	95% CI
Tibaldi	7.7	6.2	0.7	(0.5, 0.99)	0.3	0.26										
Rosenstock	69	66.5	0.88	(0.66, 1.17)	10.8	9.3	0.86	(0.71, 1.04)	28.9	28.6	0.99	(0.74, 1.32)	2.26	1.83	0.81	(.58, 1.12)
Wysham	22.5	31.6	-9.1	(-13.1, -5)	2.2	2.75	0.77	(0.7, 0.85)								
Lane	83	86.5	0.94	(0.91, 0.98)	22	24.6	0.89	(0.85, 0.94)					2.77	4.28	0.64	(0.56, 0.73)
Marso	4.9	6.6	0.73	(0.6, 0.89)	3.7	6.25	0.6	(0.48, 0.76)	4.9	6.25			3.7	6.25	0.6	(0.48, 0.76)
Warren	26.4	36.6	0.594	(0.39, 0.901)	1.92	2.88			9.35	11.35			0.38	0.63		(0.29, 0.48)
Pan et al	23.1	28.4	0.8	(0.59, 1.1)	85	97	0.8	(0.9, 1.1)	7.2	9			22	24	0.77 (0.43 to 1.37)	
Hollander	86	86.4	0.76	(0.62, 0.94)	9.84	12.76	0.85	(0.72, 1.02)	42	52			1.34	1.76	0.76	(0.58, 0.99)
Gough	28.5	30.7	0.86	(0.58, 1.28)	1.22	1.42	0.86	(0.58, 1.28)	6.1	8.8			0.18	0.28	0.64	(0.3, 1.37)
Onishi	50	53	0.82	(0.6, 1.11)	3	3.7							0.8	1.2	0.62	(0.38, 1.04)
Mathieu	93.9	96.9	0.47	(0.23, 0.94)	82.4	79.7	1.03	(0.85, 1.26)	67.7	72.7			6.2	10	0.62	(0.44, 0.82)
Zinman 2013			1.04	(0.69, 1.55)	1.3	1.3									0.62	(0.38, 1.04)
Rodbard	58	55	0.84	(0.68, 1.04)	1.72	2.05			20.6	23.7			0.27	0.46	0.57	(0.4, 0.81)
Meneghini	51	49	1.03	(0.75, 1.4)	388	378			11	21			0.6	0.8		(0.38, 1.04)
Hellar					42.5	40.1	1.07	(0.89, 1.28)					4.41	5.86	0.75	(0.59, 0.96)
Zinman 2012	46.5	46.3			1.52	1.85	0.82	(0.64, 1.04)	13.8	15.2			0.25	0.39	0.64	(0.42, 0.98)
Garber					11.1	13.6	0.82	(0.69, 0.99)					1.4	1.8	0.75	(0.58, 0.99)
Birkeland Type 1					47.9	66.2	0.72	(0.52, 1)					8.8	12.3	0.42	(0.25, 0.69)

Deg (Degludec), Gla (Glargine), ERR (estimated Rate Ratio), CI (Confidence interval)

Glycemic Control: The HbA1c and the changes from the baseline to the endpoint levels were reported in all the 20 included studies. Our study found that the mean reduction in HbA1c level was

1.06% with insulin degludec while treatment with insulin glargine led to a greater mean reduction in HbA1c level of 1.156%. The overall meta-analysis revealed no statistically significant difference between the two groups with MD of 0.09% in the HbA1c level, with nonsignificant heterogeneity (MD=0.09%, 95% CI=-0.155 to 0.035, p=0.867). **Table 3, Fig. 2.**

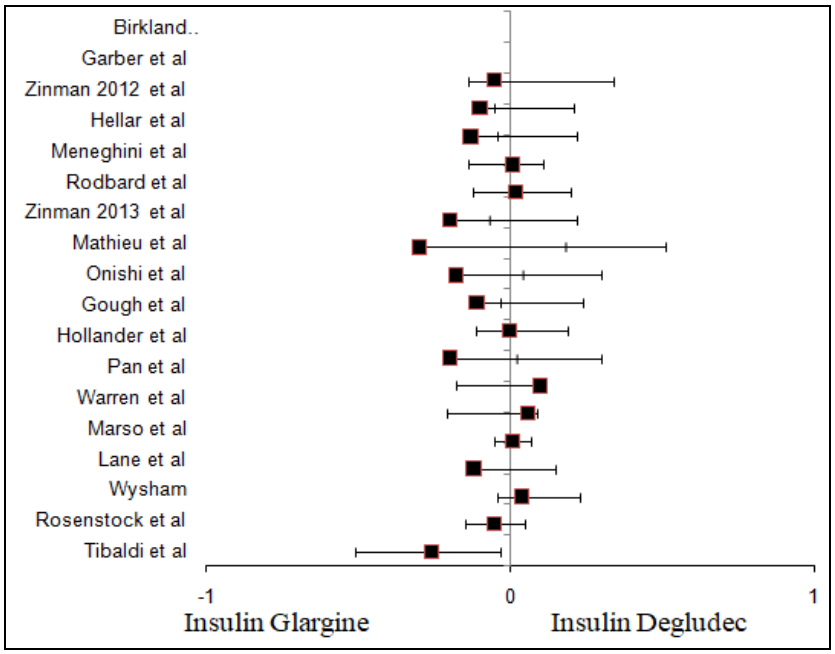

FIG. 2: FOREST PLOT (MEAN DIFFERENCE IN CHANGES IN GLYCOSYLATED HAEMOGLOBIN (HBA1C) BETWEEN INSULIN DEGLUDEC AND INSULIN GLARGINE)

Fifteen studies that included 5850 patients in the insulin degludec group and 3632 patients in the insulin glargine group reported the changes in FPG between baseline and the end of the intervention. A pooled analysis of 15 trials revealed that the insulin degludec treatment was associated with a greater mean decrease in FPG levels of 48.4 mg/dl as compared to insulin glargine, which showed a mean decrease of 41.7 mg/dl. This difference between the two groups was statistically significant. (MD = 6.74, 95% CI=1.703 to 11.79 to 12.94, p=0.013 **Table 3**, **Fig. 3.**

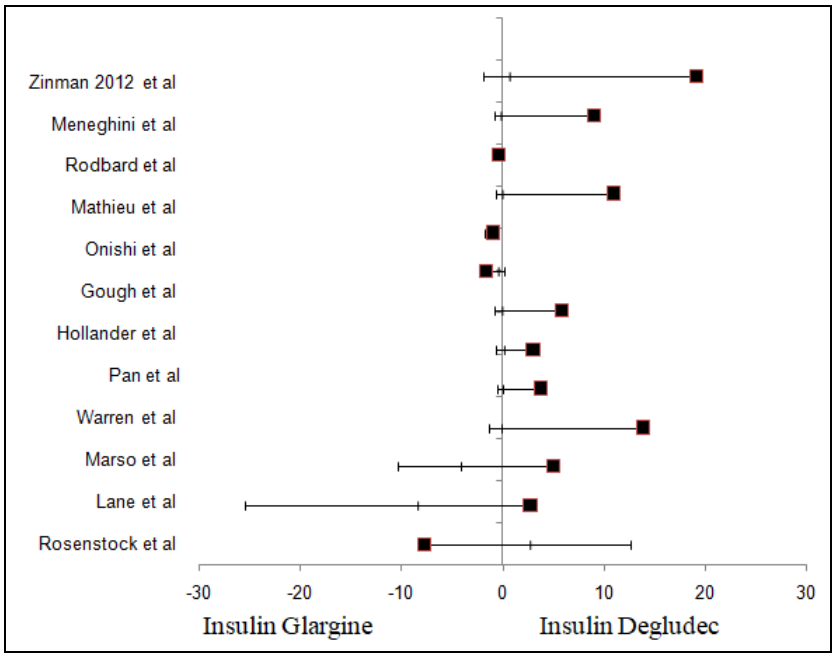

FIG. 3: FOREST PLOT (MEAN DIFFERENCE IN CHANGES IN FASTING PLASMA GLUCOSE (FPG) BETWEEN INSULIN DEGLUDEC AND INSULIN GLARGINE)

Safety Endpoints: Out of 20 trials included in the study, only 9 reported hypoglycemia incidences. Pooled analysis of these showed insulin degludec to have lesser mean hypoglycemic episodes (52.36) as compared to insulin glargine (54.48). The difference was not statistically significant. (p = 0.183, CI = -5.48 to 1.24). We identified 18 studies that reported the events per patient-year of overall hypoglycemia **Table 4.**

Eleven trials included in the study mentioned incidences of nocturnal hypoglycemia. Analysis showed a lesser number of nocturnal hypoglycemic episodes than insulin glargine and was found to be statistically significant (p = 0.026, CI = -5.51 to -0.42). Insulin degludec produceda lesser number of events of nocturnal hypoglycemia per patient-year which was statistically significant (p = 0.004, CI = -1.67 to -0.37) **Table 4.**

DISCUSSION: This systematic review and meta-analysis was done to evaluate the safety and efficacy of two long-acting insulin analogues, insulin degludec and insulin glargine in patients of type 1 as well as type 2 diabetes mellitus. After screening the studies, as per inclusion and exclusion criteria, 20 RCTs were included. To analyze efficacy between the insulin degludec and insulin glargine, we assessed overall glycemic control, mean reduction in HbA1c and reduction in FPG. For the analysis of safety between the insulin degludec and insulin glargine, we assessed the overall incidence of adverse effects, incidence of overall and nocturnal hypoglycemia, and events per patient-year. In the analysis's pooled results, a clinically significant difference was found in glycemic control between the insulin degludec and insulin glargine. The treatment with insulin degludec had better glycemic control than treatment with insulin glargine.

The mean reduction in HbA1c level was more with insulin glargine as compared to insulin degludec but it was not statistically significant (p = 0.867). These results are consistent with most of the studies included in the meta-analysis. The glycemic control in terms of reduction in FPG level was higher in the insulin degludec group than in insulin glargine group in the study, which was statistically significant (p = 0.013). These results are similar to the findings of most of the studies included in the trial [6-7, 9-12, 14, 15, 17, 20, 22, 24]. The RCTs by Hollander *et al.* [14] and Onishi *et al.* [16] showed a greater reduction in FPG levels with Insulin glargine, which was not statistically significant. The most common adverse effect of insulin therapy is hypoglycemia. In the present study, the rates of overall hypoglycemia (p=0.183) and hypoglycemic events per patient year (p=0.192) were lower in patients treated with insulin degludec.

This observation was in line with most of the studies. The RCTs conducted by Rosenstock *et al* [6], Rodbard *et al* [19], and Zinman (2012) *et al* [22] showed increased rates of overall hypoglycemia as well as hypoglycemic events per patient-year in patients treated with insulin degludec but it was not statistically significant. The overall risk of hypoglycemia was similar in both groups.

In this meta-analysis, we found that Insulin degludec treatment was associated with a lower rate of nocturnal hypoglycemia in both type 1 and type 2 diabetes mellitus as compared to insulin glargine treatment (p=0.026). The RCT by Rosenstock *et al.* [6] was conflicting as it demonstrated lower rates of nocturnal hypoglycemia with insulin glargine. The results were supported by most of the trials included in the study [11-15, 17, 19, 20, 22]. This decreased rate of nocturnal hypoglycemia is likely attributed to ultralong action, the stable pharmacokinetic profile of insulin degludec, and lower day-to-day variability. A meta-analysis by Zhou W *et al.* [26] supports the results of our study. It reported that insulin glargine and insulin degludec produced similar glycemic control and insulin degludec was associated with a lower rate of severe hypoglycemic events and nocturnal hypoglycemic events as compared to insulin glargine.

Results of a meta-analysis by Liu W *et al.* [27] showed non-inferiority of insulin degludec to insulin glargine with respect to glycemic control. It reported a statistically significant decrease in hypoglycemia and nocturnal hypoglycemia with insulin degludec treatment. Findings of a meta-analysis by Kant R *et al.* [28] were conflicting as it showed both insulin glargine and insulin degludec to be equally effective in reducing FPG and HbA1c with lower rates of hypoglycemic episodes in insulin glargine. Thus, treatment with insulin

degludec resulted in a greater reduction in FPG levels and a lower rate of overall and nocturnal hypoglycemia.

CONCLUSION: Hypoglycemia is the main limiting factor in achieving the target glycemic control. This pooled meta-analysis results showed that the insulin degludec had more efficacy (good glycemic control in terms of reduced FPG levels) and safety than insulin glargine (decreased rate of nocturnal hypoglycemia).

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