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ORIGINAL ARTICLE

INITIATE STUDY: Insulin versus Oral Hypoglycemic Agent as Initial Therapy for Newly Diagnosed Diabetes Mellitus Type 2: A Systematic Review and Meta-Analysis

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Abstract

Objectives. This study aims to evaluate the effectiveness of initial insulin therapy versus oral hypoglycemic agents in glucose control among newly diagnosed Type 2 diabetes patients.

Methodology. This is a systematic review and meta-analysis of RCTs with quality grade B searched using the medical subject headings (MeSH): diabetes mellitus type 2, insulin, oral hypoglycemic agent, with adults newly diagnosed with type 2 DM as subjects and given insulin (± metformin) vs. OHA. Results were summarized as graphs and forest plots using the random effects due to foreseen sources of heterogeneity using Review Manager version 5.1.

Results. Presence of substantial heterogeneity prevents us from making a conclusion. All four studies showed lower post treatment BMI among participants in the insulin treatment arm. An opposite finding was expected as insulin is known to cause weight gain. Main adverse effect was hypoglycemia.

Conclusion. Among newly diagnosed type 2 DM patients, there is insufficient evidence for or against the use of insulin compared to oral hypoglycemic agents as initial management in terms of improvement in glycemic control, decrease in insulin resistance, and improvement in beta cell function.

Keywords: Insulin; Oral hypoglycemic agent; Diabetes mellitus type 2; glycemic control; beta cell function

INTRODUCTION

Diabetes mellitus has become a worldwide pandemic with an estimated adult prevalence of 382 million in 2013. Prevalence is predicted to rise to around 592 million by 2035.[1] The disease currently has no known cure, and because of its serious complications, tight sugar control and reduction of glycosylated hemoglobin is important. The initial management of lifestyle modification involving medical nutrition therapy and exercise often is not sufficient to reduce blood glucose levels to acceptable levels. Applying the 2013 American Association of Clinical Endocrinologist (AACE) Comprehensive Diabetes Management Algorithm, the next step after lifestyle will be to use oral hypoglycemic agents; initially, as monotherapy progressing to triple therapy as stratified by the entry HbA1c level. Insulin enters the algorithm only after failure of triple therapy or when glucose control is very poor, with HbA1c > 9%.[2]

The rate of progression of β-cell failure determines the rate of disease progression in Type 2 diabetes. From the time of diagnosis, the β-cells produce less insulin, and this is believed to be due to the wearing out of the β-cell after it has been forced to continuously hypersecrete insulin—which is the mechanism of action of sulfonylureas.[3]

Rarely do physicians start insulin therapy in newly diagnosed stable diabetic patients. Most, if not all, patients would also choose oral hypoglycemic agents over insulin especially at time of diagnosis. In 2011, the age-adjusted percentage of adults with diabetes who reported taking pills only was 3 times higher than those who reported using insulin only (50.3% vs. 17.8%).[4] However, it has been hypothesized that using oral hypoglycemic agents further pushes pancreatic beta cells to failure. The initial benefits of sulfonylurea agents are caused by increasing insulin secretion from already deteriorating pancreatic beta cells.[5] Initial insulin therapy can rapidly address the glucose toxicity and improve beta cell function in newly diagnosed type 2 diabetics.[6,11] Hence, there are many proponents of initiating therapy with insulin before maintaining patient on oral hypoglycemic agents.[7,8]

Several measures of glycemic control, insulin resistance and pancreatic beta cell function are available. Glycated

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hemoglobin or HbA1c is a form of hemoglobin commonly used to measure the average plasma glucose concentration for 120 days—the life of the red blood cell.

The homeostatic model assessment (HOMA) first described by Matthews, et al., in 1985, is used to quantify beta cell function (HOMA-B) and insulin resistance (HOMA-IR). HOMA is a widely validated clinical and epidemiological tool and is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from insulin and fasting glucose levels. It only requires a single measurement of insulin and glucose in the basal state. HOMA-IR is the product of basal glucose and insulin levels divided by 22.5 and is a simple, inexpensive, and reliable surrogate measure of insulin resistance. HOMA-B, computed as the product of 20 and basal insulin levels divided by the value of basal glucose concentrations minus 3.5, has been proposed to be a good measure of β-cell function.[9]

Insulin is the most effective hypoglycemic agent known. Early insulin therapy had shown good outcomes on both short-term and long-term glycemic control.[7] Rapid reduction of glucotoxicity can immediately improve β-cell function and would preserve its ability to secrete insulin. Hence, glycemic improvement would lead to longer periods of good glycemic control or even remission and could even prevent the development of complications.[10]

Randomized controlled trials have been done to evaluate the benefits of initiating therapy on newly diagnosed diabetics with insulin versus oral hypoglycemic agents.[13-18] However, no conclusive evidence were available to verify this hypothesis.

The objective of this study is to evaluate the effectiveness of initial insulin therapy versus oral hypoglycemic agents in terms of glucose control, pancreatic beta cell function and adverse effects such as hypoglycemia and weight gain.

METHODOLOGY

Trials were identified by searching PubMed (June 2012), EMBASE (June 2012), Cochrane Library, Science Direct and Clinical Trials.gov. Search terms using medical subject headings (MeSH) were the following: diabetes mellitus type 2, insulin, oral hypoglycemic agent, randomized controlled trial. Manual search was done at St. Luke's College of Medicine Library. Articles published in any language were considered. Abstracts of the articles selected from each of these multiple searches were reviewed and those which met the inclusion criteria were retrieved for the meta-analysis. Search was also done using Google Scholar and other search engines for additional articles that may be included in this study. Inclusion criteria were as follows: studies of randomized controlled trial which have newly diagnosed type 2 diabetic adults as subjects given insulin with or without metformin versus oral hypoglycemic agent or agents; with the following outcomes: glycemic control (HbA1c), measures of insulin resistance or beta cell function, weight, or episodes of hypoglycemia. Studies with subjects with HbA1c >10%, diabetic emergency or any serious comorbid conditions were excluded.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
1. Randomized controlled trial 2. Subjects: a. Newly Diagnosed Type 2 DM b. Adult 3. Exposure: Insulin (± Metformin) vs. Oral hypoglycemic agent (OHA) (multiple or monotherapy) 4. Outcome: a. Glycemic control (HbA1c) b. Measures of Insulin Resistance or Beta cell function c. Weight d. Hypoglycemia	1. Subjects: a. HbA1C ≥ 10% b. Diabetic emergency c. Serious comorbid condition

A total of 2618 articles were found by searching five databases and by cross-referencing relevant studies from bibliographies (Figure 1). Fifty-two articles were excluded because these were duplicate articles and an additional 2537 articles were excluded because these studies failed to fulfill the selection criteria. The selection process yielded 29 related articles using insulin as the initiation therapy for newly-diagnosed diabetes mellitus type 2. These articles were retrieved and their abstracts reviewed and appraised by two independent persons to check for validity. Any incompatibility or question was addressed by a third person.

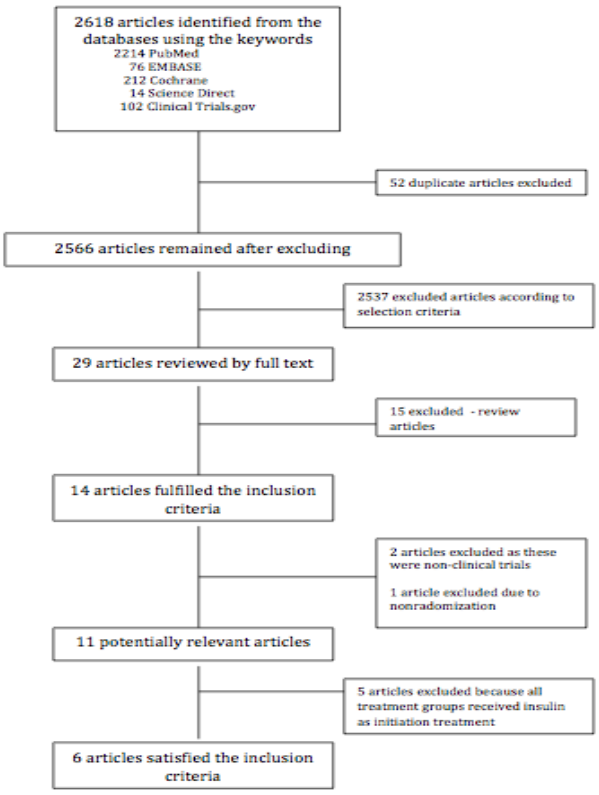

Figure 1. Search strategy for the identification of relevant articles.

Out of the 29 articles, 15 were excluded since they were review articles. Fourteen articles were left from the initial screening. Two of these articles were again excluded as these were non-clinical trials. One article was excluded since randomization was not done. We were left with eleven potentially relevant articles and these were retrieved, reviewed in full text and assessed. Out of the 11 articles, 5 were excluded as these articles compared two different types of insulin as initial therapy for newly-diagnosed type 2 diabetes mellitus. Of the remaining studies, six out of the eleven potential articles satisfied the inclusion criteria for this meta-analysis.

Table 2. List of excluded studies and reason for exclusion

TITLE	AUTHORS	Reason for Exclusion
Glycemic Response and Attainment of A1c Goals Following Newly Initiated Insulin Therapy for Type 2 Diabetes	Nichols, Gregory, et. al. (2011)	Study design was prospective cohort
The Effect of Early Insulin Therapy on Pancreatic B-cell Function and Long-Term Glycemic Control in Newly Diagnosed Type 2 Diabetic Patients	Chon, Suk, et. al. (2010)	Study design was retrospective cohort
Targeting B-cell Function Early in the Course of Therapy for Type 2 Diabetes Mellitus	Leahy, Jack L., et. al (2010)	Examined current perspectives regarding likely mechanisms of B-cell failure in type 2 diabetes and their clinical implications for protecting or sparing B-cells early in the disease progression
Comparison of Gliclazide with Insulin as Initial Treatment Modality in Newly Diagnosed Type 2 Diabetes	Chandra, Satish T., et. al. (2008)	Study was not randomized. The type of treatment the subjects received were left to their discretion. Quality assessment score of C (poor quality)
Comparison of Glycemic Control in Patients with Type 2 on Basal Insulin and Fixed Combination Oral AntidiabeticTreatment: Results of a Pilot Study	G. De Mattia, et. al. (2009)	Compared the coefficient of variance of fasting and post prandial blood glucose of Type 2 DM subjects treated with insulin glargine (Glargine) versus neutral protamine Hagedorn (NPH) insulin
Introducing a Simplified Approach to Insulin Therapy in Type 2 Diabetes: a Comparison of Two Single-Dose Regimens of Insulin Glulisine plus Insulin Glargine and Oral Antidiabetic Drugs	M.R. Lankisch, et. al. (2009)	Compared hypoglycemic effect of the addition of a single bolus of insulin glulisine in combination with basal insulin glargine and oral antidiabetic drugs
Non-inferiority Effects on Glycemic Control and B-cell Function Improvement in Newly Diagnosed Type 2 Diabetes Patients: Basal Insulin Monotherapy Versus Continuous Subcutaneous Insulin Infusion Treatment	Chen, Harn-Shen (2008)	Compared the effects of basal insulin monotherapy with continuous subcutaneous insulin infusion treatment
Recognition of Fasting or Overall Hyperglycemia When Starting Insulin Treatment in Patients with Type 2 Diabetes in General Practice	Vahatalo, Marrku, et. al. (2008)	Compared diurnal glucose variation in subjects treated with insulin only, bedtime insulin with sulphonylurea, bedtime insulin with metformin

Table 3. Quality assessment of included studies

Quality Assessment	B Cell function after 3.5 yrs	Short term intensive therapy in newly diagnosed DM	Effects of Insulin and oral anti-diabetic agents on glucose metabolism	Glycemic control with diet, sulfonylurea, metformin, or insulin	Beneficial effects of insulin	Effect of intensive insulin therapy on B cell function
	Harrison, et al, 2012[5]	Hu, et al 2011[6]	Joya-Galeana, et al, 2011[7]	Turner, et al, 1999[8]	Chen, et al, 2008[9]	Weng, et al, 2008[10]
Randomization	Yes	Yes	Yes	Yes	Yes	Yes
Allocation Concealment	Yes	Not stated	Not stated	Yes	Not stated	Yes
Blinding	No	Not stated	Not stated	Not stated	Not stated	Not stated
Intention to Treat	Yes	Yes	Yes	Yes	Yes	Not stated
Adequacy of Follow-up	Yes	Not stated	Not stated	Not Stated	Yes	Yes
Quality Scale	B	B	B	B	B	B
No. of Subjects	58	48	21	4075	50	382
Patient	21-70 y/o; diagnosed DM within previous 2 months	50.6±7.9 y/o; bmi 25.7+-3.3, no anti hyperglycemic therapy	21 diabetic Mexican American with HbA1c 7%	25-65 y/o, newly diagnosed DM 2, fasting plasma glucose (FPG) more than 108 on 3 occ,	Newly dx dm 2 with severe hyperglycemia	25-70 y/o newly diagnosed with DM 2, treatment naïve with FBS 7-16.7 mmol/L
Exposure	Insulin + metformin vs triple oral therapy (metformin, glyburide, pioglitazone)	Continuous sq insulin infusion; multiple daily insulin injection; OHA	Pioglitazone 15-45mg/day ± metformin ± glipizide vs insulin glargine plus glulisine	Diet alone, insulin, sulfonylurea, metformin	NPH vs obese metformin, lean gliclazide MR	Multiple daily insulin injection (MDI) with Novolin R and NPH; continuous subcutaneous insulin infusion (CSII) with Novo Nordisk; gliclazide ± metformin
Outcome	B-cell response at 0, 6, 12, 18, 30 42 months. Glucose, c peptide, Total insulin secretion, weight	Homeostasis model assessment (HOMA) B and IR	Fasting blood glucose; HbA1c, endogenous glucose production	Fasting blood glucose; HbA1c	A1c change and proportion of subjects who reached target treatment target a1c less than 7 and 6.5 at 6 and 12 months; HOMA B; HOMA IR	Time of glycemic remission and remission rate at 1 year; HbA1c, FBS, 2h post prandial glucose; lipids, HOMA B; HOMA IR
Method	Randomized open label clinical trial	Randomized trial	Randomized trial	Randomized controlled trial	Randomized controlled trial	Randomized parallel-group trial
Duration	3.5 years	1 year	6 months	9 years	6 months	1 year

RESULTS AND DISCUSSION

Glucose Control

Four studies evaluated the effect of initial insulin treatment on glucose control in term of glycosylated hemoglobin (HbA1c). Of the total of 315 patients analyzed, 176 received insulin while 139 received oral hypoglycemic agents. The studies by Harrison and Chen noted slightly better glycemic control with use of insulin however the studies by Weng and Joya-Galeana showed an opposite result. (See Figure 2.)

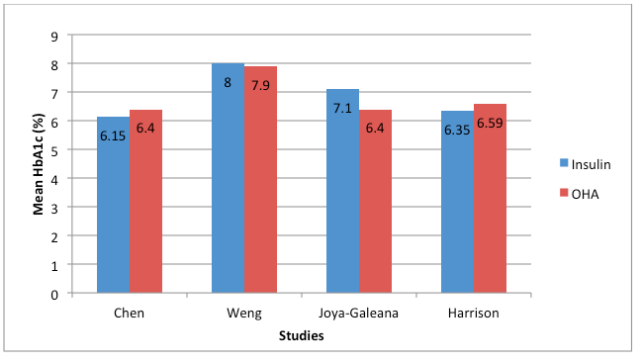

Figure 2. Mean HbA1c (%) of subjects treated with insulin vs OHA in 5 different studies.

Noteworthy is that in both treatment arms, the majority were able to achieve HbA1c of less than 7% and a significant number achieved a value of less than 6.5%. These HbA1c values are the usual treatment goal recommended by clinical guidelines.[2,12]

Figure 3 demonstrates that although there is a trend indicating lower HbA1c among participants who were given OHAs as initial treatment, the difference between the two groups is not statistically significant. Furthermore, the Tau^2 of 0.27 and an I^2 of 88% indicate presence of substantial heterogeneity. Even using the random effects model, this level of heterogeneity remains an issue.

Of the four studies, only Weng did not clearly state intention to treat. A sensitivity analysis was done and Weng's study was excluded from the analysis, however the results as well as the level of heterogeneity remained essentially the same.

Looking at Figure 2, we can see that in studies of Weng, and Joya-Galeana, HbA1c in the insulin group increased after a year and six months, respectively, however were not statistically significantly different from the oral hypoglycemic agents group (p value of 0.97, and 0.92, respectively).

The relatively short duration of follow up of the included studies may explain the lack of statistically significant difference in HbA1c between the two study arms. In the study of Turner, 1999—the UKPDS 49—the proportion of patients maintaining target HbA1c levels declined over the follow-up of 9 years. After 9 years of monotherapy with diet, insulin and sulfonylurea, 9%, 28%, and 24% respectively achieved HbA1c levels below 7%.[8] A study with a longer follow-up is needed in line with the hypothesis that insulin in the early phases of diabetes mellitus type 2 treatment will result in improvement of beta cell function and subsequent better glycemic control in the long term.

Beta Cell Function and Insulin Resistance

HOMA-Beta reflects the function of pancreatic beta Cells. Two studies reported HOMA-Beta as an outcome. The study by Chen revealed significant improvement in Beta cell function among participants who received initial insulin treatment[17] however the study by Weng contradicts this result.[9,10]

When we analyzed the results from the two studies, the difference between the HOMA-Beta among the two groups is not statistically significant. Likewise, the Tau^2 of 1951 and an I^2 of 91% indicate presence of substantial heterogeneity. (Figure 4)

The subjects in the study of Chen were newly diagnosed patients with type 2 diabetes mellitus with relatively more severe hyperglycemia despite the fact that they only chose patients with HbA1c less than 7%. The higher the level of hyperglycemia, the glucotoxicity is worse and theoretically, the greater effect of insulin on HOMA B. Unsurprisingly, the study noted better HOMA B index in the insulin group.[17]

On the effect on insulin resistance, the studies by Weng and Chen showed conflicting results.[9,10] Weng showed improvement in the insulin resistance among patients in

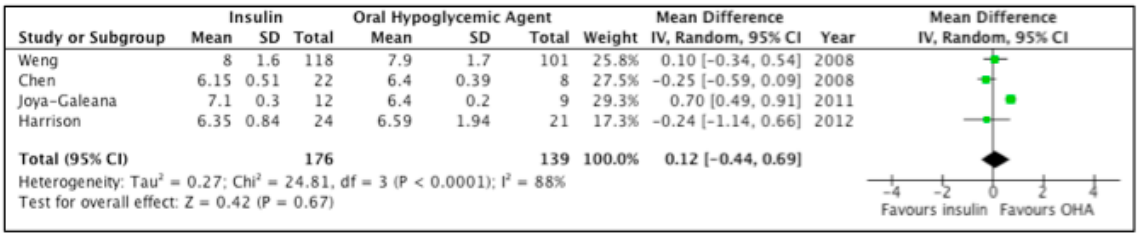

Figure 3. Forest plot comparing the HbA1c of subjects who received insulin versus OHA as initial therapy for type 2 DM.

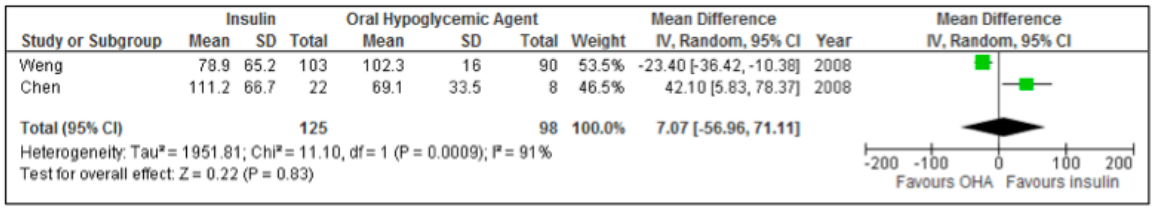

Figure 4. Forest plot comparing HOMA-Beta of subjects treated with insulin versus OHA as initial therapy for type 2 DM.

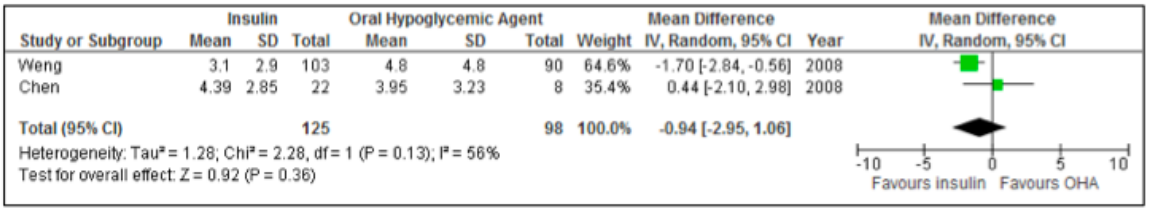

Figure 5. Forest plot comparing the HOMA-IR of subjects treated with insulin versus OHA as initial therapy for type 2 DM.

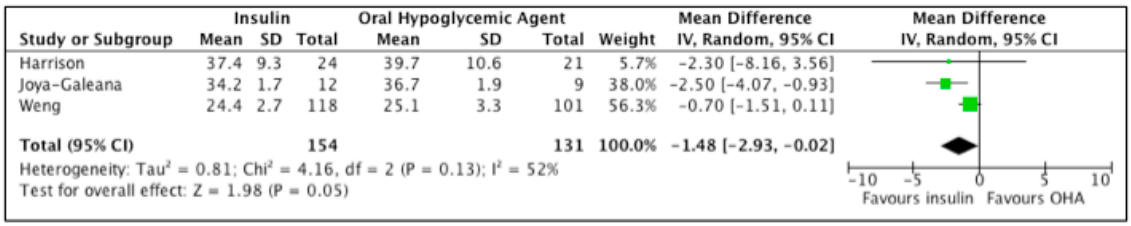

Figure 6. Forest plot comparing the post-treatment BMI of subjects treated with insulin versus OHA as initial therapy for type 2 DM.

the insulin treatment arm, while an opposite finding was seen in the study by Chen.

In terms of insulin resistance as noted by HOMA IR, no significant change from baseline to the end of the intervention and between the insulin groups were noted. However Weng with a greater population of 382 versus 50 in Cheng's study, noted HOMA B was significantly increased in all patients and HOMA IR significantly decreased in all patients with both p value of <0.0001.[9] However when the groups were compared, the difference was not statistically significant.

Analyzing the result further, Figure 5 shows a trend indicating lower HOMA-IR among participants who used insulin. However, the difference between the two groups is not statistically significant. Furthermore, the Tau² of 1.28 and an I^2 of 56% indicate presence of substantial heterogeneity.

Weight Gain, Hypoglycemia and Other Adverse Effects

Four studies included post treatment BMI as an outcome. Of the 345 patients analyzed, 184 received insulin while 161 received oral hypoglycemic agents. All four studies showed lower post treatment BMI among participants in the insulin treatment arm. An opposite finding was expected as insulin is known to cause weight gain. However, other OHA such as sulfonylureas specifically glyburide, glipizide, gliclazide, which were given in the studies of Harrison, Hu, Joya-Galeana, Chen and Weng are also known to cause weight gain. (Figure 6)

Further analysis showed that indeed there is significantly lower post treatment BMI among participants who used insulin. However the Tau² of 0.81and an I^2 of 52% indicate presence of heterogeneity. (Figure 8)

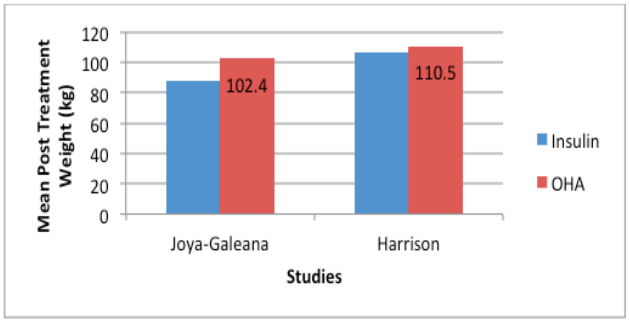

Figure 7. Mean post-treatment weight (kg) of subjects treated with insulin versus OHA in 3 studies.

Only three studies reported post treatment weight as an outcome. All of the three studies showed a lower weight (however statistically insignificant) among patients who received insulin.

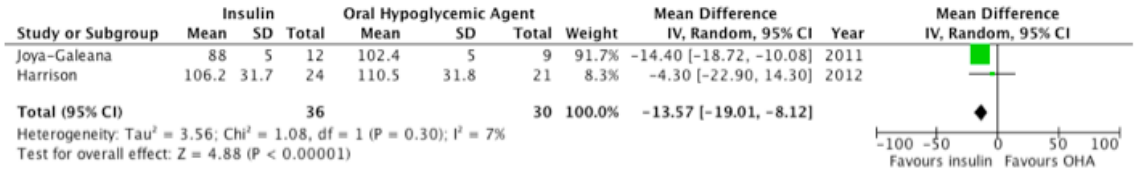

Figure 8. Forest plot comparing the post-treatment weight of subjects treated with insulin versus OHA as initial therapy for type 2 DM.

Similar to post treatment BMI, there is a trend of lower post-treatment weight among participants who used insulin, however, the difference between the two groups is not statistically significant.

There were no noted severe hypoglycemic episodes reported in the study of Weng. The proportion of patients with minor hypoglycemic events—prompt recovery after patient self-administered carbohydrate—were also the same in all groups. In the study of Harrison, two subjects in the insulin group had three severe hypoglycemic episodes compared with four subjects with four episodes in the oral hypoglycemic group. Both groups have a comparable number of mild hypoglycemic events, 0.5 ± 0.8 events per month in the insulin group and 0.4 ± 0.5 events per month in the oral hypoglycemic group. The hypoglycemic event is affected by the close monitoring of blood sugar, with proper dose adjustment of the intervention.

Issues Regarding Heterogeneity

A number of factors could have contributed to the heterogeneity (Table 4). Methodological differences such as differences in the interventions as well as different outcome measures and study duration are factors contributing to methodological and statistical heterogeneity. We have anticipated such methodological differences so we used the Random Effects model to analyze this. However, the heterogeneity remains an issue in interpreting the result.

Table 4. Possible sources of heterogeneity

Type	Possible Sources of Heterogeneity
Clinical Heterogeneity	• Variation in insulin and oral hypoglycemic agents used • Different run in period with intervention • Different primary outcomes
Methodological Heterogeneity	• In most studies, blinding was not stated.
Statistical Heterogeneity	• The primary outcome measures of the included studies were different. Since statistical power have been computed for the primary outcomes, this presents as a possible source of statistical heterogeneity. • Results at the end of the study were used instead of difference between start and end of study results.

Limitations

In all studies, it was noted that the absolute values were used instead of the mean difference in the laboratory values in the analysis of results. This could have affected the final outcome since the actual change caused by the treatment was not represented. Data were lacking to be able to compare the mean change in terms of HbA1c, HOMA beta, HOMA IR and BMI between the two groups.

CONCLUSION

Among newly diagnosed type 2 DM patients, there is not enough evidence for or against the use of insulin compared to oral hypoglycemic agent as initial management in terms of improvement in glycemic control, decrease in insulin resistance and improvement in beta cell function..

Heterogeneity of data, short duration of follow-up and lack of clinically relevant outcomes are critical issues that preclude a conclusion on the effectiveness of insulin compared to oral hypoglycemic agents as initial therapy for newly diagnosed diabetes type 2 patients.

There is no clear evidence that insulin offers a clear advantage over oral hypoglycemic agents as initial therapy for newly diagnosed type 2 diabetes mellitus during the first 6 months to 3 years of treatment.

A study of significantly longer duration of follow up of at least 10 years may be needed to establish the long term effects of initial insulin treatment. Likewise, future studies should also include clinical end points such as cardiovascular events and mortality as outcomes of interest and utilize new oral hypoglycemic agents other than sulfonylureas.

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