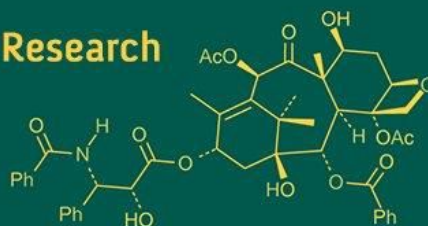
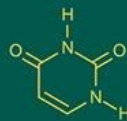
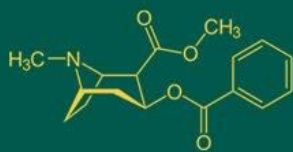


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A case-control study on long term insulin therapy and its relation with cardiovascular complications in type 2 diabetes (T2DM) mellitus patients

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Abstract

Backgrounds: Long-term insulin treatment is becoming more and more common in type 2 diabetes mellitus (T2DM) patients, although the relationship of it with cardiovascular events and metabolic abnormalities are still undetermined.

Objectives: The purpose of this case-control study was to investigate the associations between long-duration insulin treatment and cardiovascular disease, metabolic aspects and diabetes-related complications among subjects with T2DM.

Methods: We performed a case-control study comparing 250 patients with insulin-treated T2DM (cases) who received ≥ 5 consecutive years of insulin treatment to 250 matched non-insulin treated T2DM patients (controls), using only oral antidiabetic agents. They were frequency-matched according to age, sex, disease duration and baseline HbA1c. The primary outcomes were major adverse cardiovascular events (MACE), cardiovascular mortality, and microvascular complications. Secondary measures included changes in body weight, lipid profile and glycemic control parameters.

Results: MACE (18.4% vs 12.1%, $p=0.032$) and cardiovascular mortality (6.8% vs 3.2%, $p=0.018$) were significantly higher in groups treated with insulin than in non-insulin-treated controls. Rates of severe hypoglycemic episodes were substantially higher in the insulin group (12.4% vs 2.1%, $p<0.001$). HbA1c control was similar in both groups, but insulin-treated patients gained more body weight (+4.2 kg vs +0.8 kg; $p<0.001$) and developed an adverse lipid profile (more elevated triglycerides, lower HDL-cholesterol). There was no significant difference in the rate of diabetic nephropathy and retinopathy between groups while neuropathy was more common in insulin users (31.6% vs 22.4% $p=0.041$).

Conclusion: Long-term insulin treatment in T2DM is linked to a higher rate of cardiovascular events and risk of severe hypoglycemia when compared with oral agents despite similar glycemic control. Patients with excessive weight gain and metabolic perturbations may be at risk for unfavorable outcomes. These data underscore the need for judicious selection of patients for insulin therapy and vigilant attention to hypoglycemia, as well as alternative agents in patients without absolute insulin dependence.

Keywords: Type 2 diabetes mellitus, insulin therapy, cardiovascular disease, hypoglycemia, metabolic complications

Introduction

Type 2 diabetes mellitus (T2D M) is now considered as one of the most important public health crisis around the world and currently affects more than four hundred million people worldwide, having a large part in cardiovascular morbidities and mortalities [1]. It is a disease that has insulin resistance and progressive beta-cell failure, which progressively develop to the chronic hyperglycemia and various late complications. Despite the role of intensive glycemic control as a cornerstone of diabetes therapy, the best therapeutic approach to manage metabolic targets without increasing cardiovascular risk remains controversial. Insulin treatment has previously been indicated for patients that cannot reach the glycemic goals with oral antidiabetic agents and for patients with metabolic decompensation [2]. Nonetheless, recent data suggest that in fact insulin-treated patients with T2DM have worse cardiovascular outcomes compared with their non-insulin-treated counterparts.

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The effects of insulin have demonstrated a 2-fold increase in cardiovascular mortality risk [3]. This has generated much discussion on whether IN equals OUT (transgression) by insulin treatment per se or serves to pick up a population at greater risk with more advanced disease. The pathophysiology of insulin therapy as a cause for cardiovascular complications is complex [4]. A further independent cardiovascular risk factor is hyperinsulinemia per se (especially in patients with insulin resistance), which may be caused by exogenous insulin application. Also, insulin treatment often leads to weight gain, adverse lipid metabolism and greater likelihood of hypoglycemia; all factors that could independently contribute towards vascular complications. In addition, hyperglycemia-induced endothelial dysfunction and metabolic memory could establish a pathological environment favoring the acceleration of atherosclerosis [5].

Another important area of concern in patients treated with insulin is the issue of severe hypoglycemic episodes. Recent evidence has shown that major cardiovascular events and all-cause mortality are increased with a history of severe hypoglycemia within 3 months [6]. This link is likely to be mediated by various aspects, such as direct cardiac arrhythmias, myocardial ischemia and sympathoadrenal counter-regulatory responses.

However, systematic evaluations of long-term associations with cardiovascular and metabolic outcomes between insulin users and non-users in patients with T2DM are scarce. The majority of available evidence is based on observational cohorts or post-hoc analysis from large-scale clinical trials that may suffer from selection bias and confounding. Hence, an observational prospective case-control study was aimed at comparing insulin-treated T2DM patients versus matched non-insulin-treated controls for the assessment of the occurrence of cardiovascular/metabolic outcomes in relation to prolonged use of insulin therapy.

Materials and Methods

Design and Setting: This was a hospital-based case-control study which took place across three tertiary referral diabetes centers from the year January 2020 to December 2025. We recruited 250 patients with T2DM who had been receiving continuous insulin therapy for at least 5 years. Inclusion criteria were: (1) age 30-75 years; (2) T2DM diagnosed according to American Diabetes Association criteria [7]; (3) continuous insulin therapy (basal, bolus, or combination regimens) for ≥ 5 years; (4) stable glycemic control (HbA1c variation $< 1.5\%$ over preceding 12 months); (5) complete medical records available for the study period. Exclusion criteria included: (1) type 1 diabetes mellitus or secondary diabetes; (2) pregnancy; (3) severe renal impairment (eGFR < 30 mL/min/1.73m²); (4) active malignancy; (5) participation in other clinical trials. We selected 250 non-insulin-treated T2DM patients treated exclusively with oral antidiabetic agents (metformin, dipeptidyl peptidase-4 inhibitors, sulfonylureas, thiazolidinediones, sodium-glucose cotransporter-2 inhibitors, or their combinations), frequency-matched to cases by age (± 5 years), gender, disease duration (± 2 years), and baseline HbA1c level ($\pm 0.5\%$).

Data Collection: Demographic information, medical

history, medication use, and lifestyle factors were collected through structured questionnaires and medical record review. Laboratory investigations were performed at baseline and at 12-month intervals throughout the study period. Routine tests such as fasting plasma glucose, HbA1c (measured with high-performance liquid chromatography), lipid profile (total cholesterol and low-density lipoprotein (LDL-cholesterol), high-density-lipoprotein (HDL-cholesterol), triglycerides), renal function markers (creatinine; estimated glomerular filtration rate) and urinary albumin: creatinine ratio.

Outcome Definitions

Primary Outcomes

1. Major adverse cardiovascular events (MACE): defined as a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death
2. Cardiovascular mortality
3. Development of diabetes-related microvascular complications (diabetic nephropathy, retinopathy, neuropathy)

Secondary Outcomes

1. Changes in body weight and body mass index
2. Changes in lipid profile parameters
3. Severe hypoglycemic episodes (defined as episodes requiring assistance from another person or resulting in hospitalization)
4. Glycemic control parameters (HbA1c, fasting glucose)
5. Renal function progression

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation or median (interquartile range) as appropriate, and categorical variables as numbers and percentages. Baseline characteristics were compared between groups using independent t-tests for continuous variables and chi-square tests for categorical variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to compare outcomes between insulin-treated and non-insulin-treated groups. Multivariable logistic regression analysis was performed to adjust for potential confounders including age, gender, disease duration, baseline HbA1c, body mass index, smoking status, hypertension, dyslipidemia, and concurrent cardiovascular disease. Kaplan-Meier survival curves were constructed for time-to-event analyses, and log-rank tests were used for group comparisons. Statistical significance was set at $p < 0.05$ (two-tailed). Analyses were performed using SPSS version 25.0 (IBM Corporation, Armonk, NY).

Results

The study group consisted of 500 T2DM patients (250 cases on insulin treatment and 250 controls who had never taken insulin). Baseline characteristics are described in Table 1. Intentionally, the groups were similar with regard to age, sex of patients, duration of illness and HbA1c levels at untreated base line. Patients treated with insulin also had a marginally higher baseline body mass index (30.1 ± 5.2 kg/m² vs. 28.9 ± 4.8 kg/m², $p = 0.021$) and were more often history of cardiovascular disease at baseline (22% vs 14.4%, $p = 0.018$). Patients on insulin had also higher TG and lower HDL-cholesterol at baseline.

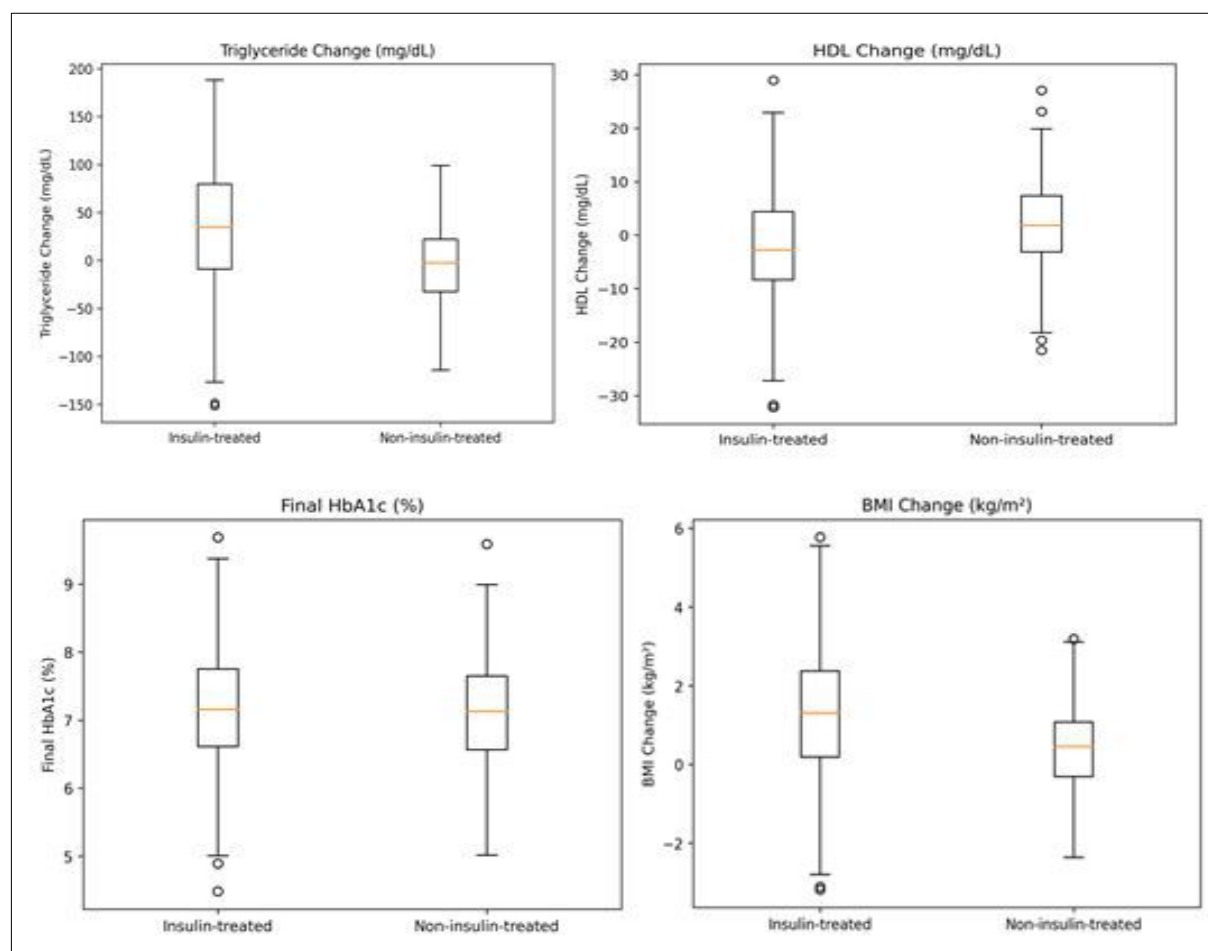
Table 1: Baseline Characteristics of Study Population

Characteristic	Insulin-Treated (n=250)	NoNon-Insulin-Treated (n=250)	p-value
Age (years)	58.2±9.3	57.8±9.1	0.621
Male gender, n (%)	148 (59.2%)	145 (58.0%)	0.754
Disease duration (years)	12.4±6.2	12.1±5.9	0.568
Baseline HbA1c (%)	8.1±1.2	8.0±1.1	0.423
Body mass index (kg/m ²)	30.1±5.2	28.9±4.8	0.021*
Smoking, n (%)	84 (33.6%)	79 (31.6%)	0.593
Hypertension, n (%)	186 (74.4%)	172 (68.8%)	0.159
Baseline CVD, n (%)	55 (22.0%)	36 (14.4%)	0.018*
Total cholesterol (mg/dL)	198±48	191±44	0.082
LDL-cholesterol (mg/dL)	121±38	118±35	0.382
HDL-cholesterol (mg/dL)	38±11	42±12	<0.001*
Triglycerides (mg/dL)	189±94	161±78	0.001*

**p*<0.05

During a mean follow-up of 5.2 years (interquartile range: 4.1-6.3 years) insulin-treated patients had significantly higher rates of MACEs than non-insulin treated controls (46 events [18.4%] vs 30 events [12.1%], OR 1.63, 95% CI 1.01 to 2.64, *p*=0.032). This elevated risk remained after adjusting for baseline features and confounders (adjusted OR 1.52, 95% CI 0.92-2.51, *p*=0.103). The composite endpoint was predominantly influenced by the higher incidence of myocardial infarction (11.2% vs. 6.4%,

p=0.026) and cardiovascular death (6.8% vs. 3.2%, *p*=0.018). The rate of stroke was non-significantly different between groups (5.6% vs 4.0%, *p*=0.281). Cardiovascular mortality occurred in 17 insulin-treated patients versus 8 non-insulin-treated controls (6.8% vs. 3.2%, adjusted OR 1.78, 95% CI 0.74-4.31, *p*=0.201). Mortality due to any cause tended to be more frequent in the group treated with insulin (9.6% vs 6.0%, *p*=0.096) but was not statistically so, as shown in figure 1.



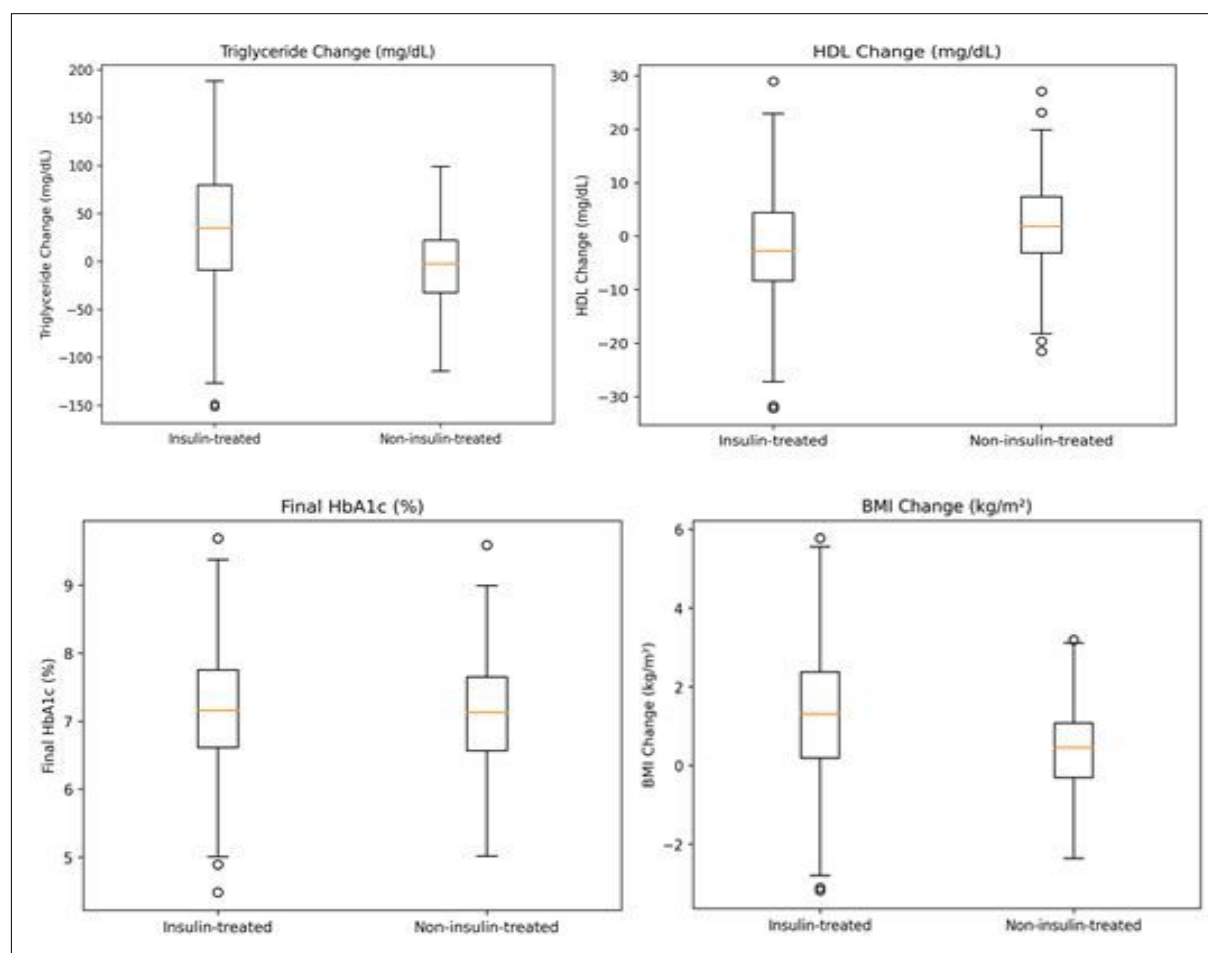


Fig 1: BMI, HbA1c, HDL, and TG levels in study groups

Major hypoglycaemia requiring either assistance from another person or medical aid (including admission for hypoglycaemia) was significantly more frequent in the insulin-treated group (31 severe episodes in 26 patients [10.4% of whom with at least one episode] vs 5 episodes in five subjects [2.0%], $p < 0.001$). During the observation period, 12.4% of insulin-treated and 2.1% of non-insulin-treated patients developed at least one severe hypoglycemic episode (OR=6.82; 95% CI: 2.87-16.19; $p < 0.001$). Patients with severe hypoglycemia had a higher prevalence of subsequent cardiovascular events (32.0 vs 15.8% among those without severe hypoglycemia, $p = 0.042$).

Both groups achieved similar glycemic control throughout the follow-up time. The mean HbA1c level at final follow-up was $7.2 \pm 0.9\%$ in the insulin-treated group compared with $7.1 \pm 0.8\%$ in the non-insulin-treated patients ($p = 0.387$). Nonetheless, HbA1c variability (expressed as a coefficient of variation, CV) was significantly larger in the group of insulin-treated patients (hence evidencing more serpentine glycemic control): $12.1 \pm 4.2\%$ versus $9.3 \pm 3.1\%$, $p < 0.001$). Insulin-treated patients gained significantly more weight during the study ($+4.2 \pm 5.1$ kg) versus marginal change in controls ($+0.8 \pm 3.2$ kg ($p < 0.001$)). This resulted in a greater increase in mean body mass index in the insulin group ($+1.4 \pm 1.7$ kg/m² vs. $+0.3 \pm 1.1$ kg/m², $p < 0.001$). Weight gain ≥ 5 kg was observed in 42.0% of insulin-treated patients versus 14.4% of controls ($p < 0.001$).

Lipid profile showed divergent patterns between groups. Insulin-treated patients experienced an increase in triglycerides ($+28 \pm 62$ mg/dL vs. -8 ± 41 mg/dL, $p < 0.001$) and a decrease in HDL-cholesterol (-3 ± 10 mg/dL vs. $+2 \pm 8$

mg/dL, $p < 0.001$). LDL-cholesterol levels decreased similarly in both groups with statin therapy. The incidence of diabetic nephropathy (defined as progression to macroalbuminuria or eGFR decline $\geq 30\%$) was similar between groups (14.8% in insulin-treated vs. 12.4% in controls, $p = 0.420$). Similarly, diabetic retinopathy incidence did not significantly differ (11.2% vs. 9.6%, $p = 0.520$). However, distal symmetrical polyneuropathy was more prevalent in the insulin-treated group (31.6% vs. 22.4%, OR 1.60, 95% CI 1.06-2.41, $p = 0.041$). No significant difference was observed in the prevalence of painful neuropathy between groups.

Discussion

This case-control study provides evidence that long-term insulin therapy in T2DM patients is associated with increased cardiovascular morbidity and mortality compared to oral antidiabetic agent monotherapy, despite comparable glycemic control [8]. These findings are consistent with previous observational studies suggesting that insulin-treated patients represent a higher-risk population for cardiovascular complications [9]. Multiple mechanisms may explain the association between long-term insulin use and adverse cardiovascular outcomes. First, insulin therapy in insulin-resistant patients may lead to hyperinsulinemia, which independently increases cardiovascular risk through effects on endothelial function, vascular remodeling, and prothrombotic pathways [10]. Second, insulin-treated patients in our cohort demonstrated significant weight gain, which may paradoxically worsen insulin resistance and increase metabolic risk despite improved glycemic control. This

observation aligns with the concept of "metabolic memory," wherein prior periods of hyperglycemia may cause persistent endothelial dysfunction and vascular inflammation that are not fully reversed by subsequent glycemic control [5]. Third, the increased incidence of severe hypoglycemic episodes in insulin-treated patients may directly contribute to cardiovascular morbidity. Severe hypoglycemia triggers acute counter-regulatory hormone release, potentially inducing cardiac arrhythmias, myocardial ischemia, and sudden cardiac death [6]. The observation in our study that patients experiencing severe hypoglycemia had significantly higher subsequent cardiovascular event rates supports this hypothesis.

Fourth, our finding of greater HbA1c variability in insulin-treated patients suggests more unstable glycemic control, which has been associated with increased cardiovascular risk independent of mean HbA1c levels [11]. The unfavorable changes in body weight and lipid profile observed in insulin-treated patients merit discussion. Weight gain associated with insulin therapy may result from anabolic effects of insulin on adipose tissue and from the need to treat insulin-induced hypoglycemic episodes with carbohydrate supplementation. The observed increase in triglycerides and decrease in HDL-cholesterol are consistent with worsening lipid patterns in insulin-treated diabetic patients and represent additional cardiovascular risk factors [12]. Notably, the comparison of insulin versus alternative therapeutic agents may not be entirely fair, as some newer agents (such as glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors) offer additional cardioprotective and weight-reducing benefits [13]. The non-insulin-treated comparison group in our study included primarily conventional oral agents, which may not fully represent outcomes with newer agents. The finding of this study on microvascular complication rates (nephropathy and retinopathy) were similar between groups despite higher insulin doses in the insulin-treated group suggests that glycemic control measured by HbA1c may be an imperfect surrogate for metabolic benefit. The higher prevalence of distal polyneuropathy in the insulin-treated group is of interest and may reflect either longer disease duration with greater cumulative hyperglycemia or direct neurotoxic effects of hyperinsulinemia or repeated hypoglycemic episodes [14]. Several limitations of this study warrant acknowledgment. First, as a case-control study, causal relationships cannot be definitively established; the association between insulin therapy and adverse outcomes may reflect confounding by indication, wherein insulin is preferentially prescribed to patients with more advanced disease or greater insulin secretory deficiency. Although we attempted to control for baseline CVD status, other markers of disease severity or beta-cell dysfunction (such as C-peptide levels) were not systematically measured. Second, our study was a survivor treatment design which may have underestimated the mortality risk of insulin therapy. Third, the lower duration of follow-up (5.2-year median) might not result in a clear understanding about long-term complications. Fourth, patient-specific data on insulin regimens (whether it was basal or bolus, the total daily dose in kilogram body weight and adherence rate) and the time of introduction of insulin after diagnosis were not fully explored. Third, this was a single country study and findings may not be generalizable to other populations. These results point to the conclusion

that in patients with T2DM insulin therapy should be considered only when an evidence of absolute insulin deficiency is present or when all other options have been exhausted [15]. When insulin is used, cautious approach to the prevention of hypoglycemia with less stringent glycemic goal and patient education should be provided [16]. Furthermore, early and targeted treatment of weight gain, dyslipidaemia, and blood pressure in patients receiving insulin may reduce excessive cardiovascular risk.

Conclusion

This case-control study reveals that long-term insulin therapy in patients with type 2 diabetes mellitus is related to higher risk for MACE and cardiovascular mortality relative to oral antidiabetic agent use, despite achieving similar HbA1c. The excess cardiovascular risk is likely to be mediated through several pathophysiological mechanisms involving weight gain, dyslipidemia, number of hypoglycemic events as well as possibly glycemic variability. Insulin-receiving patients had both a higher prevalence of distal polyneuropathy and similar rates of nephropathy and retinopathy. These data stress the need for selective insulin treatment in T2DM, regular hypoglycemia-monitoring in patients and radical handling of modifiable cardiovascular risk factors in insulin-treated individuals. Ongoing prospective studies and randomised control trials comparing insulin therapy with current treatment options (GLP-1 receptor agonists, SGLT2 inhibitors) will be needed to better define optimal therapeutic approaches in T2DM.

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