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Review Article

Chronic Heart Failure in Insulin-Treated Patients with Type 2 Diabetes Mellitus: A Systematic Review of Clinical Trials

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Abstract

It is well established that there is a reciprocal association between heart failure (HF) and type 2 diabetes mellitus (DM). In the current study, we aim to give an overview of chronic HF in insulin-treated patients with type 2 diabetes mellitus. For that, we conducted a systematic electronic database search for suitable studies from inception till 8th June 2020 in seven databases. We included all relevant randomized controlled studies (RCTs) reporting insulin-related chronic HF in patients with type 2 diabetes mellitus. Finally, we included five papers in this systematic review. Patients allocated to Insulin + sulphonylurea had a higher risk of HF with an incidence of 8% compared to 3.6% of patients allocated to conventional treatment. Of patients receiving pioglitazone 45 mg + insulin or pioglitazone 30 mg + insulin, 4 patients experienced HF with an incidence of 1%. For Balaglitazone 20 mg + insulin group or the placebo group, the incidence was 2%, while it was 0% for patients received Balaglitazone 10 mg + insulin. No significant difference was observed between HF hospitalization rates between patients randomized to insulin glargine or standard care (0.63). In conclusion, close monitoring of heart pathologies-especially heart failure- in type 2 DM patients is of extreme importance for improving the quality and expectancy of life in those patients.

Keywords: *Diabetes Mellitus; Low Level Laser Therapy (LLLT); Streptococcus thermophilus; Neutrophils; Lymphocytes; Macrophages*

Introduction

It is well established that there is a reciprocal association between heart failure (HF) and type 2 diabetes mellitus (DM) [1,2]. On one hand, the risk HF incidence is doubled in patients with type 2 DM in male patients, and up to five times more in female patients [1,2]. On the other hand, about one-third to half of HF patients have type 2 DM, compared to only 20% of matched peers without underlying HF [3]. Moreover, diabetic/pre-diabetic patients with HF had higher rates of bad outcomes and more difficult to adequately maintain glycemic control [4-8]. Furthermore, there is a strong association between ischemic heart diseases and diabetes mellitus with further progression to heart failure; there is a two to four times increase in the risk of myocardial infarction in diabetic patients compared to no-diabetics [9-11].

In patients with type 2 diabetes mellitus, old age, disease duration, insulin administration, presence of coronary artery disease (CAD) and high serum creatinine; are all contributing risk factors for the development of heart failure [12]. In type 2 DM, there is an impairment in cardiac glucose metabolism and shift to free fatty acids' oxidation with consequent inhibition of cardiac contractility and left ventricular dysfunction, even without underlying CAD [13-15]. Insulin resistance and increased serum glucose also have a share in developing heart failure mediated through different mechanisms: including impaired cardiac metabolism, microvascular endothelial dysfunction, myocardial fibrosis, oxidative stress, and renin-angiotensin system activation [13-15].

About one-third of patients with concomitant DM and HF will be using insulin as a second line of treatment; however, the exact safety profile of insulin in these patients is not firmly established, especially with its sodium-retaining action [16-19]. The insulin-induced sodium and water retention, in patients with type DM, would exaggerate signs of congestion with higher N-terminal pro-B-type natriuretic levels, compared to those who are not treated with insulin [20,21]. Nevertheless, diuretic prescriptions are higher in type 2 DM patients treated with insulin, compared to non-insulin-treated diabetics, which may have a cofounding effect of this association [22,23].

Aim of the Study

In the current study, we aim to give an overview of insulin-related chronic HF in patients with type 2 diabetes mellitus.

Methods

Search strategy and study selection

Research and review process of the current study was conducted following the recommendations of the PRISMA checklist for systematic reviews [24]. A search for relevant studies was conducted in seven databases, from inception till 8th June 2020; including System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), Clinical trials.gov and New York Academy of Medicine (NYAM) databases. This was done using a combination of the following search terms: Insulin [Title] AND Chronic heart failure AND type 2 diabetes. A further manual search of relevant literature was done, whether by going through the references of included studies or electronic databases [25].

For studies to be included, they should be randomized controlled trials (RCTs) and reporting insulin-related chronic HF in patients with type 2 diabetes mellitus. There were no restrictions on country, language, or date of publication. In contrast, the studies were excluded if they another study design (non-RCT), non-human studies, duplicate datasets, secondary analyses, conference abstracts, book chapters, data are not possible to be extracted, and no- available full-texts. The screening procedure was done in layers; the first step is the title and abstract screening followed by a full-text screening step. All steps were done by eight independent authors and a senior author was consulted to resolve any conflict in decisions among authors.

Data extraction

Two authors performed the extraction sheet on Microsoft Excel file by pilot extraction of at least three papers. Three reviewers independently extracted data from included studies using the excel sheet. The final three reviewers performed data checking for checking the accuracy of the extracted data. All the disagreements and discrepancies were resolved by discussion and consultation with a senior member when necessary.

Quality assessment

Three independent reviewers evaluated the risk of bias in included studies. To determine the quality of each study; we used the Cochrane risk of bias tool [26]. Any discrepancy between the reviewers was solved by discussion.

Results

Search results

We identified 120 records before the exclusion of 13 duplicates by using Endnote X9 software. Title and abstract screening resulted in 14 records for further full-text screening. The later yielded 4 eligible papers for inclusion in our study. We added another trial after performing a manual search of relevant studies (Figure 1).

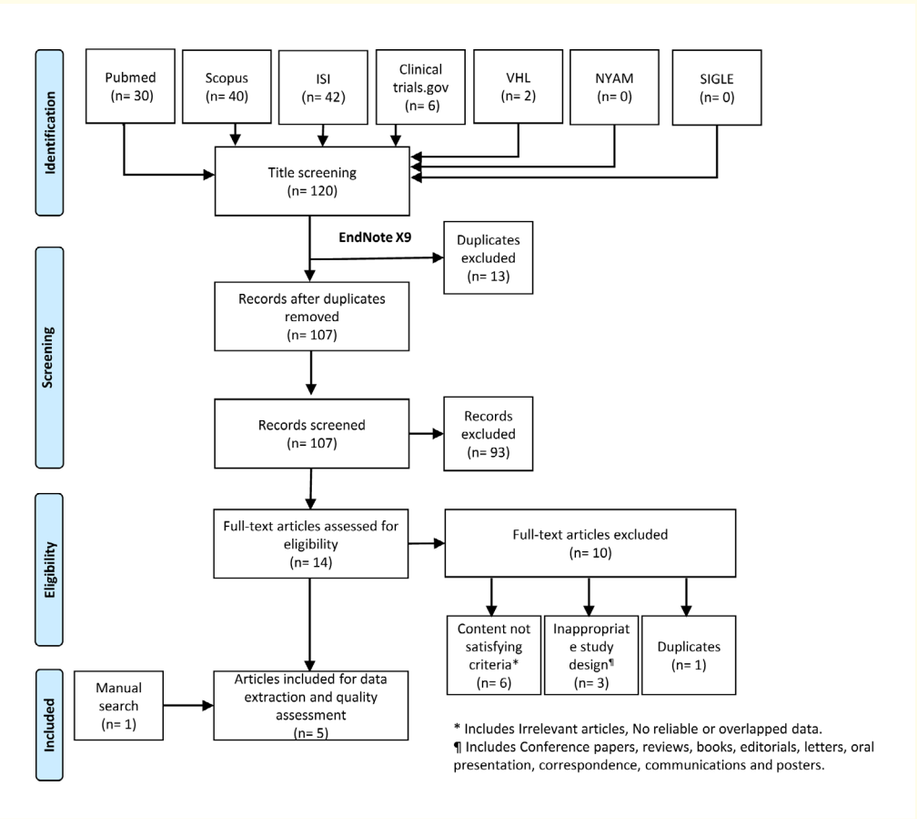

Figure 1: *PRISMA flowchart of the search and review process.*

Study characteristics and quality of the included studies

One study was conducted in the UK, one in the USA, one in Denmark, Sweden and Finland, and two studies were multicenter (Table 1). The follow-up period was 5.5 years, 5 years, 2.7 years, 26 weeks and 24 weeks for each of the included studies. Four studies were high risk of bias and one paper was a low risk of bias (Table 2).

Reference ID	Population	Treatment arm	Sample size	Follow up period	Male (event)	Mean age (SD)
Davidson/2006/USA [27]	Adults (>18 years of age) with type 2 diabetes mellitus	Pioglitazone 30 mg + Insulin	345	24 weeks	189	56.6 (10.9)
		Pioglitazone 45 mg + Insulin	345		188	56.3 (10.5)
Henriksen/2011/Denmark, Finland, Sweden [28]	Type 2 diabetes mellitus being diagnosed at least 3 months earlier according to the 1999 World Health Organization criteria, taking insulin 30 U/day (for at least 75 days)	Pioglitazone 45 mg + insulin	102	26 week	62	60.1 (8.6)
		Balaglitazone 20 mg + insulin	97		53	60.9 (9)
		Balaglitazone 10 mg + insulin	97		70	61 (8.8)
		Placebo + insulin	106		66	60.9 (7.8)
UKPDS Group/1999/UK [29]	Type 2 diabetes aged 25-65 years	Conventional	896	5.5 years	555	54 (9)
		Chlorpropamide	619		359	54 (9)
		Glibenclamide	615		381	54 (8)
		Insulin	911		656	54 (8)
Pratley/2019/Multicenter [30]	Type 2 diabetes	Insulin degludec	3818	5 years	NR	NR
		Insulin glargine U100	3819		NR	NR
ORIGIN Trial/2016/Multicenter [31]	People aged ≥ 50 years with impaired fasting glucose, impaired glucose tolerance, or type 2 diabetes	Insulin glargine	2351	2.7 years	1604	63.1 (7.6)
		Standard care	2367		1542	63.3 (7.5)
		Omega-3	2368		1582	63 (7.4)
		Placebo	2403		1583	63.3 (7.6)
NR = Not Reported						

Table 1: *Characteristics of the included studies.*

Reference ID	Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Reporting bias	Other bias	The overall risk of bias
ORIGIN Trial/2016/ Multicenter [31]	High risk	High risk	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	High risk
Davidson/2006/ USA [27]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	High risk	Unclear risk	High risk
Henriksen/2011/ Denmark, Finland, Sweden [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Pratley/2019/ Multicenter [30]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	High risk
UKPDS Group/1999/ UK [29]	Low risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	High risk

Table 2: *Risk of bias of the included studies.*

Regarding treatment arms, 447 patients received pioglitazone 45 mg and insulin, 345 received pioglitazone 30 mg + insulin, 97 received Balaglitazone 20 mg + insulin, 97 received Balaglitazone 10 mg + insulin, 106 received placebo + insulin, 6170 received insulin glargine, 3818 received insulin degludec, 896 received conventional therapy, 619 received chlorpropamide, 615 received Glibenclamide, 2367 received standard care, 2368 received omega 3 and 2403 received placebo.

Heart failure (HF) hospitalization

No significant difference was observed between HF hospitalization rates between patients randomized to insulin glargine or standard care (0.63) (Table 3). However, Insulin glargine U100 was associated with significantly higher rates of HF hospitalization compared to insulin degludec.

Reference ID	Treatment arm	Event	Total	Events/1000 patients	Risk ratio	P-value
Punthakee/2016/ Multicenter [31]	Insulin glargine	336	2351	8.2	0.91 (0.54-1.52)	0.63
	Standard care	370	2367	9.0		
Pratley/2019/ Multicenter [30]	Insulin degludec	173	3818	NR	1.6	0.036
	Insulin glargine U100	238	3819			
NR = Not Reported, # = Hazard Ratio						

Table 3: *Showing heart failure hospitalization across studies.*

Incidence of heart failure (HF)

The incidence of HF was variable across the included studies (Table 4). Patients allocated to Insulin + sulphonylurea had a higher risk of HF with an incidence of 8% compared to 3.6% of patients allocated to conventional treatment. Of patients receiving pioglitazone 45 mg + insulin or pioglitazone 30 mg + insulin, 4 patients experienced HF with an incidence of 1%. For Balaglitazone 20 mg + insulin group or the placebo group, the incidence was 2%, while it was 0% for patients received Balaglitazone 10 mg + insulin.

Reference ID	Treatment arm	Event	Total
Henriksen/2011/Denmark, Finland, Sweden [28]	Pioglitazone 45 mg + insulin	3	102
	Balaglitazone 20 mg + insulin	2	97
	Balaglitazone 10 mg + insulin	0	97
	Placebo	2	106
Davidson/2006/USA [27]	Pioglitazone 30 mg + Insulin	3	345
	Pioglitazone 45 mg + Insulin	1	345
UKPDS Group/1999/UK [29]	Conventional	36	1138
	Insulin + sulphonyleurea	80	2729

Table 4: *Incidence of heart failure across studies.*

Discussion

Diabetes management has been improved in the past years by lowering the blood glucose level and preventing both short and long term complications for increasing the expectancy and quality of diabetic patients. Physicians usually care about the micro and macro-vascular complications of DM; however, in the past two decades, more attention was devoted towards an early complication which is the development of heart failure in patients with type 2 DM [32]. Willbert and colleagues' prospective study has shown that the risk of developing heart failure is higher in diabetic patients compared to the non-diabetic population with a prevalence of 40% after nearly 4 years of follow up [33]. Additionally, Wang., *et al*. reported several predictors for heart failure development in diabetic patients. Insulin use, hemoglobin A1C (HbA1C), old age group, fasting blood glucose, male gender and coronary artery disease are the potential predictors for driving heart failure in type 2 DM [12].

Many hypotheses were settled for investigating how type 2 DM can induce heart failure affection through short or long term process. It is well known that hypertension is one of the most important risk factors for developing heart failure [34]. Notwithstanding the fact that hypertension is the main co-existing comorbidity in diabetic patients [35]. Moreover, subjects with poor glycemic control are more prone to develop heart failure. The prospective cohort study of Iribarren., *et al*. reported that higher levels of HbA1C are associated with a subsequent rise in heart failure incidence after adjusting of all potential confounders [36]. Furthermore, the contractile power of the heart is greatly affected through induction of left ventricular remodeling [37].

Recent research suggests the possible role of treatment agents in inducing heart failure in type 2 DM patients [38-40]. Heart failure patients treated with insulin had a lower survival rate compared to those who do not receive insulin as a treatment for type 2 DM [41]. Furthermore, patients with type 2 DM randomized to sulphonylureas or insulin had more risk of developing heart failure compared to patients allocated to conventional therapy [42]. However, the randomized controlled trial of Pratley., *et al*. which recruited type 2 diabetic patients with a high risk of cardiovascular complications, indicated that patients treated with insulin degludec had no significant difference in terms of heart failure incidence compared to patients allocated to insulin glargine U100 [30].

To our knowledge, insulin comprises one of the last lines of type 2 DM management [43]. Inulin produces a salt and water retention effect, though increase the workload of the heart of type 2 diabetic patients and increase the susceptibility of heart failure affection [44]. Additionally, the growing incidence of insulin resistance in type 2 DM patients, increases the risk of poor glycemic control that drives many heart pathologies including heart failure comorbidity [45].

Very few randomized controlled trials have addressed the role of insulin treatment (either alone or combined with other treatment agents) in patients with type 2 DM in increasing the incidence of heart failure affection. Therefore, we encourage the emergence of more trials with confounders control to assess the different dosage, types and time factor of the used insulin that can progress to heart failure pathology.

Conclusion

Close monitoring of heart pathologies-especially heart failure- in type 2 DM patients is of extreme importance for improving the quality and expectancy of life in those patients.

Funding

None.

Conflicts of Interest

No conflicts related to this work.

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