Clinical question: Are glucose lowering drugs used for diabetes associated with a higher incidence of heart failure in persons with type 2 diabetes?

Authors’ conclusions:

- Certain classes of anti-diabetic drugs are associated with an increased risk of heart failure. Thiazolidinediones show a high risk association, while DDP4 inhibitors (Gliptins) show an intermediate risk association.
- On the contrary, glucose lowering strategies showed a modest protective effect against incidence of major adverse coronary events and myocardial infarction.

Persons with type 2 diabetes are at risk for heart failure which is a common cause for poor prognosis and a reduced quality of life. Paradoxically however, usage of certain classes of anti-diabetic drugs such as thiazolidinediones or gliptins has been reported to increase the risk of heart failure in some studies. This may be because these drugs have hemodynamic effects that predispose to heart failure.

Udell and colleagues have attempted a meta-analysis to investigate the usage of glucose lowering drugs and incidence of heart failure in patients with or at risk for type 2 diabetes. They included 14 randomised control trials (RCTs) with 95,502 participants that investigated anti-diabetic interventions in type 2 diabetes. Incidence of heart failure was considered as the primary endpoint, while other coronary events and mortality due to other causes were secondary endpoints. The mean (SD) follow up duration of the trials was 4.3 (2.3) years.

Summary of Results

- About 4% of participants (3097 out of 95502) developed heart failure during the follow up period.
- Overall, the data showed a significant increase in incidence of heart failure in participants with better glycemic control (RR 1.14, 95% CI 1.01-1.3; p=0.041). Treatment with glucose-lowering drugs or strategies resulted in a 14% relative increase in the risk of heart failure.
- The authors then went on to compare the individual treatment strategies and risk of heart failure. Incidence of heart failure was higher with use of thiazolidinediones (RR 1.42, 95% CI 1.15-1.76; P=0.001) and DPP4 inhibitors - Gliptins (RR 1.25, 95% 1.08-1.45; P=0.0033).
- On further analysis, heart failure risk was also seen to be associated with weight gain and HbA1 levels. For every 1 kg increase in body weight the relative risk was higher by 7.1%. For every 0.1% improvement in HbA1c the relative risk was higher by 4·1%.
- There was a 5% decreased relative risk for incidence of major adverse cardiovascular outcomes like myocardial infarction with anti-diabetic interventions (RR 0.95, 95% CI 0.91-0.99; p=0.014).

Discussion:

This was the largest meta-analysis looking at the association between anti-diabetic drugs and risk of heart failure. Lowering of blood glucose was associated with a 14% increased relative risk of heart failure in this study. This increased risk was limited to specific classes of drugs - Thiazolidinediones and Gliptins are associated with a high and moderate risk of heart failure respectively. Other groups of drugs were not associated with a similar risk. The mechanism of action responsible for this association with heart failure is controversial. It is possible that this is because Thiazolidinediones can result in weight gain due to fluid retention which can have hemodynamic consequences.

(Expert comments – next page)
Expert comments: Dr. Asha H.S., Associate Professor, Department of Endocrinology, Diabetes & Metabolism, CMC Vellore.

This meta-analysis attempts to address an important issue about the risk of heart failure with various glucose lowering strategies in those with or at risk of diabetes. The analysis has also assessed the effect of other factors that may increase heart failure risk such as weight gain, change in HbA1c, pre-existing cardiovascular disease and the duration of follow-up.

It is well known that uncontrolled hyperglycemia is associated with increased cardiovascular risk. Hence, while assessing the adverse cardiovascular effects of glucose lowering strategies, one should also carefully weigh the risks and benefits of such interventions. A 5% relative risk reduction in major cardiovascular events was observed in this meta-analysis, which translates to an absolute risk reduction of 0.49%. Two hundred and four patients will have to be treated with glucose lowering drugs or other strategies to prevent one cardiovascular event (NNT=204). On the other hand, the absolute increase in risk of heart failure of 0.51%, implying risk of one heart failure event upon treatment of 196 patients (NNH= 196). The effects cancel each other in view of similar numbers needed to treat or harm with regard to cardiovascular effects.

Another important observation of this meta-analysis was the association of weight gain with heart failure. Every one kilogram relative increase in weight was associated with 7.1% relative increase in risk of heart failure. Lastly, after removal of the PPAR class of drugs from the analysis, the pooled effect of other glucose lowering strategies on the risk of heart failure was not significant, implying that this adverse effect is specific to the thiazolidinedione class. Thiazolidinediones cause fluid retention which leads to weight gain and adverse hemodynamic effects.

In conclusion, Thiazolidinediones and weight gain increase the risk of heart failure in those with dysglycaemia. It is essential to sequentially record the weight of all patients on glucose lowering strategies, and emphasize on life style measures to prevent weight gain and its long term adverse consequences. The choice of glucose lowering strategies will have to be individualized weighing the risks and benefits.

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Cessation of smoking impairs glycemic control temporarily


Clinical question: Does glycemic control improve with smoking cessation?

Conclusion: Smoking cessation is associated with temporary impairment in glycemic control for up to 3 years following the quitting event during the first year of abstinence

Background
The association between smoking and risk of diabetes is well known. Evidence from a systematic review indicates that smokers have a 44% higher risk of developing diabetes compared to non-smokers ¹. However, there are also studies which show a contradicting observation - the risk of incident diabetes is higher in recent quitters compared to continuing smokers ². Based on this observation, the authors of this study hypothesized that smoking

cessation in known diabetics would impair glycemic status.

**Methods and findings**

The authors explored this possibility by a retrospective cohort study using the data from the Health Improvement Network (THIN), a primary care database of UK’s National Health Service (NHS). The time frame for the cohort was from 2005-2010. Only type 2 diabetics, whose smoking status was known before 2005 with HbA1c values measured before and after 2005 were included. Based on the smoking status during the follow-up period (2005-2010), the cohort was further categorized into continual smokers (no change in smoking status), long term quitters (abstinence from smoking at least for a year) and relapers (had abstinence periods of less than a year). Changes in HbA1c levels between the different groups were then analyzed by regression models.

The demographics of participants showed an increase in body weight in long time quitters; hence authors also studied effect of change in body weight and HbA1c levels. The observations were adjusted so that it represents a male aged 60–65 years with diabetes for a duration of 1–5 years, and on treatment with diet and lifestyle intervention plus metformin, and prescribed a statin. The models showed an increase in HbA1c levels by about 0.21% (95% CI 0.17–0.25) during the first year of abstinence. The levels gradually fell with duration of abstinence after year 1, and it reached levels comparable to continual smokers after 3 years of abstinence. After adjustments of confounding factors and body weight it was seen that increase in HbA1c levels in long time quitters was unaffected.

**Discussion**

This is the one of the first large studies that has compared the direct association between smoking cessation and glycemic control. The clinical implication is that, since the initial phase of abstinence is associated with a worsening of glycemic control, a vigilant therapeutic intervention may be required during the period. It is also worthwhile to note that although there was a gain in body weights of participants during abstinence, its contribution to rise in HbA1c levels were negligible. The authors also considered the possibility whether continual smokers had better glycemic control since their treatment regimen was more intensive. However, further exploration of data indicated that the opposite was true and long time quitters were the group that had an aggressive anti-diabetic management. The change in HbA1c levels by 0.21% may appear insignificant at the individual level, but at the population level it could result in a several fold increase in microvascular complications.

**References**


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**Evidence profile**

Type of study: Retrospective Cohort study - The Health Improvement Network (THIN), a primary care database of UK’s National Health Service

Number of participants: 10692 participants categorized into continual smokers, long term quitters and relapers

Comparison: Changes in HbA1c levels between the different groups analyzed by multilevel regression modeling

Adjusted confounding factors: Body weight, age, sex, duration of diabetes, treatment, time difference during abstinence

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