HEALTHCARE GROUP

CENTRE FOR DIABETES & ENDOCRINOLOGY

CDE Academy - Diabetes Literature Review

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Type 2 diabetes - do higher insulin doses increase the risk of mortality?

Study partly resolves opposing findings between previous observational studies and randomised clinical trials

Background Existing studies have shown conflicting evidence regarding the safety of exogenous insulin therapy in people with type 2 diabetes. In particular, observational studies have reported an increased risk of death and cardiovascular disease among users of higher versus lower doses of insulin. We aimed to quantify the association between increasing dosage of insulin exposure and death and cardiovascular events, while taking into account time dependent confounding and mediation that might have biased previous studies.

Methods We did a cohort study using primary care records from the UK-based Clinical Practice Research Datalink (CPRD). New users of metformin monotherapy were identified in the period between 1 January 2001, and 31 December 2012. We then identified those in this group with a new prescription for insulin. Insulin exposure was categorised into groups according to the mean dose (units) per day within 180-day time segments throughout each person's follow-up. Relative differences in mortality and major adverse cardiovascular events (non-fatal myocardial infarction, non-fatal stroke, cardiovascular-related mortality) were assessed using conventional multivariable Cox proportional hazards models. Marginal structural models were then applied to reduce bias introduced by the time-dependent confounders affected by previous treatment.

Findings We identified 165 308 adults with type 2 diabetes in the CPRD database. After applying our exclusion criteria, 6072 (mean age 60 years [SD 12·5], 3281 [54%] men, mean HbA1c 8·5% [SD 1·75], and median follow-up 3·1 years [IQR 1·7–5·3) were new add-on insulin users and were included in the study cohort; 3599 were new add-on insulin users and were included in the sub cohort linked to hospital records and death certificate information. Crude mortality rates were comparable between insulin dose groups: <25 units per day (46 per 1000 person-years), 25 to <50 units per day (39 per 1000 person-years), 50 to <75 units per day (27 per 1000 person-years), 75 to <100 units per day (34 per 1000 person-years), and at least 100 units per day (32 per 1000 person-years; p>0·05 for all; mean rate of 31 deaths per 1000 person-years [95% CI 29–33]). With adjustment for baseline covariates, mortality rates were higher for increasing insulin doses: less than 25 units per day [reference group]; 25 to <50 units per day, hazard ratio (HR) 1·41 [95% CI 1·12–1·78]; 50 to <75 units per day, 1·37 [1·04–1·80]; 75 to <100 units per day, 1·85 [1·35–2·53]; and at least 100 units per day, 2·16 [1·58–2·93]. After applying marginal structural models, insulin dose was not associated with mortality in any group (p>0·1 for all).

Interpretation In conventional multivariable regression analysis, higher insulin doses are associated with increased mortality after adjustment for baseline covariates. However, this effect seems to be confounded by time-dependent factors such as insulin exposure, glycaemic control, bodyweight gain, and the occurrence of cardiovascular and hypoglycaemic events. This study provides reassurance of the overall safety of insulin use in the treatment of type 2 diabetes and contributes to our understanding of the contrasting conclusions from non-randomised and randomized studies regarding dose-dependent effects of insulin on cardiovascular events and mortality.

Gamble JM, Chibrikov E, Twells LK, et al. Association of insulin dosage with mortality or major adverse cardiovascular events: a retrospective cohort study. ***Lancet Diabetes Endocrinol. 2017 Jan;5(1):43-52.*** **DOI: 10.1016/S2213-8587(16)30316-3.**

Dentists Can Play a Key Role in Management of Diabetes

People with type 2 diabetes and periodontitis may experience significant improvements in glycaemic control if they have their gum disease properly treated. Comparing thorough periodontal treatment with superficial plaque and calculus removal, the researchers found that people who underwent intensive gum management experienced significant improvements in fasting plasma glucose (FPG) and HbA1c, despite already receiving diabetes treatment.

The study demonstrates "that the nonsurgical treatment of periodontitis improves glycaemic status and levels of HbA1c, and therefore proves the great importance of oral health in these patients," said hor José López-López, MD, PhD, from the Dental School, University of Barcelona, Spain, in a press release. The research was published online in the *Journal of Clinical Periodontology*, by Miquel Viñas, et al.

It follows Dutch findings indicating that people with severe periodontitis may have undiagnosed type 2 diabetes, as reported by *Medscape Medical News*. That analysis of 300 dental clients revealed HbA1c levels increased significantly with increased severity of periodontitis, and severe periodontitis was linked to a doubling of the risk of suspected diabetes.

Viñas said the current study shows that there is a relationship, not only from diabetes to periodontal disease, but also "the other way round." "Dentists play a critical role in the management of diabetes patients, identifying those at high risk of diabetes and helping them to control their periodontal disease and therefore their metabolic status," he and his colleagues assert.

"Patients with type 2 diabetes and periodontitis may experience significant improvements in glycaemic control if they have their gum disease properly treated"

Spanish Study: Patients Had Diabetes for 10 Years on Average

Although previous studies have suggested that periodontal treatment could be linked to improved glycaemic control, there has not been enough evidence to demonstrate a causal relationship. The Spanish researchers conducted a randomized clinical trial to examine the impact of nonsurgical periodontal treatment on glycaemic control in 90 people previously diagnosed with type 2 diabetes and who had generalized chronic periodontitis. Specifically, clients were randomized to treatment, comprising scaling and root planing using ultrasound and Gracey curettes, or to a control group, who underwent supragingival removal of plaque and calculus using ultrasound. Both groups also received oral hygiene instruction.

A full periodontal assessment, including plaque index (PI), gingival index (GI), and probed pocket depth, was carried out at baseline and after 3 and 6 months. HbA1c and FPG were determined up to 30 days before baseline and at 6 months, as were bacterial counts.

Mean age of participants was 61 years, and mean duration of diabetes was around 10 years. Approximately 45% of clients were receiving oral hypoglycaemic agents, and around 40% were taking these agents alongside insulin.

There were no significant differences between the treatment and control groups in terms of age, sex, duration of diabetes, body mass index, daily brushing, and mouthwash habits. There were, however, significant differences in smoking history (P = .002), with the patients in the treatment group substantially more likely to be current smokers and less likely to be former smokers or having never smoked than control patients. The authors note that a worse response to periodontal therapy in smokers than nonsmokers has previously been reported, but they still had a significant difference between groups in spite of the fact there were more smokers in the treatment group.

Significant Improvements in FPG and HbA1c With Intensive Treatment

Clients in the treatment group experienced significant improvements in PI and GI at 3 and 6 months (P = .000), while the changes in the control group were minimal and not significant (P = .487).

At baseline, both HbA1c and FPG levels were similar in the treatment and control groups. FPG levels decreased by a significant 18.61 mg/dL (1.03 mmol/l) in the treatment group at 6 months (P = .022), while they increased by 16.25 mg/dL (0.90 mmol/l) in the control group, with a significant difference between the groups (P = .019). The researchers also note that patients in the treatment group had a significantly greater improvement in HbA1c compared with the control group, at −0.51% vs −0.06% (P = .023).

Some, but not all, clients experienced marked reductions in bacterial counts. However, this was not associated with changes in glycaemic control, leading the researchers to observe "even if treatment had no effect on bacterial counts, it leads to an improvement in the clinical condition of the patient."

The team concluded that periodontal evaluation is essential for individuals with diabetes, who should be aware of their increased risk of periodontal disease. Periodontal therapy could lead to cost savings in people with type 2 diabetes, thanks to its effect on metabolic control.

Medscape Medical News (2018). *Dentists Can Play a Key Role in Management of Diabetes*. Available from: https://www.medscape.com/viewarticle/892394

Liver Disease Gets a New Name and Diagnostic Criteria

Non-alcoholic fatty liver disease will now be called metabolic dysfunction–associated steatotic liver disease, or MASLD, according to new nomenclature adopted by a global consensus panel composed mostly of hepatology researchers and clinicians.

The new nomenclature, published in the journal *Hepatology*, includes the umbrella term steatotic liver disease, or SLD, which will cover MASLD and MetALD, a term describing people with MASLD who consume more than 140 grams of alcohol per week for women and 210 grams per week for men. Metabolic dysfunction–associated steatohepatitis, or MASH, will replace the term non-alcoholic steatohepatitis, or NASH.

Mary E. Rinella, MD, of University of Chicago Medicine led the consensus group. The changes were needed, Dr Rinella and her colleagues argued, because the terms 'fatty liver disease' and 'non-alcoholic' could be considered to confer stigma, and to better reflect the metabolic dysfunction occurring in the disease. Under the new nomenclature, people with MASLD must have a cardiometabolic risk factor, such as type 2 diabetes. People without metabolic parameters and no known cause will be classed as having cryptogenic SLD.

While the new nomenclature largely conserves existing disease definitions, it allows for alcohol consumption beyond current parameters for non-alcoholic forms of the disease. "There are individuals with risk factors for NAFLD, such as type 2 diabetes, who consume more alcohol than the relatively strict thresholds used to define the non-alcoholic nature of the disease [and] are excluded from trials and consideration for treatments," the authors wrote.

"Metabolic dysfunction-associated steatohepatitis, or MASH, will replace the term nonalcoholic steatohepatitis, or NASH."

Moreover, they wrote, "within MetALD there is a continuum where conceptually the condition can be seen to be MASLD or ALD predominant. This may vary over time within a given individual."

Respondents overwhelmingly agreed, however, that even moderate alcohol use alters the natural history of the disease and that people with more than minimal alcohol consumption should be analysed separately in clinical trials.

The new nomenclature reflects a 3-year effort involving some 236 panellists from 56 countries who participated in several rounds of online surveys using a Delphi process. Paediatricians, gastroenterologists, and endocrinologists also participated as well as some patient advocates. Changes were based on a super-majority of opinion (67% or higher), though the consensus on whether the term 'fatty' was stigmatizing never reached that threshold. In early rounds of surveys only 44% of respondents considered the word 'fatty' to be stigmatizing, while more considered 'non-alcoholic' to be problematic.

"Substantial proportions of the respondents deemed terms such as 'fatty' stigmatizing, hence its exclusion as part of any new name," Dr. Rinella and her colleagues wrote. "Although health care professionals may contend that patients have not reported this previously, this likely reflects in part a failure to ask the question in the first place and the power imbalance in the doctor-patient relationship." The authors noted that the new terminology may help raise awareness at a time when new therapeutics are in sight and it becomes more important to identify at-risk individuals.

Of concern was whether the new definitions would alter the utility of earlier data from registries and trials. However, the authors determined that some 98% of people registered in a European NAFLD cohort would meet the new criteria for MASLD. "Maintenance of the term, and clinical definition, of steatohepatitis ensures retention and validity of prior data from clinical trials and biomarker discovery studies of patients with NASH to be generalizable to individuals classified as MASLD or MASH under the new nomenclature, without impeding the efficiency of research," they stated.

The effort was spearheaded by three international liver societies: La Asociación Latinoamericana para el Estudio del Hígado, the American Association for the Study of Liver Diseases, and the European Association for the Study of the Liver, as well as the cochairs of the NAFLD Nomenclature Initiative.

MDedge.com/Internal Medicine (2023). *Liver Disease Gets a New Name and Diagnostic Criteria*. Available at: https://www.mdedge.com/internalmedicine/article/264079/gastroenterology/liver-disease-gets-new-name-and-diagnostic-criteria

Beta cells from Stem Cells: Nearing a Cure for Type 1 Diabetes?

Those of us in the field of diabetes have long wanted to cure type 1 diabetes, and there are little steps making me feel like this might be a possibility. One of those steps is that a company named Vertex has made beta cells from stem cells. Now, instead of waiting for a cadaveric donor, we can make little beta cells. They started giving them to people in human trials. The US Food and Drug Administration has been cautious because it's new, and I get that.

In the first part of these trials, we could only give half a dose of these beta cells. The doses were determined based on what we know from giving beta-cell transplants from cadaveric donors. We gave half a dose of these stem cell-derived beta cells to two people who were having episodes of severe hypoglycaemia.

In patient 1, these beta cells worked incredibly well. He became insulin independent, and now after over a year, he's basically free of his type 1 diabetes. Patient 2 received half a dose, and she did get some activity of the beta cells, but not enough to achieve insulin independence, so she got a second dose. Shortly after the second dose, she decided she didn't want to participate in the trial anymore and she was lost to follow-up.

Patient 2 didn't get the same response as patient 1, but then we moved on to four more patients who got a full dose to start with. Now, there's a total of six patients. Of those additional four patients, one of them has now been followed for a year. Just like patient 1, he's off insulin. It's as though his body has normal beta cells and he's doing great. For the next three patients, we don't have enough follow-up data to tell you what's going to happen to them at a year.

I can tell you that, in all six patients, the beta cells worked. They basically were producing insulin, they had positive C-peptide levels, and it showed that these beta cells work when given to human beings. Now the trial is going to start giving more patients these stem cell–derived beta cells.

One of the things that's important to realize is that this is a very small sample size, at just six individuals. Even within those six individuals, there was variation in terms of the response to the treatment. Probably, just like with all things in medicine, there will be different doses, different ways in which people do respond, people who get off of insulin completely, and people who may require some ongoing insulin therapy. I have no idea what this is going to look like as we test this in more people.

Everybody did start making C-peptide, they were having an effect of these beta cells, and it was working. We'll have to see how well it works, how well it works in whom, and how we're going to be able to use these types of therapies in the future.

In terms of side effects, they were really related to immunosuppression. There were no real surprises, but again, this is a very small sample size.

In summary, I think this is really hopeful. I don't like to give false hope, but each step of this development process has shown that these beta cells derived from stem cells do seem to work in human beings as native beta cells might. Hopefully, this portends a future of newer therapies in the treatment of people with type 1 diabetes.

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Medscape Diabetes & Endocrinology > Peters on Diabetes > ADA 2023.
COMMENTARY: Beta *Cells From Stem Cells: Nearing a Cure for Type 1 Diabetes?*
Available from: https://www.medscape.com/viewarticle/993713#:~:text=We%20gave%20half%20a%20dose,of%20his%20type%201%20diabetes.