Evidence Review

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Nov 19th, 2023

University of Victoria

HINF 381: Epidemiology, Population Health and Public Health

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INTRODUCTION

This paper aims to assess the strength of evidence provided by three separate studies on Type 1 Diabetes Mellitus (T1DM) and personally advocate for the strongest one. The first study is a case-control study based in Poland that looks at the nutritional status of T1DM patients [1], the second is a cohort study in Sweden that compares T1DM determinants of mortality [2], and the third is a randomized control trial (RCT) in France that tests the effects of text-message insulin injection reminders on Hemoglobin A1c (HbA1c) levels [3]. These papers will be analyzed for their primary and secondary endpoints, study design, sampling, selection, biases, data analysis, confounding factors, and assessments of causality.

CASE CONTROL STUDY

The case-control study in Poland primarily aimed to measure the nutritional status in T1DM patients by measuring Body-Mass Index (BMI) through impedance analysis; height and weight; circumference of upper arms, waist, hips and shoulder blades. An interview and questionnaire was also given to each patient where they were assessed for nutritional behavior such as their types and frequencies of meals and snacks; patients were also asked to provide recent HbA1c test results. They study facilitators hypothesized that nutritional levels would be worse in the diabetic group and that the type of insulin injection has an effect.

The sample population consisted of 280 pediatric T1DM patients from two locations (Voivodeships) in Poland; the study group came from a diabetic rehabilitation camp and the control group was a selection of healthy students. Immediately, sampling bias is present since the selected patients do not adequately represent T1DM patients who don't end up in rehabilitation camps, and a group of health students with no other diseases does not adequately represent a population of youth without T1DM.

Of the 280 participants, 111 were excluded and 169 were included. Inclusion criteria required that individuals be living in either the Warmiam-Masurian or Podlaskie Voivodeships and be 9-15 years old. Exclusion criteria applied to anyone not living in those areas, not within the age bracket, having other chronic diseases, or missing required data—some participants refused to participate for unspecified reasons. The study group consisted of 85 individuals and the control group 84 individuals. HbA1c levels less than 7% (53 mmol/mol) were used to classify children as suitable for the T1DM group. Groups were of unequal size with no randomization, stratification, or blinding performed. Additionally, a minimum sample size was calculated to a maximum error value (11%) and a set confidence of (95%), but the exact calculated number was not given, though this may be implied the achieved 280. In total, the included 169 consisted of 95 girls (study group n=49, control group n=46), 74 boys (study group n=36, control group n=38), and of the study group, 59 (70%) used personal insulin pumps (PIP) and 26 used insulin injection pens (30%). The mean ages for T1DM boys was 12.0 years old, and 11.0 years for the control group boys. The mean heights were not equal between groups, and the mean body-weights were much larger in the T1DM group. Participants were not matched by age, gender, or family income level. Biases included selection bias, exclusion bias, healthy user bias, and volunteer bias.

Interviews were conducted separately to assess the metabolic management of participants. During the questionnaire, individuals were asked about nutritional behaviors such as the number and types of meals consumed during the day, and the frequency of certain snacks. T1DM patients were asked to provide recent HbA1c test results, but the controls were not—furthermore, it was not confirmed that all study group members provided results. Participants were asked to fast and not perform physical exertion for a period of 10 hours before being measured at a consistent room temperature. Bioelectrical Impedance Analysis (BIA) was used to measure BMI with a BC-1000 device—no given specificity or sensitivity. BMI levels were compared against developmental norms centile grids for underweight, overweight, and obesity. Waist-hip ratios (WHR) and Waist-to-height ratios (WtHR) were chosen to accurately measure the distribution of abdominal fat and participants were categorized into low, medium, and high body fat content. Strong opportunities existed for interview bias, recall bias, response bias and reporting bias. Instrument bias was accounted for with controlled factors and averaging repeated measurements.

An odds ratio was not provided by this study, and inconsistent statistical methods were used for measuring correlations between qualitative data; primarily chi-squared but also V-square and Yates correction in other cases. With an alpha of $P < 0.05$, it was found that the percent distribution of BMI between groups was "statistically higher" ($P < 0.001$; 21.3 kg/m^2; 17.8 kg/m^2) in the T1DM group than the control group, and that between the two insulin therapies, "there is a difference in favor of PIP over insulin injection (7.1 vs 8.0%; 54 vs 64 mmol/mol; $P<0.001$)"—but given the degree of sampling and selection bias I find this baseless along with all other results. No causality was established. Acknowledgements that the small sample size might affect results was given.

COHORT STUDY

The cohort study did not state a hypothesis, but instead examined how the duration of different T1DM complications, age, and age at diagnosis affected T1DM related mortality rates in Sweden; all-cause mortality, cardiovascular (CV) mortality, and non-CV mortality. The facilitators followed standard cohort study design closely and made no deviations.

The researchers selected 33,396 individuals from the Swedish National Diabetes Register (NDR) and cross-referenced new cases of T1DM complications and deaths (between 2001 and 2012) with Statistics Sweden, Swedish Inpatient Register and a Cause of Death Register. Given that the NDR covers over 95% of adults with T1DM in Sweden, that 100% of Swedish outpatient diabetes clinics are represented in the data, and that no patients were interviewed or assigned groups, there is little room for sampling bias, selection bias, and information biases in this study. Randomization was not necessary as a cohort study, but results were stratified by age. There is the possibility that this study missed undiagnosed or unregistered T1DM patients, and mis-labeled causes of death, but given the low percentage this error is likely negligible and should not be considered biased.

Between 2001 and 2012, the facilitators conducted 198,872 pearson-years of follow-up and observed 1748 deaths out of the 33,396 sample. Inclusion criteria addressed 97% of cases as the study cites an effective way of assessing T1DM: "anyone with diabetes onset at 30 years of younger who were treated with only insulin." Given the accuracy of the Cause of Death Register, corrections were not necessary and room for analysis bias was low. Poisson models were used consistently for each

mortality outcome (all cause, CV, non-CV, Diabetic Kidney Disease, and Retinopathy) to gauge the time and risk between complication onset and death.

Confounders and interactions were calculated with Mortality Rate Ratios (MRRs) and adjustments were made for sex, region of birth, marital status, smoking status, income, education level, HbA1c, systolic blood pressure, BMI, and low-density lipoprotein cholesterol. Multiplicative interactions were found for individuals with more than one effect. All cause MRRs for each patient outcome was as follows: diabetic kidney disease, 2.25 (95% CI: 1.99-2.54); cardiovascular disease, 4.00 (95% CI: 3.56-4.50); retinopathy, 0.98 (95% CI: 1.99-2.54). MRRs were 8 times highest during the first period of CVD diagnosis and 2 times higher with diabetic kidney disease, but stabilized after 5 years. The casualties had a temporal relationship with the measurable endpoint, biological plausibility, consistency with other studies and current knowledge, and gave the specificity of the association.

RANDOMIZED CONTROL TRIAL STUDY

The responsibility of this RCT study changed hands after sampling and its direction changed with it. The original hypothesis was not stated and the study was adapted to assess the effects of a text-message-reminder (SMS) service for insulin pump injection on T1DM patients, with the claim that poor glycemic control is a problem for T1DM patients and leads to complications. Ultimately, the intervention and control groups were compared by their proportion of patients who saw a HbA1c level decrease by at least 1% over 6 months of intervention, and a secondary endpoint was established to qualitatively measure quality of life and patient satisfaction with the SMS service at the end of the study. It seems that the original hypothesis, whatever it was, was not intended for this intervention and that the final hypothesis was created after the results.

This study was a two-arm, open label, randomized control trial that deviated twice; first when the facilitators offered a satisfaction survey to the intervention group, and second when extending the age eligibility of participants from 12-18 to 12-21 due to slow recruitment. Participants were recruited from only one location in October of 2015; the endocrinology department at Necker Children's Hospital in Paris. A small sample of 159 T1DM patients with poor glycemic control were assessed for eligibility in the study. Strong sampling bias is present in this study due to the restriction of the participant pool to one location, the small sample size, and focus on patients with assessed glycemic control prior to forming the new hypothesis. Patients were not asked if they had other diabetes-management apps on their phones if they were using a continuous glucose monitor, or even personal injection pumps. Additionally, only patients complying with standard T1DM check in appointments were found eligible, excluding an important population of non-compliant T1DM patients, indicating volunteer bias.

Of the 159 patients, 92 were included and randomized into unequal groups; 45 to the intervention arm, and 47 to the control. Computer randomization was conducted by the first author, not the final facilitators, possibly attributing to sampling bias. Included patients were 12-21 years old with a T1DM diagnosis at least 6 months earlier, HbA1c level greater than or equal to 69 mmol/mol (8.5%), ownership of a personal cell phone, fluency in French, no diagnosis for an acute psychiatric disease, no pregnancy, and willingness to participate in interviews at 3 and 6 months. Of the 67 excluded, 46 did not meet the inclusion criteria, and 21 either refused or did not participate for no given reason.

There was no stratification, matching, or blinding in the trial due to “the nature of the intervention” but was not explained any further; blinding of the facilitators could have at least taken part, or a “placebo text” occurring at random intervals with unhelpful messages. The control arm was not informed of the intervention as an attempt to somewhat blind the experiment, but because all the children were selected from the same community there is significant chance of interaction between groups; something that could have been avoided had multiple locations been sampled. The SMS group was given an additional 10-minute interview explaining how the intervention worked, but not the control group, and were allowed to set their own SMS schedule and content which may have invalidated other findings. Selection bias is remarkably strong in this study.

The facilitators wanted to detect a difference in HbA1c levels between groups of at least 1% after 6 months, with a two-sided alpha risk of 5% and study power of 80% and calculated a required sample size of 100 patients, but only achieved 92. Due to possible flaws in randomization, study design, sample size, sample bias, and selection bias, a common baseline level HbA1c could not be established between groups—a critical limitation in this study. They decided to change direction again and perform a post-hoc comparison of the proportions within groups of HbA1c level decreases by at least 1% over 6 months. They claimed that a significant change (P = 0.03) within the SMS by the end of the trial; “HbA1c greater than or equal to 80 mmol/mol (9.5%) (n = 56): 60% in the SMS arm and 30.6% in the control arm had lowered their HbA1c”, but if one group had higher average HbA1c levels then any reduction might be more pronounced simply due to the potential for greater improvement. Frequent disruptions also occurred in the intervention group; SMS services were unavailable for 2 weeks and an additional 20 participants were lost to follow-up.

The facilitators illuminated the lower HbA1c trend in the intervention group but could draw firm conclusions from the study; no causality was established, no interactions, and no confounders.

CONCLUSION

The case-control study and RCT both suffered strong sampling bias, small sample sizes, and crucial design flaws. However, the worst mistake of these papers was not their biases, but their statements of baseless conclusions. The case-control did not provide an odds ratio to back up their claim and the RCT’s proclaimed trend in HbA1c was a lost opportunity to own what really went wrong. It is not common that a cohort study outweighs an RCT in reliability, but in this case the caliber and scope of the Swedish cohort study was undeniable.

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