Obesity Research & Clinical Practice (2017) xxx, xxx—xxx

ORIGINAL ARTICLE

Effects of obesity on metabolic and cardiovascular outcomes following insulin initiation in patients with type 2 diabetes

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Received 5 June 2017; received in revised form 4 August 2017; accepted 23 August 2017

KEYWORDS
Type 2 diabetes;
Obesity;
Insulin;
Cardiovascular;
Mortality

Summary
Objectives: Insulin therapy induces weight gain but whether it causes long term adverse metabolic and CV outcomes in obese patients remains unclear.
Methods: A retrospective cohort study of 12,725 insulin initiators with T2D derived from UK General Practices. Multivariate linear, logistic regression analyses and Cox proportional hazard models were used to estimate HbA1c, BMI, risk of composite CV events between baseline BMI categories at 5 years.
Results: Mean age was 58.6 ± 13.8 years. The proportion of patients achieving HbA1c targets decreased across increasing BMI categories at 6 and at 12 months; p = 0.0001, but not significant beyond 24 months. 1095 composite events of all-cause mortality, non-fatal stroke and MI occurred with an adjusted hazard risk (aHR) relative to normal of: (1.10; 95%CI: 0.90—1.35) in the overweight, (1.05; 95%CI: 0.86—1.29) in the obese class I, (1.03; 95%CI: 0.83—1.29) in the obese class II and (1.30; 95%CI: 1.02—1.66) in the obese class III BMI categories.
Conclusion: Among patients with T2D insulin initiators, obesity adversely influences HbA1c up to 12 months, but not beyond 24 months and is associated with a decrease in BMI compared to non-obese groups. Morbidly obese patients initiating insulin have 30% increased risk of composite CV events after 5 years.

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http://dx.doi.org/10.1016/j.orcp.2017.08.005
1871-403X/

Please cite this article in press as: Anyanwagu U, et al. Effects of obesity on metabolic and cardiovascular outcomes following insulin initiation in patients with type 2 diabetes. Obes Res Clin Pract (2017), http://dx.doi.org/10.1016/j.orcp.2017.08.005

What is already known about this subject?

1) Insulin therapy is the most effective therapy to lower HbA1c levels but is well recognised to be associated with weight gain.
2) Weight gain and obesity is a recognized risk factor for the development of type 2 diabetes, and adverse cardiovascular outcomes.

What does this study add?

1) Despite the well-recognised correlation between obesity, exogenous hyperinsulinaemia and CV, there is little direct evidence relating to the impact of baseline obesity on metabolic and mortality outcomes following insulin initiation in routine clinical practice.
2) In the short term, increasing level of obesity is significantly associated with reduced likelihood of achieving target HbA1c levels, but this observation was not significant in the longer term.
3) Patients with morbid obesity who are started on insulin therapy is associated with a 30% increased risk of developing adverse cardiovascular outcomes.

Introduction

In the UK, obesity is estimated to affect 1 in every 4 adults [1], is prevalent in patients with type 2 diabetes (T2D) worldwide [2,3] and is recognised to be associated with adverse cardiovascular (CV) events including mortality [4]. The therapeutic management of T2D aims at maintaining good glycaemic control in order to minimise long-term vascular complications but in the obese population, balancing the appropriate choice of therapy with the unintended effects such as weight gain presents a dilemma and therefore needs to be individualised [5]. Insulin therapy is the most effective therapy to lower Glycated Haemoglobin (HbA1c) levels but is well recognised to be associated with weight gain [6]. In the United Kingdom Prospective Diabetes Study (UKPDS), patients in the intensive intervention cohort was observed to gain approximately 5 kg during the 10-year follow-up period, with most of this gain occurring in the first 12 months [7]. We and others have also shown that in routine clinical practice, the effectiveness of insulin therapy to lower HbA1c levels is dependent on patients' baseline weight [8,9], and is speculated to be due to insulin-induced weight gain resulting in an increase in the amount of insulin required to control hyperglycaemia [10,11] at the expense of further weight gain, possible poor treatment compliance and increased insulin resistance.

Despite the well-recognised correlation between obesity, exogenous hyperinsulinaemia and CV risk [12], there is little direct evidence relating to the impact of baseline obesity on mortality outcomes following insulin initiation in routine clinical practice. However, there is indirect evidence that weight gain does adversely affect CV risk. The ACCORD study designed to investigate whether an aggressive therapeutic strategy to achieve tight glucose target (HbA1c < 6.5%) would reduce CV events surprisingly showed an increased mortality in the intensively treated group [13], with weight gain by more than 10 kg occurred in 27.8% of the intensively treated patients compared with 14.1% in the standard therapy. While no causal relationship between obesity and adverse CV outcomes can be assumed, other retrospective studies have shown that people with diabetes who actively lose weight improve not only their risk profile [14—16] but also survival rate. Previous similar studies focusing on the association between obesity at insulin initiation were limited by either by their choice of patients as in the UKPDS which used predominantly obese patients [7]; study population size [6]; the exclusion of younger patients with T2D, short follow up period, or failure to adjust for important risk factors associated with obesity [17].

To our knowledge, no real-world study has explored the long-term effects of obesity at insulin initiation on metabolic and CV outcomes. So, we aimed therefore to investigate the association between obesity, metabolic outcomes (HbA1c and weight), CV events and mortality in patients with T2D who initiated insulin therapy.

Methods

Study design and data source

This was a retrospective cohort study using data derived from the UK anonymised longitudinal electronic Primary Care data called The Health Improvement Network (THIN). This database has details of over 12.4 million patients (3.61 million currently active) from about 587 UK general practices. It has been validated and shown to be representative of the UK population in terms of demography, life-event rates and other health-related events; and has been extensively used in diabetes-related researches [18—20]. Anonymised

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