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Carbohydrate counting at meal time followed by a small secondary postprandial bolus injection at 3 hours prevents late hyperglycemia, without hypoglycemia, after a high-carbohydrate high-fat meal in Type 1 diabetes

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Short running title: insulin and high-fat meals in Type 1 diabetes

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Type 1 diabetes patients are provided guidance and structured education on adjusting their meal time bolus-insulin dose based on meal carbohydrate content. However, recent research in patients using continuous subcutaneous insulin infusion (CSII) has highlighted the role of dietary fat in increasing prandial insulin requirements, particularly late into the postprandial period (1, 2).

Many patients are treated with basal-bolus insulin injections, which is a less flexible method of insulin therapy than CSII; for example, patients are unable to dual wave/extended bolus at meal time. It is important to consider that patients are encouraged to carbohydrate count and administer rapid-acting insulin units at meal-time, and that the time-action profiles of lispro/aspart vary in a dose dependent manner; while the peak insulin concentration after a pre-meal bolus usually occurs within the first 60 minutes (3), the peak action is usually observed between 90-120 minutes, and this duration can vary between 4-6 hours. However, peak postprandial lipemia occurs after 3-4 hours (4), which can promote acute peripheral insulin resistance and increase hepatic glucose output (5), and thus, hyperglycemia.

We investigated the influence of rapid-acting insulin dose and timing after high-carbohydrate high-fat meals in type 1 diabetes patients using insulin analogue injections.

10 male patients (mean±SD; age 26±4 years, BMI 25.4±1.6, diabetes duration 17±5 years, age at diagnosis 9±4 years; HbA_{1c} 52.5±5.9 mmol/mol[7.0±0.5%]) using insulin aspart, and either basal insulin glargine (n=8) or detemir (n=2) attended the Newcastle NIHR Clinical Research Facility at 07:30h on four occasions.

Experimental trials were randomized and involved consuming either a 1) low-fat meal with bolus insulin dictated by carbohydrate counting (**Low-Fat100%**), 2) high-fat meal with bolus insulin dictated by carbohydrate counting (**High-Fat100%**), 3) high-fat meal with a bolus insulin dose increased by 30% (**High-Fat130%**), or 4) high-fat meal with bolus insulin dictated by carbohydrate counting, with an additional 30% administered at 3-h post-meal (**High-FatSplit**). Meals were matched for carbohydrate and protein content, but differed in fat (low fat: 68 g carbohydrate, 26 g protein, 5 g fat; High-fat: 68 g carbohydrate, 26 g protein, 55 g fat). Interval blood samples were collected over a 6 hour post-prandial period and were processed for glucose (Biosen C-Line, EKF-Diagnostic GmbH, London) and exogenous insulin (Invitron Insulin-Assay, Invitron, Monmouth, UK).

Glucose and insulin are presented in Figure 1-A and B, respectively. **High-Fat100%** was associated with late-hyperglycemia, while during **High-Fat130%**, 60% of patients experienced hypoglycemia (glucose<3.9 mmol/L), with no incidences under the other conditions. Post-prandial glycemic excursions (time-course changes and area under the curve) were similar between **Low-Fat100%** and **High-FatSplit**, despite the additional 50 g of fat consumed in the latter trial.

When a meal has a high-carbohydrate and high-fat content, using the carbohydrate counting method for insulin dose adjustments at meal time, and administering additional bolus-insulin units 3 hours later, provides similar postprandial glucose control to a meal containing negligible fat, without causing hypoglycemia. Patients should be advised that increasing meal-time insulin dose alone is not an effective strategy, and is an approach that may increase the risk of early post-prandial hypoglycemia.

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DUALITY OF INTEREST

There are no potential conflicts of interest relevant to this article.

AUTHOR CONTRIBUTIONS

MDC and **DJW** contributed to the study concept and design, researched data, and wrote the manuscript. **MW** and **JAS** contributed to participant recruitment and reviewed and edited the manuscript. **DK, JTG and DA** aided in data collection and data analysis. **EJS** contributed to the study concept and design, provided materials and reviewed and edited the manuscript. **DJW** is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of data analysis.

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Figure Legends

Figure 1 A-B. A Time course changes in blood glucose; **B** in Serum Insulin. Blue trace = **Low-Fat100%**; Black trace = **High-Fat100%**; Red trace = **High-FatSplit**; Green trace = **High-Fat130%**. Data presented as mean±SD (n=10). * indicates that all conditions are significantly different from **High-Fat130%**, ** indicates that all conditions are significantly different from **High-Fat100%** and **High-Fat130%**.