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Insulin Doses for Dietary Fat and Protein in Children and Adolescents with Type 1 Diabetes Mellitus; Strategies and Challenges: Review Article

Ahmed M. Hegab, Susana E. Hasaballah*, Montaser M. Mohamed
Department of Pediatrics, Faculty of Medicine, Sohag University, Sohag, Egypt
***Corresponding author:** Susana E. Hasaballah, **Mobile:** (+20) 01283109511, **E-mail:** sawsanaewieda1@gmail.com

ABSTRACT
Background: The present approach for treating type 1 diabetes mellitus (T1DM) in children and adolescents relies heavily on carbohydrate restriction and rigorous insulin treatment. The amount of carbohydrates in each meal or snack is the main factor used to determine the insulin dosages given during meals. Consuming fat and protein along with carbs, however, might postpone stomach emptying and result in late postprandial hyperglycemia. Recent research has emphasised the need of modifying insulin dosages for dietary protein and fat to reduce postprandial glucose excursions. To predict insulin needs for meals' protein and fat compositions, many insulin dosage techniques have been devised. Nevertheless, the contemporary clinical practice still faces difficulties in regulating insulin dosages for dietary fat and protein.
Objective: This review presents different studies that assessed the effects of dietary fat and protein on postprandial glycemic responses.
Methods: The following search terms were used in PubMed, Google Scholar, and Science Direct searches: Insulin treatment, Dietary fat and protein, and T1DM. The authors carefully analysed all relevant references from the relevant literature, including all respectable research and reviews, and only the most recent or comprehensive study was included.
Conclusion: To achieve postprandial euglycemia, insulin dosage adjustments for dietary fat and protein are necessary. The best insulin dosage methods to account for the protein and fat composition of the meals are yet unclear. Combination boluses offer better postprandial glycaemic control for T1DM patients using insulin pumps than conventional and prolonged boluses. It is yet unknown if dividing insulin dosages among patients on the MDI regimen would improve postprandial glycaemic control.
Keywords: Insulin therapy, Dietary fat and protein, T1DM.

INTRODUCTION
Intensive insulin treatment and carbohydrate counting are essential for the management of T1DM in children and teenagers [1]. One of two insulin regimens, the multiple daily injection (MDI) regimen or insulin pump treatment, can be used to administer intensive insulin therapy. Bolus insulin is delivered before each meal and snack, and basal insulin is given once or twice day as part of the MDI protocol. Insulin pumps make it possible to employ several boluses each day without the need for individual injections [2].

The main macronutrient that influences postprandial blood glucose levels is carbohydrate. By counting carbs, one may estimate the amount of carbohydrates in each meal and modify bolus insulin dosages in accordance with the carbohydrate content of each meal or snack. Calculating the pre-meal dosage involves dividing the grams of carbohydrates in a meal or snack by the ICR [3].

However, dietary protein and fat have been shown in numerous studies to have an effect on postprandial blood glucose levels [4]. Consuming fat and protein together with carbs might cause late postprandial hyperglycemia and prolong stomach emptying. To enhance postprandial glucose control following high-fat and protein meals, the prandial insulin dosages must be changed [5].

Blood sugar effects of dietary fat and protein
Increased dietary fat reduces peripheral tissues' sensitivity to insulin and boosts hepatic glucose production through promoting gluconeogenesis. When taken with carbs, dietary fat can cause delayed stomach emptying, which can first reduce the postprandial glycemic response before increasing and extending it for several hours after the meal [5]. By increasing plasma levels of glucagon, and ghrelin, dietary protein has an impact on glucose homeostasis. Additionally, dietary protein promotes gluconeogenesis by increasing hepatic blood glucose synthesis [6].

Protein intake's impact on postprandial blood sugar levels
The amount of protein and other macronutrients in a meal can have an influence on postprandial glycemia in different ways [7, 8]. According to **Paterson *et al.*** [9] eating a meal with 75 grams or more of protein on its own caused a considerable rise in postprandial blood sugar levels 3 to 5 hours after the meal. Additionally, it was shown that increasing the protein in a low-fat meal while maintaining the amount of carbs reduced the blood glucose excursion in the first hours following the meal, with a later dose-dependent rise in blood glucose levels [10].

Klupa *et al.* [11] on the other hand found that in individuals utilising insulin pumps, the eating of a meal high in pure protein had no effect on postprandial blood glucose levels. Furthermore, in 28 patients with

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T1DM receiving MDI treatment and pump therapy, **Borie-Swinburne *et al.*** [12] did not discover any difference between a protein-enriched meal and a regular evening meal in post-prandial, overnight, or late-night glucose levels.

Effect of dietary fat on blood sugar levels after meals

According to earlier research, eating fat makes T1DM patients' postprandial blood glucose levels higher and their need for insulin higher. According to **Wolpert *et al.*** [13], a high-fat supper considerably raised insulin needs and exacerbated hyperglycemia with noticeable individual variability. Additionally, **O'Connell *et al.*** [14] showed that eating fat alone increased blood glucose excursions 4 to 8 hours after the meal in a dose-dependent manner.

However, the impact of dietary fat type on insulin need and glycemic control was only examined in a small number of research. When compared to meals high in saturated fat, **Rocca *et al.*** [15] found that meals high in monounsaturated fats were related with more delayed stomach emptying. Additionally, **Bozzetto *et al.*** [16] noted that the early postprandial glucose response that was shown when a meal was ingested with either low fat or saturated fat (butter) was diminished when the meal had monounsaturated fat.

Combined high-fat and protein meals' effects on postprandial blood sugar levels

According to a number of research [17, 18], meals heavy in protein and fat have a longer effect on postprandial blood glucose levels. Meals with more protein and fat had a greater postprandial glycemic response than meals with solely carbs, lasting up to 3 hours after the meal. According to **Smart *et al.*** [17] meals heavy in fat or protein cause blood sugar excursions to climb 3 to 5 hours after eating. Dietary fat and protein also have an additive effect on this rise. **Neu *et al.*** [18] also discovered that blood glucose levels were considerably higher twelve hours following the fatty, protein-rich evening meal.

According to **Bell *et al.*** [19] meals heavy in protein and fat caused a two-fold rise in the incremental blood glucose area under the curve (AUC) and necessitated more insulin to achieve within-target glycemic control. Similar findings were reported by **van der Hoogt *et al.*** [20] who found that after eating high-fat and protein meals, longer periods of time over the target blood glucose level necessitated greater insulin dosages [20]. **Gingras *et al.*** [21] discovered that the amount of protein and/or fat in the meal had an impact on the timing of the postprandial glycemic peak, the need for insulin, and the late glycemic excursion. The blood glucose AUC at 5 hours after eating, however, remained unaffected.

Dosing methods for dietary fat and protein in insulin

For patients with T1DM utilising either the MDI regimen or insulin pump treatment, many insulin dosing techniques have been proposed for the adjustment of insulin dosages for dietary fat and protein [4]. According to **Kordonouri *et al.*** [22] compared to carbohydrate counting alone, counting carbohydrates along with fat and protein resulted in considerably lower 6-hour postprandial blood glucose AUC and lower average blood glucose levels. However, combined carbohydrate plus fat and protein counts considerably increased the frequency of postprandial hypoglycemia episodes. Similar to this, **Haak *et al.*** [23] found that adult patients with T1DM using insulin pumps experienced more hypoglycemia after eating meals high in fat and protein.

Adjustment of insulin doses for patients using the MDI regimen

To stop the late postprandial rise in blood glucose levels following high-fat and protein meals, more insulin was recommended [24]. The ideal dosage and time for this extra insulin in T1DM patients taking the MDI regimen are yet unknown. Though, according to **Campbell *et al.*** [25], combining a rapid-acting insulin bolus dose for a high-carbohydrate, high-fat meal with another dose three hours later resulted in postprandial glycemic control that was comparable to that of a meal with little to no fat while posing no additional risk of hypoglycemia. They came to the conclusion that raising the lunchtime insulin dosage alone was not an effective strategy and might raise the risk of early postprandial hypoglycemia. Additionally, using the MDI regimen on 25 adult patients, **Jabłońska *et al.*** [26] assessed the effectiveness of administering normal insulin, which has a later onset and a longer duration of action, to counteract the late postprandial hyperglycemic effects of mealtime fat and protein intake. However, their findings showed that utilising ordinary insulin rather than rapid-acting insulin to address the late hyperglycemic response of dietary fat and protein did not provide any benefits.

Giving 125% intensive care rehabilitation (ICR) as a supplement to insulin before a high-fat, high-protein meal dramatically improved postprandial glycemia without hypoglycemia, according to research by **Smith *et al.*** [27]. However, they found no further glycemic improvement from splitting the dosage of insulin or switching from aspart to normal insulin. Furthermore, using the MDI protocol, 27 children and adolescents were tested by **Frohock *et al.*** [28] to determine the effects of utilising extra rapid-acting insulin for the fat and protein contents of a standardised high-fat and protein meal at three different time periods (before the meal, after 1 hour, and after 2 hours). Based on the amount of carbohydrates and the fat-to-protein ratio, the insulin dosage was estimated. The study did not discover any advantages to administer more insulin in two dosages for meals heavy in protein and fat, though.

Adjustment of insulin doses for insulin pump users

Although it was advised that insulin pump users take greater insulin doses with mixed fat and protein meals, the precise amount of extra insulin has not yet been determined. **Smith *et al.*** [29] found that a dose-dependent decrease in postprandial blood glucose excursions was related with increasing the prandial insulin dosage for high-fat and protein diets. Furthermore, 26 children and adults using insulin pumps were tested by **Paterson *et al.*** [30] to determine the effects of utilising 100%, 115%, 130%, 145%, and 160% of ICR for test meals heavy in protein and carbohydrate but low in fat. Postprandial hyperglycemia was seen when the 100% ICR dosage was used. Postprandial hyperglycemia excursions were greatly reduced in doses of 130% of ICR or more. However, the risk of hypoglycemia increased noticeably when ICR was used at 145% and 160% [30].

Previous studies have found that the late postprandial glycemic response (after 4 to 6 hours) brought on by mixed fat and protein meals can be successfully controlled by a combination dual-wave insulin bolus. Insulin pump users reported seeing this effect [28-31].

Three alternative methods for bolus insulin delivery are available with insulin pumps. Combination doses divide the bolus dose into two portions delivered immediately as standard boluses and another portion delivered over a longer period of time as extended boluses. Standard boluses deliver the bolus insulin dose immediately. Extended boluses deliver the bolus dose over a longer period of time [32]. The combination bolus is preferred in meals high in fat and protein because the standard bolus portion helps to offset the meal's high fat and protein content's delayed hyperglycemic effect, while the extended portion helps to offset the early hyperglycemic effect of the meal's carbohydrate content [33].

The ideal combined bolus splitting ratio for a supper that is both fatty and filling has not yet been identified. Following high-fat and high-protein meals, **Paterson *et al.*** [9] assessed the usual bolus and five alternative combination boluses administered over a 2-hour period. They showed that the regular bolus and the combined boluses of 60/40 (60% standard and 40% prolonged) and 70/30 (70% standard and 30% extended) regulated blood glucose levels for the first two hours following meals. However, compared to the normal bolus given 4 to 5 hours after meals, the 30/70 combination bolus (30% standard and 70% prolonged bolus) was linked to a considerably lower blood glucose AUC [32, 33].

Adjusting insulin dosage for dietary fat and protein presents difficulties.

Finding the best insulin dosage methods for meals high in fat and protein presents a number of difficulties, despite mounting evidence that dietary fat and protein alter postprandial blood glucose levels in people with T1DM [30].

Gaps in literature and the need for further research

The bulk of participants consisted of a small number of persons of research that examined various insulin dosage methods to counteract the postprandial glycemic effects of dietary fat and protein in the paediatric population. Most of the research enrolled both adults and children in their study populations. Additionally, there were significant differences between trials in the test meal specifications, blood glucose monitoring techniques and durations, and outcome measures [28]. Future research has to include more children as volunteers. In light of the current findings, prolonged monitoring of postprandial blood glucose levels for up to 12 hours is required. It is also necessary to have a uniform definition for the high-fat and/or high-protein meals as well as the outcome metrics [30-32].

Individual differences in how they react to dietary fat and protein.

Previous research revealed that among T1DM patients, there was a significant individual variation in the amount of mealtime insulin required to compensate for dietary protein and fat. Some individuals may have early postprandial hypoglycemia and other patients may experience late postprandial hyperglycemia if a fixed increased proportion of the ICR is used to cover the fat and protein components of the meal. The emergence of various postprandial glycemic responses among T1DM patients may be influenced by a number of variables, including the pace of stomach emptying, the rate of digestion and absorption, the degree of insulin resistance, and hepatic glucose generation following high fat and protein meals [28-33].

The effects of various dietary fat and protein types

More research is still needed to determine how various dietary proteins and fats affect postprandial blood glucose levels. When compared to meals high in polyunsaturated or monounsaturated fats, several earlier research found that meals high in saturated fat enhanced insulin resistance [34]. In contrast to meals rich in saturated fat, meals high in monounsaturated fats were linked to more delayed stomach emptying, according to other research [15, 30-33]. Additionally, whey protein was typically employed in the test meals in research that evaluated the glycemic response to varying quantities of protein [8, 12]. Proteins of different kinds may have varying effects on blood glucose levels. For the best estimation of postprandial insulin, the kind and amount of food protein and fat must be taken into account.

The difficulty of dietary protein and fat-based insulin dosing schemes

To compensate for the insulin requirements of the protein and fat compositions of the meals, doctors, nutritionists, and patients must select a number of factors. Patients using insulin pumps must calculate the amount of additional insulin given with high fat and protein meals, the percentage of the splitting proportions of combination boluses, and the length of the extended bolus in addition to the standard carbohydrate counting and determining the prandial dosage depending on the amount of carbohydrates in the meal [4]. The pre- and post-meal sections of the dosage, as well as the time of the post-meal component of the dose, must all be adjusted by patients utilising the MDI regimen. This also applies to the higher bolus dose for dietary fat and protein [24, 27].

It is necessary to provide more user-friendly, straightforward guidelines for T1DM patients to follow when adjusting their insulin levels for dietary protein and fat. Thankfully, the use of bolus calculation technology may offer a workable option to combine several algorithms for the estimation of premeal insulin dosages in response to various quantities and kinds of macronutrients present in each meal [35].

CONCLUSION

To achieve postprandial euglycemia, insulin dosage adjustments for dietary fat and protein are necessary. The best insulin dosage methods to account for the protein and fat composition of the meals are yet unclear. Combination boluses offer better postprandial glycaemic control for T1DM patients using insulin pumps than conventional and prolonged boluses. It is yet unknown if dividing insulin dosages among patients on the MDI regimen would improve postprandial glycaemic control.

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