Turkish Journal of Endocrinology and Metabolism, (1999) 3 : 129-136 **ORIGINAL ARTICLE**

Effect of Added Fat on Plasma Glucose and Insulin Response to Ingested Potato Given in Various Combinations as T wo Meals in Type 2 Diabetic Patients

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In healthy su bjects, following the ingestion of two meals containing potato and butter in different combinations, glucose area responses are always greater after the second meal contrary to the Staub-Traugott effect. We aimed to show the effect of added fat in the first or second meal, or both, on plasma glucose and insulin responses to ingested carbohydrate in type 2 diabetic patients.

Eight subjects with type 2 diabetes were enrolled in the study. The subjects ingested two meals consisting of potatoes containing 50 g carbohydrate, either alone or with 50 g fat in the form of butter in four different combinations on four separate days. Plasma glucose and C-peptide, serum insulin, glucagon, triglyceride, and free fatty acid concentrations were determined over an 8 hour period. The integrated area responses to the meals were quantified.

Following the first meal the glucose area responses and peak glucose concentrations were significantly lower when fat was ingested with carbohydrate. There was a delay of glucose peak time. A delay of insulin and C-peptide peak times were also documented without a decrease of peak concentrations and area responses. Addition of fat to the first or second meal caused a lower glucose area response following the second meal compared with the first.

These findings are consistent with a greater insulinogenic index which may be due to increased incretin hormone secretion consequent to fat ingestion.

KEY WORDS **Carbohydrate, fat, ingestion, two meals, triglyceride, free fatty acids, type 2 diabetes**

Introduction

An adequate diet is the mainstay of the treatment of diabetes mellitus. A high carbohydrate and low fat containing diet is currently recommended for diabetic patients (1). Yet these recommendations are still lacking a scientific basis. Recent studies have shown that in type 2 diabetic patients high carbohydrate diets caused persistent deterioration of glycemic control and accentuation of hyperinsulinemia, as well as increased plasma triglyceride and very low density lipoprotein cholesterol levels (2-4).

It is well known that plasma glucose and insulin responses to macronutrients are quite different in type 2 diabetic patients compared with non-diabetic individuals (5). In this respect, more studies in patients with type 2 diabetes are needed for appropriate dietary recommendations.

In healthy subjects, ingestion of butter with potato in a single meal resulted in lower blood glucose

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levels and similar or higher insulin concentrations compared with the results observed in the same subjects after potato ingestion alone (6,7). In contrast to the results in normal subjects, after ingestion of butter with potato, the glucose response was not lower in subjects with type 2 diabetes in spite of a greater insulin response (8). In normal subjects, after ingesting three identical high-fat mixed meals four hours apart, there was a progressive decrease in the amplitude and a delay in the rise of both glucose and insulin concentrations following the second and third meals (9). On the other hand, in a recent study in normal subjects ingesting two meals four hours apart containing carbohydrate and fat in different combinations, the glucose area responses were all greater after the second meal compared with those after the first meal (10). This was contrary to the Staub-Traugott effect (11-12).

The results of these multiple-meal studies cannot be applicable to diabetic patients. Therefore we performed a similar study in individuals with type 2 diabetes. Our aim was to determine the effect of added fat given in the first or second meal, or both, on plasma glucose and insulin responses to ingested carbohydrate. In this study, plasma glucose, insulin, serum C-peptide, glucagon, triglyceride, and free fatty acid responses to 50 grams carbohydrate in the form of potato, ingested in random order, with or without 50 grams of fat in the form of butter, were determined after two meals, four hours apart.

Patients and Methods

Eight subjects with type 2 diabetes (6 female, 2 male) were enrolled in the study group. All patients met the National Diabetes Data Group criteria for the diagnosis of type 2 diabetes (13). The mean age of the patients was 62.2±10 years with a range of 45-71 years. The mean HbA1c was 7.5±0.5 % (normal 4.4-6.4%). The mean body mass index was 29.8±2.6 kg/m^2 with a range of 26-33 kg/m^2. None of the subjects had been treated with oral hypoglycaemic agents or insulin before the study. The clinical characteristics of the patients are listed in Table 1.

The study protocol was approved by the Human Ethics Committee of Marmara University. All patients gave written informed consent after the nature of the procedure was explained.

Table 1. Clinical characteristics of type 2 diabetic patients

	Age/sex	BMI*	HbA1c**	duration of diabetes/year	other illness
1	60/M	28	7.17	2	hypertension
2	45/F	27.6	6.99	1	-
3	70/F	26	7.54	1	hypertension
4	69/F	33	8.1	1	hypertension
5	66/M	32	7.07	2	hypertension
6	47/F	30	7.5	7	hypertension, degenerative arthritis
7	71/F	33	8.5	4	-
8	70/F	29	7.6	1	hypertension, glaucoma

*kg/m^2, ** Normal range = 4.4-6.4 %

All subjects were on a weight maintenance diet consuming minimally 200 grams of carbohydrate per day for at least three days prior to and during the test days.

After a 10 hours overnight fast, a 20 gauge plastic catheter was placed in a forearm vein for venous sampling and kept patent with intravenous saline. Two baseline samples were drawn at 7:30 and 7:45 am. The first meal was given at 8:00 am and the second at noon. The subjects were requested to consume the food in ten minutes. Blood samples were taken at 30 min, 1, 2, 3 and 4h after each meal. All subjects received two meals on each study day consisting of 50 grms of carbohydrate in the form of potatoes, either alone or with 50 grams of fat in the form of butter. The meals were served in four combinations as follows: 1) potato for the first meal, potato for the second meal; 2) potato and butter for the first meal, potato and butter for the second meal; 3) potato and butter for the first meal, potato for the second meal; 4) potato for the first meal, potato and butter for the second meal. All subjects were studied with these four combinations on four different days, at least three days apart and in random order.

Peeled potatoes (300 grams) were cooked in an oven at 200°C for 45 minutes. They were then mashed with or without butter (62 grams) and refrigerated. The next day meals were served without being reheated. The amount of carbohydrate and fat in the meals was measured at the Turkish Scientific and Technical Research Association laboratories from identical samples. All subjects were allowed to ingest water freely through out the study period.

Plasma glucose was determined by a glucose oxidase method using a Technicon RA 1000 spectrophotometry. Serum insulin, plasma c-peptide, and serum glucagon were measured using a double-antibody radioimmunoassay method with kits produced by Diagnostic Products Corporation (Los Angeles, USA). The interassay coefficient of variation was 4.9 % for insulin, 3.4% for C-peptide, and 15.7% for glucagon measurements. Serum triglyceride levels were determined by Technicon RA 1000 spectrophotometry. Serum free fatty acid concentrations were determined by a Wako Kit (Neuss, Germany). The four-hour area responses were calculated using the trapezoid rule (14). The mean of the two initial fasting concentrations was used as the baseline from which the areas after the first meal were calculated. The concentrations of the parameters measured at noon were taken as the initial values from which the areas after the second meal were calculated.

Statistics were done by Kruskal-Wallis two-way analysis of variance, using the Instat II program for IBM. Multiple comparisons were done by Bonferroni or Dunn's tests where appropriate. The Least squares method was used for linear regression analysis. Also the results after the first meal were compared by Kruskal-Wallis test, comparing potato ingestion alone versus potato plus butter ingestion as two groups. A p value of less than 0.05 was the criterion of significance. Data are presented as mean ± Standard error.

Results

The mean basal glucose concentration in the four studies was 136.6±3.5 mg/dl and they were not significantly different from each other. Following the first meal, the peak glucose concentration occurred at 60 min after potato ingestion alone but at 120 min after potato plus butter ingestion. After the second meal, peak glucose concentration occurred at 60 min when subjects ingested only potato at both meals, at 120 min when subjects ingested potato plus butter in the second meal regardless of the first meal. When the subjects ingested butter in the first meal but not in the second, peak glucose concentration after the second meal occurred at 120 min rather than 60 min (Figure 1A).

Following the first meal, peak glucose level was 249.8±11.8 mg/dl after potato ingestion alone and 203±8.2 mg/dl after potato plus butter ingestion ($p<0.005$). Peak glucose levels were not different after the second meal, comparing four different combinations with each other (Table 2).

Table 2. Peak glucose concentrations (mg/dl).

	First meal (mg/dl)	Second meal (mg/dl)
pot / pot	260.7±21.9	205.3±13.8
pot / pot+fat	237±9.1	185.3±15.5
pot+fat / pot	203.3±13.7	213.3±9.1
pot+fat / pot+fat	220.2±12.1	196.7±11.2

Following the first meal peak glucose level was 249.8±11.8 mg/dl after potato ingestion alone and 203±8.2 mg/dl after potato+fat ingestion ($p<0.005$).Peak glucose levels were not different after the second meal, comparing four different combinations with each other.

Similarly glucose area response was greater after potato ingestion alone (210.4±22.6 mg.h/dl) compared with potato plus butter ingestion (143.8±15.3 mg.h/dl) ($p<0.05$) following the first meal (Table 3).

Table 3. Plasma glucose area response.

	First meal (mg.h/dl)	Second meal (mg.h/dl)
pot / pot	195±39.1	130.7±25
pot / pot+fat *	203.7±32.5	52.5±14.4
pot+fat / pot **	180.5±16.8	57.2±10.5
pot+fat / pot+fat	164.8±14.4	114.5±26.9

Plasma glucose area response was greater after potato ingestion alone (210.4±22.6 mg.h/dl) compared with potato+fat ingestion (143.8±15.3 mg.h/dl) ($p<0.05$) following the first meal.Second meal glucose area responses were not different.The glucose area response were smaller if subjects ingested potato+fat at the first ** ($p<0.0005$) or at the second * ($p<0.0005$) meal only.

Glucose area responses were not different after the second meal, comparing four different combinations with each other. There were the following differences when the glucose area responses after the second meal were compared with the first meal: When the subjects ingested only potato at the first and second meals glucose area responses were not different from each other. This was also valid when the subjects ingested potato plus butter at both meals. The glucose area responses following the second meal were smaller if the subjects ingested potato plus fat at the first ($p<0.0005$) or at the second ($p<0.0005$) meal only (Figure 1B).

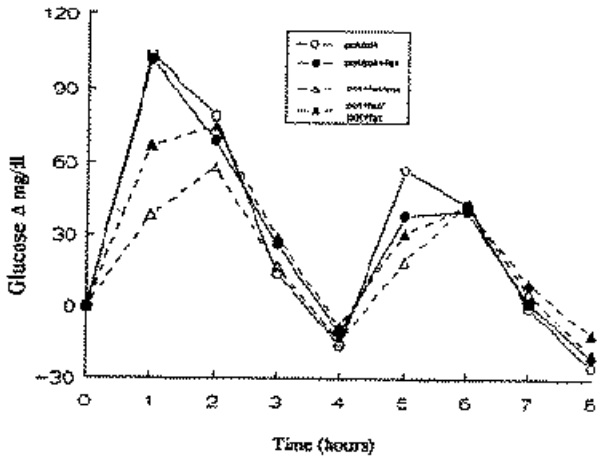

Fig. 1A.

Top: Effects of ingestion of potato with fat in various combinations as two meals on plasma glucose response.

Bottom: Plasma glucose area response was greater after potato meal than potato+fat meal ($p<0.05$). The glucose area response was smaller if subjects ingested potato+fat at the first ($p<0.0005$) or at the second meal only ($p<0.0005$).

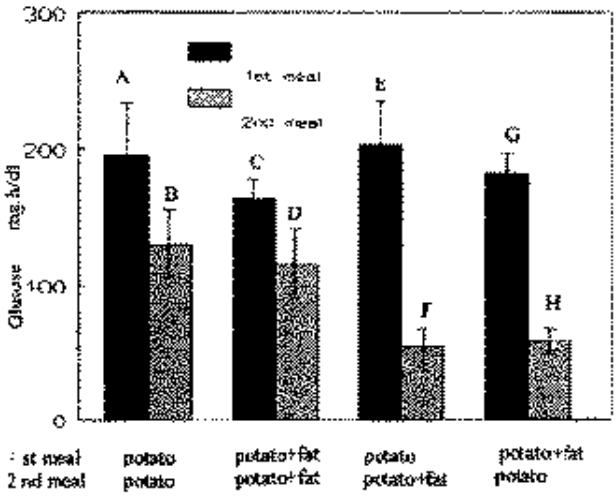

Fig 1B.

Top: Effects of ingestion of potato with fat in various combinations as two meals on plasma glucose area response.

Bottom: The glucose area responses following ingestion of potato with fat (C,G) were significantly less than after ingestion of potato alone (A,E) in the first meal ($p<0.05$). The glucose area responses following the second meal were smaller if subject ingested potato+fat at the frst (G) or at the second meal ($p<0.0005$).

The time intervals to reach peak serum insulin concentrations were similar with glucose peak times. Following the first meal the peak insulin concentration occurred at 60 min when subjects ingested only potato but at 120 min when the subjects ingested potato plus butter. Following the second meal, peak insulin concentration occurred at 120 min if the subjects ingested potato plus fat at the second meal regardless of the first meal. When the subjects ingested only potato at the second meal, peak insulin concentrations occurred at 60 min if subjects ingested only potato at the first meal, but at 120 min if subjects had potato plus butter at the first meal (Figure 2).

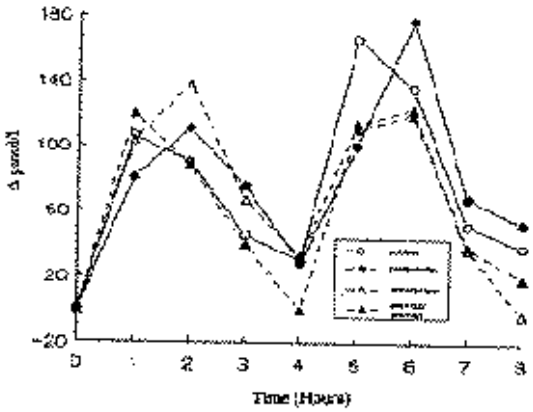

Fig. 2.

Top: Effect of ingestion of potato with fat in various combinations as two meals on serum insulin resonse.

Mean basal insulin concentration was 72±7.8 pmol/l. Peak insulin concentrations and insulin area responses were not different after the first or second meal with all combinations.

Mean fasting C-peptide concentration was 1.7±0.1nmol/l. Time intervals to reach peak C-peptide concentrations were similar to insulin peak intervals (Figure 3). C-peptide area responses and peak C-peptide values were not different after the first or second meal among all groups. C-peptide levels were correlated with insulin levels ($r = 0.59$, $p<0.0001$).

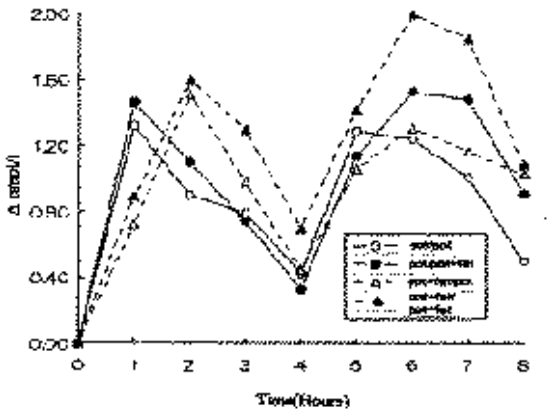

Fig 3.

Top: Effects of ingestion of potato with fat in various combinations as two meals on serum C-peptide response.

Bottom: Area responses were not different after the first or second meal with all combinations.

Mean fasting glucagon concentration was 104±5 ng/l. There were two different glucagon patterns depending on the presence of fat coingestion. Following the first meal, nadir glucagon concentration occurred at 180 min after potato plus butter ingestion and at 120 min after only potato ingestion. After potato plus fat ingestion at the first meal and only potato ingestion at the second, glucagon levels had a steady pattern without an increase or decrease. When only potato was ingested at both meals, glucagon levels showed a similar pattern after each meal (Figure 4). There was no significant difference between glucagon nadir values and area responses among all groups.

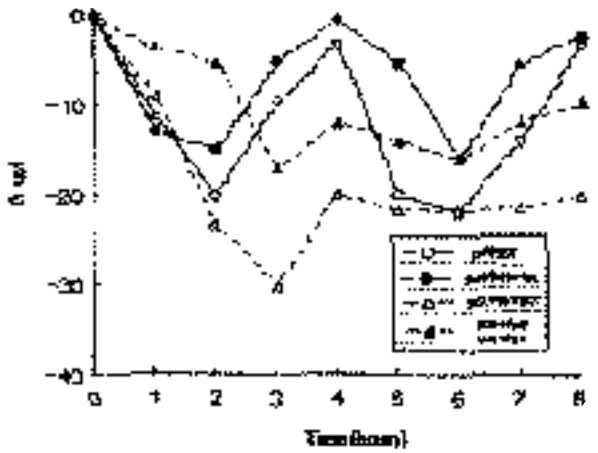

Fig 4.

Top: Effects of ingestion of potato with fat in various combinations as two meals on serum glucagon response.

Bottom: Area responses were not different after the first or second meal with all combinations.

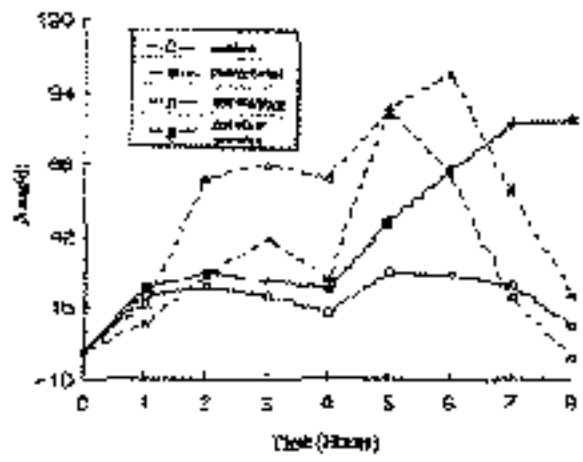

Fig 5A.

Top: Effects of ingestion of potato with fat in various combinations as two meals on serum triglyceride response.

Bottom: Area responses were greater for potato+fat combination than potato alone ($p<0.05$).

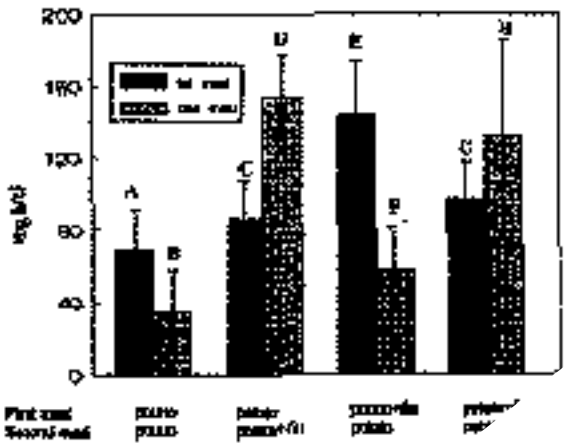

Fig 5B.

Top: Effects of ingestion of potato with fat in various combinations as two meals on serum triglyceride response.

Bottom: E+G>A+C, $p<0.05$

Mean fasting triglyceride concentration was 171±12mg/dl. Following the first meal peak triglyceride levels were reached at 180 min in the presence of butter and at 120 min after only potato ingestion. Following the second meal with a potato plus butter combination, peak triglyceride concentration occurred at 180 min if the first meal contained only potato but at 120 min if the first meal contained potato plus butter. Following the second meal with only potato ingestion, peak triglyceride concentration occurred at 120 min if the first meal contained only potato but at 180 min if the first meal contained potato plus butter (Figure 5A).

Following the first meal peak triglyceride level was higher after potato plus fat combination (247±18 mg/dl) compared to only potato ingestion (194±15.9 mg/dl) ($p<0.05$). Triglyceride area responses were also similar, being greater for potato plus fat combination (121±20 mg.h/dl) compared with only potato ingestion (64.5±14.9 mg.h/dl) ($p<0.05$). There was no significant difference in triglyceride levels after the second meals when compared with each other or the first meal peak values and area responses (Figure 5B).

Mean fasting NEFA concentration was 0.72±0.2 mg/dl. All NEFA area responses were negative and there was no discernible pattern related to meals and no difference among all groups (data not shown).

Discussion

Following the first meal, the glucose area response and peak glucose concentration were significantly lower when fat was ingested with carbohydrate and there was a delay of the glucose peak time. A delay of insulin and C-peptide peak times was also documented without a decrease of peak concentrations and area responses. A fat induced delay of glucose peak in type 2 diabetic patients has been shown previously (8). A lower glucose response to carbohydrate in the presence of fat was previously reported in healthy subjects (6-7), but not in subjects with type 2 diabetes (8). A fat induced delay of gastric emptying has been well documented (15), and the most likely explanation of these results is delayed glucose absorption from the gut secondary to the fat induced delay of gastric emptying.

Fat ingestion causes a marked increase in GIP and GLP-1 levels (16-17). It is well known that plasma GIP and GLP-1 levels are not suppressed in type 2 diabetic patients in the fasting state and after stimulation (18). Unlike GIP, GLP-1 retains much of its insulinotropic activity in type 2 diabetics (19) and also inhibits gastric emptying in this group of patients (20-21). GLP-1 causes a decrease in postprandial glucose levels without a marked increase in insulin concentrations indicating an increased insulinogenic index. GLP-1 decreases the meal induced glycemia mainly by insulin-independent mechanisms, in part by prolonging gastric emptying (21). In our study ingestion of fat with carbohydrate reduced postprandial glucose response to the carbohydrate load, but had no effect on the insulin response, a finding similar to that observed in normal subjects (6). A delayed glucose, insulin and C-peptide response was also observed. These results are consistent with the incretin effect.

A high insulinogenic index, observed after carbohydrate and fat ingestion is probably not associated with an altered hepatic insulin extraction because C-peptide levels are correlated with insulin levels and postprandial C-peptide curves are also identical with insulin curves.

The availability of FFA has been shown to affect the glucose oxidation rate (22). But the difference between glucose area responses cannot be explained on that basis because FFA responses were not different between two groups. Although gastric emptying measurements and incretin hormone levels were not available in our study, these findings may be explained by fat induced incretin hormone secretion and prolonged gastric emptying.

Our findings are conflice with the results of a previous study performed by Gannon et al (8). In that study, coingestion of fat and carbohydrate caused a similar glucose and C-peptide but an increased insulin response in type 2 diabetic patients.

We observed a delay of glucagon nadir time after fat and carbohydrate ingestion but there was no difference between nadir values and area under curves. This is in agreement with previous studies performed on normal subjects (23) and patients with type 2 diabetes (24).

Following the first meal, the triglyceride area response was higher after fat and carbohydrate coingestion as previously reported (25) and addition of fat delayed the onset of triglyceride peak, also supporting the idea of prolonged gastric emptying.

Following the second meal, time to reach peak glucose levels and glucose area responses were related to the content of the first meal. Addition of fat to the first or second meal caused a lower glucose area response following the second meal compared with the first. A similar decrease was not observed when both meals contained fat. These findings show a prolonged effect of fat on plasma glucose response, which cannot be enhanced by repeated ingestion. The same effect was observed by Ercan et al in a previous study in healthy subjects (10). Time to reach peak glucose, insulin, and C-peptide levels following the second meal was delayed if the first meal contained fat, but not if the first meal contained only carbohydrate.

Potentiation of insulin secretion by fat ingestion occurs quite early after a meal, and diminishes after one-hour (26), but GLP-1 and GIP levels remain elevated even at 180 min (27-28). The prolonged effect of fat ingestion in the first meal on the responses to the second meal, may be explained on that basis. Furthermore, it has been

shown that in type 2 diabetic patients, GLP-1 infusion has a prolonged effect on gastric emptying (21).

A Staub-Traugott effect was not observed in this study. It had been reported that the amount of carbohydrate in the first meal influenced the glycemic response to a subsequent meal. Improved glucose tolerance after the second meal was seen only after ingestion of a large amount of carbohydrate (at least 100 grams) in the first meal (29). In this study the amount of carbohydrate (50 grams) was not sufficient to cause such an effect.

In this group of patients with type 2 diabetes, effects of added fat on plasma glucose, insulin, serum C-peptide, glucagon, triglyceride, and NEFA responses to ingested carbohydrate were evaluated. Following the first meal with carbohydrate plus fat, we observed a decreased and delayed glucose response with delayed insulin and C-peptide responses compared with a diet containing only carbohydrate. This finding may be explained by prolonged gastric emptying due to incretin effect.

Following the second meal a similar pattern was observed only if the first or the second meal contained fat. This may be due to the prolonged effect of incretin hormones. But the effect of fat ingestion on serum glucose responses was not observed after the second meal when both of the two meals contained fat. This finding indicates that repeated ingestions of fat in addition to carbohydrate do not induce the same responses.

There is a constant effect of carbohydrate plus fat ingestion on glucose, insulin and c-peptide responses after a single meal. But these responses differed after a second meal. The integrants of the first meal also have an influence on the glucose and insulin responses to the second meal.

Addition of fat containing foods, rather rich in mono unsaturated fatty acids for cardiac health, to breakfasts of type 2 diabetic patients may improve postprandial glucose excursions after breakfast and lunch. More studies are needed on this issue to give the most appropriate dietary recommendation for diabetic patients because a high carbohydrate-low fat diet is probably not the most beneficial one.

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