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Comparison of a carbohydrate-free diet vs. fasting on plasma glucose, insulin and glucagon in type 2 diabetes☆☆☆



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ABSTRACT

Objective. Hyperglycemia improves when patients with type 2 diabetes are placed on a weight-loss diet. Improvement typically occurs soon after diet implementation. This rapid response could result from low fuel supply (calories), lower carbohydrate content of the weight-loss diet, and/or weight loss per se. To differentiate these effects, glucose, insulin, C-peptide and glucagon were determined during the last 24 h of a 3-day period without food (severe calorie restriction) and a calorie-sufficient, carbohydrate-free diet.

Research design. Seven subjects with untreated type 2 diabetes were studied. A randomized-crossover design with a 4-week washout period between arms was used.

Methods. Results from both the calorie-sufficient, carbohydrate-free diet and the 3-day fast were compared with the initial standard diet consisting of 55% carbohydrate, 15% protein and 30% fat.

Results. The overnight fasting glucose concentration decreased from 196 (standard diet) to 160 (carbohydrate-free diet) to 127 mg/dl (fasting). The 24 h glucose and insulin area responses decreased by 35% and 48% on day 3 of the carbohydrate-free diet, and by 49% and 69% after fasting. Overnight basal insulin and glucagon remained unchanged.

Conclusions. Short-term fasting dramatically lowered overnight fasting and 24 h integrated glucose concentrations. Carbohydrate restriction per se could account for 71% of the reduction. Insulin could not entirely explain the glucose responses. In the absence of carbohydrate, the net insulin response was 28% of the standard diet. Glucagon did not contribute to the metabolic adaptations observed.

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Abbreviations: T2DM, type 2 diabetes mellitus; CHO, carbohydrate; IRB, Institutional Review Board; h, hour; kcal, kilocalorie; kg, kilogram; DPC, Diagnostic Product Corporation; DSL, Diagnostic Systems Laboratories, Incorporated; SDTU, Special Diagnostic & Treatment Unit; AM, ante meridiem; STD, standard; SEM, Standard Error of the Mean; M.T., Medical Technologist.

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1. Introduction

In people with type 2 diabetes it has been demonstrated that a low food energy diet [1], short-term fasting [2], a low CHO-diet [3] as well as weight loss result in a rapid decrease in glucose concentration. Thus, various iterations of these have been advocated as a means of improving the hyperglycemia present in these patients. However, to our knowledge a direct comparison of the results of each of these approaches has not been reported. In order to address these issues, we have determined the metabolic effects of fasting for 3 days, a time duration in which loss of fat mass should be minimal, but the glucose and insulin concentrations have reached a new quasi-steady-state [4]. This is compared with the effects of an energy-sufficient, carbohydrate-free diet of the same duration. Both were compared with data obtained when the subjects ingested a standard, mixed diet. Twenty-four hour glucose, insulin, C-peptide and glucagon data were obtained while on each diet or when the subjects were fasting. Part of these data was published previously in abstract form [5].

2. Materials and methods

2.1. Subjects

Seven male subjects with type 2 diabetes were studied. One subject was untreated; 3 subjects had been receiving metformin. Three had been receiving a sulfonylurea. These medications

were discontinued for 24 or more days before the study. Patient characteristics are listed in Table 1.

Inclusion criteria were: 45–75 years of age, with type 2 diabetes, currently not on any oral diabetic medications, never having been on insulin, and a C-peptide > 1.5 ng/ml (reference range 0.8–3.1 ng/ml). Patients may have been on metformin and or a sulfonylurea, but would be taken off these oral agents for the time required to stabilize their HbA1c, with prior approval of their primary provider. Subjects remained off these medications until the end of the study. This was done with the patient consent, and with the approval of and coordination with the primary care physician. As a result of the dietary intervention of this study, no adverse health effects were noted during the study, nor were there adverse health effects due to the study after its completion.

Exclusion Criteria were: hematologic abnormalities, liver disease, kidney disease, macroalbuminuria (300 mg albumin/24 h), untreated thyroid disease, congestive heart failure, angina, myocardial infarction within 6 months, life threatening malignancies, proliferative retinopathy, severe diabetic neuropathy, peripheral vascular disease, serious psychiatric disorders (preventing the patient from competently signing the informed consent), fasting triglyceride > 400 mg/dl, fasting blood glucose > 250 mg/dl or HbA1c > 11%.

Written informed consent was obtained from all subjects, and the study was approved by the Department of Veterans Affairs Medical Center Institutional Review Board (IRB). All work was conducted in compliance with the principles of the Declaration of Helsinki. The study is registered at clinicaltrials.gov: NCT01469104.

Table 1 – Subject characteristics.

Subject	Age	Years of Diabetes	Diabetes Med	Days off Med	Weight (kg)	Height (cm)	BMI (kg/m ²)	FPG (mg/dl)	Concomitant Diseases	Medications
1	55	2	Metformin	54	93	183	28	160	hypogonadism, dyslipidemia	testosterone, lisinopril, rosuvastatin
2	60	4	Metformin	43	93	183	29	228	CVD, HTN	atenolol, gemfibrozil, lisinopril, simvastatin
3	60	2	Glyburide	47	81	155	34	171	dyslipidemia	simvastatin, omeprazole
4	62	18	Metformin	32	130	170	38	219	dyslipidemia, CVD, HTN	losartan, omeprazole, rosuvastatin, ezetimibe
5	64	10	Glipizide	45	108	174	36	168	dyslipidemia, HTN	hydrochlorothiazide, lisinopril, simvastatin
6	72	5	None		88	188	25	118	COPD, CVD, HTN	lisinopril, amlodipine, atenolol, simvastatin, omeprazole
7	49	3	Glipizide	24	88	170	27	225	HTN	hydrochlorothiazide, lisinopril
Average ± SEM	60 ± 3	6 ± 2		41 ± 4	97 ± 6	175 ± 4	31 ± 2	184 ± 16		
Range	49–72	2–18		24–54	81–130	155–188	28–38	118–228		

Abbreviations:

Med = medication

BMI = body mass index

FPG = overnight fasting plasma glucose

CVD = cardiovascular disease

HTN = hypertension

COPD = chronic obstructive pulmonary disease

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