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The Effect of Diabetes-Specific Enteral Formulae on Clinical and Glycemic Indicators

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A review of several studies examining enteral feeding formulae specifically designed for patients with hyperglycemia or diabetes mellitus have shown that the use of a high-fat, lower-carbohydrate enteral formula, whether used in tube- or orally-fed patients, appears to lower postprandial blood glucose levels relative to a higher-carbohydrate, lower-fat formula. These diabetic-specific formulae also seem to be tolerated similarly to standard enteral formulae and were not associated with negative short-term consequences in terms of lipid blood values. However, critical to clinicians and the healthcare community, is the absence or ability of these current published studies to demonstrate outcome benefits to warrant the additional cost of these formulas.

INTRODUCTION

The rapid increase over the past several years in the incidence of diabetes mellitus (DM) and the resultant increase in the cost of DM management continue to be of significant concern to clinicians. Current evidence indicates that careful glycemic control can

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reduce DM-associated complications; therefore, control of blood glucose is the primary goal of DM management (1–2). To achieve this goal, the American Diabetes Association (ADA) Clinical Practice Committee provides specific nutrition recommendations that may aid in DM management and prevention of DM-associated complications (3). Consequently, to improve outcomes, there is significant interest to develop enteral nutrition (EN) formulae specifically designed for patients with hyperglycemia or DM. The design of these DM-specific enteral formulae (DSEF) focuses upon the amount and type of carbohydrate and fat (mono- and poly-unsaturated) that impacts glycemic control. These DSEF are the focus of the current review.

INCIDENCE OF DIABETES

Eight percent of the United States population has DM (4); the number of people with DM reached 24 million in 2007, an increase of more than three million from 2005. Over the same two years, the percentage of people with DM who were unaware of their disease, decreased from 30% to 25%. DM is more prevalent in the elderly with 25% of individuals 60 years or older presenting with this disease. Native Americans, African Americans, and Hispanics have the highest rates of diagnosed DM among ethnic and minority populations (4).

Having DM carries significant risk to the individual. Individuals with DM have twice the risk of death relative to individuals without DM of the same age. DM was the seventh leading cause of death in 2006 according to death certificates in the United States (5). It is sobering to note that the impact of DM on risk of death is underestimated because each of the complications associated with DM, such as heart disease, stroke, and kidney disease also carry their own risk of death.

Type 1 DM (DM1) occurs in 5% to 10% of the DM population; whereas, type 2 DM (DM2) represents 90% to 95% of patients diagnosed with DM (5). Management of patients with DM1 and DM2 is primarily by oral medication (57%), no medication (16%), insulin only (14%), or insulin and oral medications (13%). DM2 is associated with older age, sedentary lifestyle, race/ethnicity, and importantly, obesity; control is aimed at lifestyle changes including diet, exercise, and weight loss, oral hyperglycemic medications, and/or insulin. The rising tide of obesity among persons in the United States is likely to continue to result in a growing population with DM2. Pregnancy represents an additional risk for developing DM. Women who have had gestational DM during pregnancy have a 40% to 60% chance of developing DM five-to-10 years after giving birth. DM may also be caused by genetic conditions, pancreatic disease, critical illness and surgery. This group accounts for 1% to 5% of those with the disease.

In addition to the above numbers of people with DM, there are approximately 57 million individuals with pre-DM (5). This group, however, is not irreversibly predestined to acquire the disease. Weight loss and increased physical activity can slow the progression or prevent the development of DM in this population.

The personal and economic impact of DM is substantial. The total cost for DM in 2007 was $174 million (5). Healthcare expenditures for someone with DM were 2.3 times greater than for a person without this disease. The indirect costs of DM in lost work, early death, and disability were estimated at $58 billion for this period. This disease is therefore very costly, not only in terms of the health of the individual, but also with respect to the impact upon healthcare resources, and, the monetary burden this disease represents.

HYPERGLYCEMIA-ASSOCIATED PATHOPHYSIOLOGY

Both short- and long-term physiologic risks are associated with hyperglycemia. In the short term, elevated blood glucose levels in hospitalized patients can, for example, lead to ketoacidosis and to both micro- and macrovascular changes that can result in tissue damage (6-8). Various long-term effects of elevated blood glucose levels include abnormal lipid metabolism that can result in elevated cholesterol and triglyceride concentrations, hypertension, susceptibility to infections and chronic inflammatory activity as evidenced by increased circulating levels of C-reactive protein (6,9–11).

PATIENT OUTCOMES ASSOCIATED WITH HYPERGLYCEMIA

Glycemic control has become a major focus for health care providers. Stricter glycemic control for people with DM in the out-patient setting has been shown to decrease the progression of the macrovascular and microvascular complications of both DM1 and DM2 (5,14). Every 1% decrease in glycosylated hemoglobin (HbA$_1$C) reduces the risk of microvascular complications by 40% (5). Intensive insulin therapy and multiple injections are used in the out-patient setting to reduce the risk of heart disease in those with DM1.

The acute care arena has expanded glycemic control to include patients who develop stress-induced hyperglycemia during critical illness and injury. Historically, clinicians had been tolerant of transient hyperglycemia as long as the serum level was less than 200 mg/dL. The focus upon glycemic control has expanded from concerns about sustained, elevated hyperglycemia to the implications of acute hyper-

Table 1. Nutritional Composition of Diabetic and Standard Enteral Formulas

Product	Cal/mL	CHO[1] (g/L, %)	CHO[1] source	Fat (g/L,%)
DIABETES-SPECIFIC				
Diabetisource® AC*	1.2	100, 36%	corn syrup, fructose, tapioca dextrin, partially hydrolyzed guar gum, vegetables, fruits	59, 44%
Nutren® Glytrol®*	1	100, 40%	maltodextrin, modified corn starch, gum arabic, oligofructose, inulin, pea fiber	48, 42%
Glucerna® 1.0 Cal**	1	96, 34.3%	corn maltodextrin, soy fiber, fructose	54, 49%
Glucerna® 1.5 Cal**	1.5	133, 33%	corn maltodextrin, isomaltulose, fructose, sucromalt, short-chain fructo-oligosaccharides, soy fiber, oat fiber	75, 45%
Glucerna® Select**	1	96, 31%	corn maltodextrin, maltitol syrup, soy fiber, fructose, fructo-oligosaccharides	55, 49%
STANDARD POLYMERIC				
Jevity® 1.2 Cal**	1.2	169, 53%	corn maltodextrin, corn syrup solids	39, 29%
Fibersource® HN*	1.2	160, 53%	corn syrup, maltodextrin	39, 29%
Osmolite® 1.5 Cal**	1.5	204, 54%	corn maltodextrin, corn syrup solids	49, 29%
Nutren® 1 Cal*	1	127, 51%	maltodextrin, corn syrup solids	38, 33%

[1]Carbohydrate; *Nestle Nutrition Store: 888/240-2713; **Abbott Nutrition: 800/544-7495; ***CWI Medical: 877/929-4633; ****Walmart (4/09)

glycemia. Studies have shown increased mortality and morbidity with hyperglycemia (15,16). Intervention studies have demonstrated that patients whose glucose levels were carefully managed had fewer complications and lower mortality (17–20). An evidence analysis reported that the benefits of tighter glycemic control in critically ill patients were reduced mortality, shorter length of stay, decreased days on mechanical ventilation and fewer infectious complications (21).

The physiologic risks associated with hyperglycemia may translate directly as risks of negative patient outcomes during hospitalization. Campbell reviewed several well designed studies that included prospective, retrospective and meta-analyses, that clearly showed that among many different types of patients, including general medical and surgical, as well as cardiac and stroke patients, mortality rates, length of hospital stay, nosocomial infections and the cost of hospitalization increased when hyperglycemia was present (22). Because of these risks, various health-related professional organizations offer guidelines and recommendations for the ideal blood levels at which glucose should be maintained. For example, the

ADA recommends for individuals with DM in a non-health care situation that blood glucose levels be maintained in the normal or as close to normal range as possible when safely indicated (23). For hospitalized patients, ADA recommends that blood glucose levels of critically ill individuals be maintained at 110 mg/dL (6.1 mM) and <140 mg/dL (7.8 mM) (23). For non-critically ill patients, the absence of clear evidence for specific blood glucose goals prevents a specific recommendation by the ADA. However, as the ADA notes, reasonable goals, if safely achievable, are a fasting glucose concentration of <126 mg/dL (7.0 mM) and all other random glucose assessments of <180–200 mg/dL (<10.0–11.1 mM). This approach is based upon data that suggest outcomes among hospitalized, non-critically ill patients, are improved if blood glucose values are maintained at these levels (23,24).

MACRONUTRIENT GUIDELINES

Distribution of macronutrients in the diet for patients with DM has historically been 55%–60% carbohydrate

Fat source	Protein (g/L, %)	Fiber (g/L)	FiberSource	mOsm/kg	Cost/ 1000 kcal
canola oil, refined menhaden fish oil	60, 20%	15	FOS[2], Benefiber® soluble fiber, soy fiber, vegetables, fruits	450	10.13*
canola oil, hi-oleic safflower oil, MCT oil, soy lecithin, monoglycerides	45, 18%	15	gum arabic, PREBIO1™ (oligo-fructose and inulin), pea fiber	280	9.50***
high oleic safflower oil, canola oil, soy lecithin, marine oil	42, 17%	14	soy fiber	355	9.20**
high oleic safflower oil, canola oil, soy lecithin	83, 22%	17	oat fiber, soy fiber, scFOS	875	11.11****
high oleic safflower oil, soy lecithin	50, 20%	21	soy fiber	470	10.07**
canola oil, corn oil, MCT, soy lecithin	55.5, 18.5%	18	soy fiber	450	6.50**
canola oil, MCT, corn oil	53, 18%	39	partially hydrolyzed guar gum, BENEFIBER®	490	4.24***
canola oil, corn oil, MCT, soy lecithin	63, 16.7%	0	0	525	5.33****
canola oil, MCT, corn oil, soy lecithin	40, 16%	0	0	315	5.83*

[1]Carbohydrate; *Nestle Nutrition Store: 888/240-2713; **Abbott Nutrition: 800/544-7495; ***CWI Medical: 877/929-4633; ****Walmart (4/09)

(CHO), 25%–30% fat, and 10%–20% protein. However, in 2008, revised recommendations from the ADA for weight loss include either a low-CHO or low-fat calorie-restricted diet up to one year. The ADA also recommends for patients on low-CHO diets, the routine monitoring of lipid profiles, renal function and protein intake (in those patients with nephropathy) (3). Also, as consistent with the general population, people with DM are encouraged to achieve the U.S. Department of Agriculture (USDA) recommendation of 14 g fiber/1,000 kcals (26). The dietary intake of protein for individuals with DM is similar to that of the general population and usually does not exceed 20%. Currently, there is not one specific combination of macronutrients that is recommended by the ADA. Individualization of the macronutrient composition will depend upon the metabolic status of the patient and may vary with individual circumstances. For enteral feeding, ADA reports that either a standard enteral formula (50% CHO) or, lower-CHO content formulae may be used. Dietary fat recommendations continue to limit saturated fat to <7% of total calories with emphasis in the reduction and minimization of *trans* fat intake (3).

DIABETES-SPECIFIC ENTERAL FORMULAE (DSEF)

Over the past several years, different enteral formulations have been specifically developed for the patient with DM or hyperglycemia. With respect to available nitrogen and total energy, all of the currently available DSEF differ only marginally from the average standard enteral formula (SEF), and usually provide values ranging from approximately 18%–20% total kcal as protein (approximately 40–60 g/L) and approximately 1,000–1,500 kcal/L total energy (Table 1). The major differences between DSEF and SEF involve the relative amounts and percentages of total energy provided in the form of CHO and fat, and, differences in the amount and source of fiber (Table 1). Relative to the average SEF, the DSEF currently available provide a decreased amount of CHO, and an increased amount of fat. These relatively high fat, low CHO formulations yield values for DSEF that range from approximately 80–120 g/L CHO (35%–50% of total kcal) and approximately 30–60 g/L (35%–50% of total kcal) as fat. The source of CHO in DSEF often includes increased amounts of fructose relative to SEF, and can approach 15% of total calories. In addition, the fat in DSEF is usually provided

in the form of higher amounts of mono-unsaturated fatty acids (MUFA) relative to SEF, and these fatty acids can represent >60% of the total fat provided. One additional component among DSEF that differs from that of SEF is the amount and source of fiber. The amount of fiber is typically increased in DSEF relative to SEF and the sources of this fiber are usually fruits, vegetables or soy polysaccharide. The clinical interest in the use of DSEF has focused primarily upon the safety and tolerance and potential short- and long-term effects these preparations may have upon various glycemic indicators. One specific interest has been to assess the safety and tolerance of the relatively higher levels of fat and fructose for any negative sequelae with respect to lipid metabolism and the risk for lactic acidosis. Another consideration is the potential effects in patients with underlying dysmotility disorders (such as gastroparesis, irritable bowel syndrome, etc.) as they may not tolerate fructose and fructooligosaccharides (FOS) well (27).

Finally, and most importantly, studies have recently begun to focus upon whether or not these DSEF formulations can improve patient outcomes.

COMPARISONS OF DSEF VERSUS SEF IN LONG-TERM ENTERALLY TUBE-FED PATIENTS

There are a limited number of studies that have compared DSEF to SEF with respect to glycemic control, lipid indices and other surrogate markers of metabolism in enterally fed patients. Only prospective, randomized controlled trials have been included here.

ENTERAL TUBE-FED LONG-TERM CARE RESIDENT STUDY

A double-blind, parallel group, prospective randomized controlled trial (PRCT) examined 30 long-term care residents with DM2 who received one of two different EN formulae over a three month period (28). The SEF provided >50% CHO or 30% fat; the DSEF provided 33% CHO and 56% fat. Each of these formulae was examined with respect to their relative effect upon glycemia indicators, serum lipids, glucose-lowering medication requirements, and various surrogate outcomes such as fever incidence, pneumonia, urinary tract infections, skin infections and pressure ulcers.

With respect to glycemic indicators, the results of this study revealed no significant differences over the course of the study, nor at the end of three months between the two groups of patients with respect to fasting serum glucose and glycosylated hemoglobin (HbA$_1$C) values. However, these values tended to be lower in the DSEF group relative to the SEF group at the end of three months and when averaged over the study period. Similarly, use of the DSEF did not significantly alter total cholesterol, VLDL, LDL, and, triacylglycerol relative to SEF, with the single exception of HDL concentration at the end of three months. Mean non-fasting capillary glucose measurements revealed inconsistent significant differences between the two formula-fed groups with only three time points, e.g., week one, five and seven, with a higher value in the SEF group; however, values were consistently higher from week five to week 12 in the SEF group. When glucose-lowering medication requirements were compared between the two groups, no significant differences in insulin requirements to control glycemia were observed. However, at baseline, the difference in the mean amount of regular insulin provided the DSEF group was higher and statistically significant relative to the SEF group. In contrast to this observation, the amount of regular insulin provided to control glycemia in the SEF group was consistently higher at all other time points through week nine. With respect to clinical outcomes in this trial, incidence of fever, pneumonia, urinary tract infection, skin infection, pressure ulcers and all infections combined were consistently lower in the DSEF group. Unfortunately, these values were provided in relative percentages as descriptive results, and were not subjected to statistical analysis. One significant limitation to this study was that the percentage of formula received by each group was not reported.

ENTERAL TUBE-FED HOSPITALIZED DM2 PATIENT STUDY

In a phase IV, multicenter, open-label, two parallel groups PRCT, Leó-Sanz, et al compared the effects of two different DSEF on various glycemic indicators and serum lipids. Hospitalized patients with neurologic or

Table 2. Diabetic Specific Enteral Formula (DSEF) in Long-Term Tube Fed Patients

Citation	Study Design/Population (n)	EN Formula Dosage	Patient Population/ Study Duration
Craig et al, (28)	Double-blind, RCT* (n=34)	Continuous or intermittent formula to maintain body weight	DM2, long term care 12 weeks
Leon-Sanz et al, (29)	RCT (multicenter) (n=103, 63 evaluable patients for primary endpoints)	Pts evaluable if > 75% of EN provided during 8 consecutive days	DM2, head/neck cancer, or neurological disorders 14 days
Pohl et al, (30)	Multicenter, double-blind RCT (n = 78, 44 completed study)	27 kcal/kg (Upper limit 2025 kcals/day)	DM2, neurological disorders 84 days
Pohl et al, (31)	Double-blind RCT (multicenter) (n = 105, 55 completed study)	27 kcal/kg body weight/day (Upper limit 2025 kcals/day)	DM2, neurological disorders 84 days
Mesejo et al, (32)	Blinded RCT (n = 50)	Harris Benedict formula with stress factor 1.2	DM1 , DM2 or stress hyperglycemia critically- ill 14 days

*RCT: Randomized Controlled Trial

head and neck cancer and DM2 receiving long-term (at least 14 consecutive days) EN were included (29). The compositions were as follows: higher-fat (50%), lower-CHO (33.3%) preparation enriched with MUFA, or lower-fat (31%), higher-CHO (54%).

Of the 54 randomized patients who participated in the lower-fat group, 14 completed the 14 day trial; of the 51 patients in the higher-fat group, 18 completed the 14 days. Patients from each group were excluded from evaluation if energy intake was <75% (n = 21 higher CHO group and n = 12 lower CHO group). The primary variables examined in this study were the mean weekly blood glucose level, based upon an average of mean daily blood glucose level obtained from three daily capillary glucose measurements, mean weekly triglyceride level and mean total daily units of insulin administered per patient and averaged weekly. The mean daily insulin dose per kilogram and daily calories per unit of insulin were also determined. Secondary variables included mean urinary glucose and ketone levels averaged weekly, fructosamine and gly-

cosylated hemoglobin levels and cholesterol in the form of total cholesterol, HDL, LDL and the cholesterol:HDL ratio. Patient data were collected weekly on days one, eight, and 15.

The results of this study showed mixed results with respect to glycemia indicators. While the lower-fat, higher-CHO group showed a statistically significant increase in blood glucose levels at 7 days, the higher-fat, lower-CHO group did not. However, this statistically significant increase in blood glucose level was not maintained in the lower-fat group, nor were there statistically significant differences in intra- or inter-group comparisons at the end of the study. No statistically significant differences were detected with use of either of the DSEF with respect to glycosylated hemoglobin, fructosamine levels or changes in urinary glucose and ketone levels, mean daily dose of insulin per kilogram and daily calories per unit of insulin and serum lipids. With respect to incidence of fever, urinary tract and respiratory infection, there were no statistically significant differences between the two formula groups. There was

Primary Endpoint	Results
Fasting blood glucose, HbA$_1$C, capillary glucose, serum lipids, infection	• DSEF vs SEF demonstrated no difference: fasting blood glucose, HbA$_1$C; • DSEF significantly lower than SEF for capillary glucose at week 1, 5 and 7 • No changes in lipid profile between groups • No difference in adverse events • Non-significant difference in infection rates
Mean weekly values for: capillary glucose, triglyceride, insulin dose, mean daily insulin dose, GI symptoms	• DSEF vs SEF significantly different for capillary glucose at 1 week, no differences at week 2 • No differences in TG or daily and weekly insulin • No changes in lipid profile between groups • Diarrhea significantly higher in SEF vs DSEF • Nausea was lower in SEF vs DSEF
Total insulin requirements, fasting blood glucose, HbA$_1$C, GI tolerance and any adverse events	• DSEF vs SEF significantly different for the following: total insulin, fasting blood glucose, HbA$_1$C • Feeding tolerance and adverse events were comparable between groups
Total insulin requirements, fasting or afternoon blood glucose, HbA$_1$C and safety criteria	• DSEF vs SEF significantly different for the following: • total insulin requirements, fasting blood glucose • No difference for HbA$_1$C • Feeding tolerance and adverse events were comparable between groups
Plasma glucose level, capillary blood glucose, Insulin/day requirements, Secondary endpoints: lipid GI tolerance, any adverse events, days of mechanical ventilation, ICU stay and mortality	• DSEF vs SEF significantly different for the following: plasma glucose levels, capillary blood glucose, insulin/day, insulin/g CHO received, insulin/g CHO received/kg • No differences in lipid profiles or clinical outcomes between groups

no statistical difference between groups in percentage of mean energy target achieved (91.6% versus 88.9% and 93.8% versus 89.5%).

One interesting aspect of this study was that hospital length-of-stay (LOS) in that the higher-fat, lower-CHO formula group showed a trend toward a significantly shorter hospital relative to the higher-CHO, lower-fat group (32.3 versus 45.5 days, respectively). Unfortunately, the data were apparently too disparate and the sample size too small to demonstrate whether differences in this variable were statistically significant.

ENTERALLY TUBE-FED STUDY IN DM2 NEUROLOGICAL DYSPHAGIA PATIENTS

Pohl, et al in a multicenter, double-blind PRCT examined the effects of long-term treatment (84 days) in two, parallel DM2 groups, each of which received either DSEF or SEF (30). The patient populations included rehabilitation centers, primary care and nursing facilities and were followed with respect to glycemic indicators and serum lipids. The SEF provided to the control group contained 52% CHO, 30% fat, and 18% protein; the DSEF had 37% CHO, 45% fat and 18% protein; both contained dietary fiber also (amount not specified).

Of the 78 patients originally selected for study, 21 completed the DSEF arm, while 23 completed the SEF arm. Primary outcomes measures included total daily insulin requirement, fasting blood glucose values, and the HDL/LDL-cholesterol index. Secondary outcomes included glycosylated hemoglobin A (HbA$_1$C), C-peptide, triacylglycerols, total cholesterol, HDL cholesterol and LDL cholesterol.

The results of this trial demonstrated statistically significant lower values for the DSEF relative to the SEF for total daily insulin used, fasting blood glucose, HgbA$_1$C, and C-peptide when analysis with data *as available* was performed. There were no statistically significant differences found between the two groups with respect to serum lipids. The significant differences noted by the authors when the available data was

analyzed were attributed to the high dropout rate at a time when the effect of the study treatment was not yet fully developed. As a result, the authors felt that this timing of the dropout of participants from the study weakened the effect size.

ENTERAL TUBE-FED STUDY IN DM2 NEUROLOGICAL DYSPHAGIA PATIENTS

A second double-blind, multicenter PRCT by Pohl, et al was conducted (31) as a stage II follow-up study to confirm the effects of DSEF over SEF as previously reported in 2005 (30). One-hundred-five patients with DM2 and indication for long-term EN (defined as a minimum of three months) due to dysphagia caused by neurological disorders were enrolled. Compositions of the two formulas were identical to their first study (30). Fifty-five of the 105 randomized patients completed the study. The high dropout rate was attributed to discharge from the inpatient rehabilitation facility, transfer to a nursing home or recovery of swallowing ability. Total insulin requirements, fasting blood glucose and afternoon blood glucose were assessed daily. HgbA$_1$C and safety criteria (adverse events, dosages, hyperglycemic and hypoglycemic events, and changes in hematologic markers) were evaluated periodically throughout the study. Analysis was performed on an intent-to-treat basis. The mean volume of formula received daily was similar between the two groups (DSEF—1,492 mL; range 999–2,335 mL and SEF—1,500 mL; range 1,036–2,000 mL). Significantly different improved results on day 84 included: median changes from baseline of total insulin requirement, fasting blood glucose and afternoon blood glucose values for the DSEF versus SEF group respectively. Hemoglobin A1C measurements, however, did not yield any significant differences between the groups after 84 days.

As demonstrated previously, the results of this trial revealed statistically significant lower values for glycemic indicators for the DSEF relative to the SEF when analysis with data as available was performed. A significant limitation of this study was the inability to reach a minimum effective sample size partially attributable to the high drop-out rate (37% DSEF group and 58% SEF group). The authors noted that many patients did not complete the study due to release from the inpatient rehabilitation, "transfer to home," or to regaining their ability to swallow.

ENTERALLY TUBE-FED COMPARISON OF HIGH-PROTEIN DSEF VERSUS HIGH-PROTEIN SEF IN HYPERGLYCEMIC CRITICALLY ILL PATIENTS

In a single-blind, PRCT conducted in two University Hospital Intensive Care Units, Mesejo, et al compared the use of a high-protein DSEF or SEF formula over a 14-day period (32). Sixty-one patients with DM or stress hyperglycemia with basal glycemia ≥60 mg/dL and indication for EN ≥ five days were enrolled. The composition of the two formulas were, SEF: 49% CHO, 29% fat, and 22% protein versus the DSEF with fiber and, 40% CHO, 40% fat, 20% protein.

Fifty patients, 26 DSEF and 24 SEF completed the study. Data was collected on plasma and capillary glucose levels, lipids (cholesterol, triglycerides, HDL and LDL), visceral proteins (retinol-binding protein, prealbumin, albumin and transferrin), acute phase reactant proteins (CRP, α-1-antitrypsin, ferritin and haptoglobin), hormones (glucagon and insulin), HbA$_1$C, and, immunological parameters (serum complement components C3 and C4, and, CD4+ and CD8+ lymphocytes and total lymphocytes), APACHE II scores, acquired infections, mechanical ventilation, length of ICU stay (ICU LOS) and mortality. Both groups received >92% of expected kcal.

The results of this study were as follows: no significant differences in lipid levels, visceral proteins, inflammatory markers (CRP, α-1-antitrypsin, ferritin and haptoglobin), hormones (glucagon and insulin), HbA$_1$C or C3, C4, CD4, CD8 and lymphocytes. However, significant improvements were seen in plasma glucose and capillary glucose levels, insulin/day, insulin/g CHO received, and for insulin/g CHO received/kg in the DSEF group. Outcome measures such as infection rate, ICU LOS, and mortality did not demonstrate significant differences between the two groups. Thus, although a statistically significant improvement in glycemic control of the patients who received DSEF was evident, this improvement was not reflected, at least over the short-term, with respect to LOS or mortality.

COMPARISONS OF DSEF VERSUS SEF IN ORAL NUTRITIONAL SUPPLEMENT PATIENTS

It is beyond the scope of this review to examine the short-term oral nutritional supplement (ONS) studies that compared DSEF versus SEF. The majority of these studies consist of small sample-size, single-meal investigations that did not examine clinical outcomes. Elia, et al (33) examined 13 short-term studies, four of which provided absolute data for meta-analysis. The results of the meta-analysis revealed that a short-term administration of DSEF in oral nutritional supplement patients lowered the postprandial rise in blood glucose relative to SEF patients.

Typically, ≤33% of total, daily energy intake is provided to patients in single-meal, short-term ONS studies. However, patients stable on EN routinely receive higher energy intakes throughout the day. One long-term PRCT ONS study involved 32 patients who received >80% of their daily energy intake as DSEF or SEF. This study examined the effects on blood glucose, serum lipid and fructosamine levels among DM2 patients who received either a high-fat, low-CHO diet, rich in MUFA, or a low-fat, high-CHO diet over a period of 28 days with a minimum of 80% of total daily energy intake provided by these diets (34). The low-fat formulation provided 55% CHO, 30.5% fat (26% MUFA) and 14.5% protein; the high-fat formulation provided 33.3% CHO, 50.0% fat (64% MUFA) and 16.7% protein. The results of this study revealed that by finger-prick sampling, the postprandial rise in blood glucose concentration was significantly lower in the high-fat ONS group. However, there were no statistically significant differences between the two groups for fasting plasma glucose, fructosamine, triglyceride or cholesterol levels.

SUMMARY AND CONCLUSIONS

It is evident from the studies described that the use of a high-fat, lower-CHO DSEF, whether used in tube- or orally-fed patients, are well tolerated and appear to lower postprandial blood glucose levels relative to a higher-CHO, lower-fat diet in patients with DM. Importantly, the use of such high-fat DSEF preparations in these patients did not lead to negative consequences. However, one must consider the short treatment period when interpreting results in many of these studies. Furthermore, the studies to date are plagued by heterogeneous patient populations, small sample size, combinations of DM1, DM2 versus stress induced hyperglycemia, and high drop-out rates make it difficult to draw conclusions of any kind. One important consideration for using $HgbA_1C$ as a surrogate marker in hospitalized patients is to ensure that the patients included have not received multiple units of packed red cells prior to the blood draw.

One of the more critical issues to clinicians and the healthcare community overall, may be the significant absence of patient enhanced outcomes, such as infectious complications or hospital-length-of-stay. It is certainly clear from many studies that if glycemic control is improved, either through diet or through insulin delivery, untoward physiological changes can be averted. One would like to assume that if DSEF can lower the postprandial glucose response without altering lipid metabolism, that better patient outcomes will result. Unfortunately, none of the studies to date were able to show statistical evidence for improvement of patient outcomes, nor have most of the studies considered such outcomes as hospital-length-of-stay. Although the combined results of these studies are provocative, more robust clinical trials are required for the recommendation and routine adoption of DSEF formulas in clinical practice. ∎

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