Targeted Nutrition Therapy

Nutrition Masters Course

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Learning Objectives

- Review clinical studies on innovative, targeted nutrition therapies for:
  - Blood glucose management
  - Dyslipidemia
  - Gastrointestinal health

Randomized Controlled Trials at Joslin Diabetes Center for Blood Glucose Management

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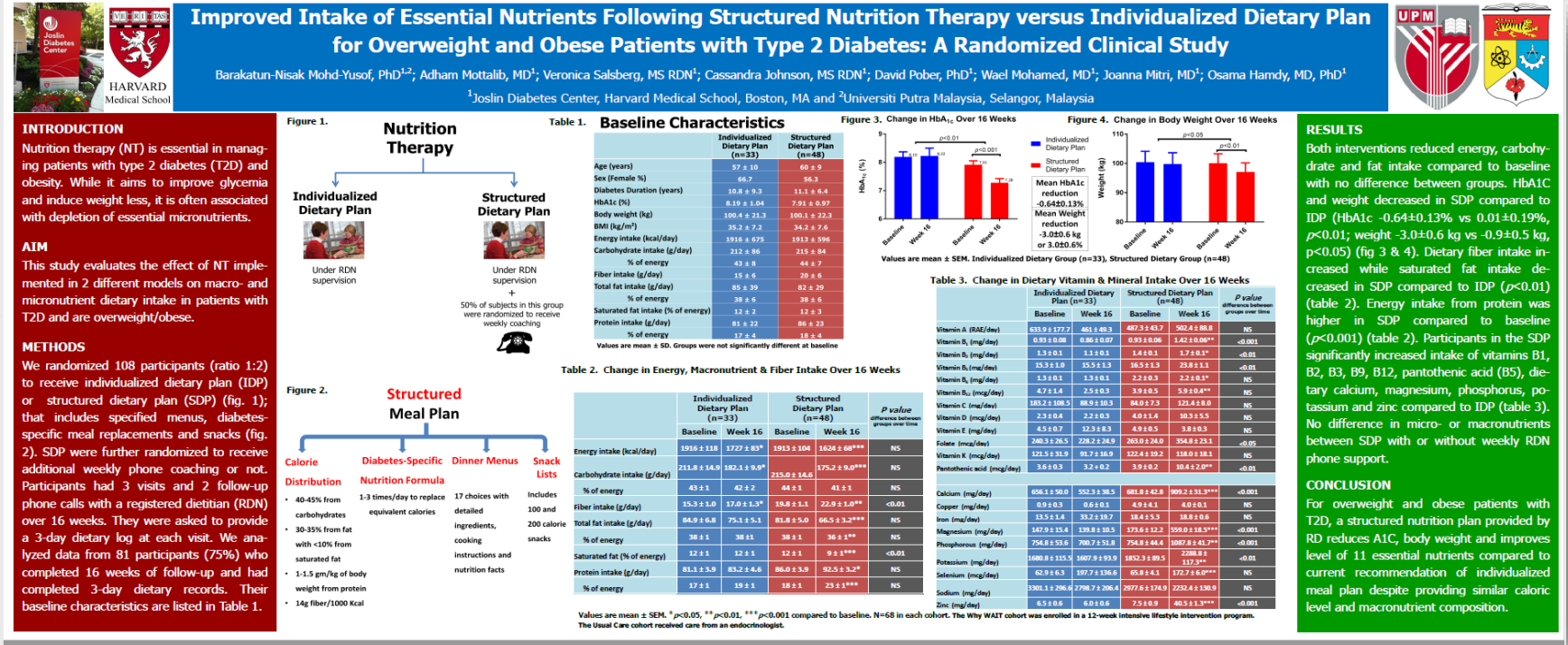
Joslin Study #1: A Randomized Clinical Study



Improved Intake of Essential Nutrients Following Structured Nutrition Therapy versus Individualized Dietary Plan for Overweight and Obese Patients with Type 2 Diabetes: A Randomized Clinical Study

Barakatun-Nisak Mohd-Yusof, PhD[1,2]; Adham Mottalib, MD[1]; Veronica Salsberg, MS RDN[1]; Cassandra Johnson, MS RDN[1]; David Pober, PhD[1]; Wael Mohamed, MD[1]; Joanna Mitri, MD[1]; Osama Hamdy, MD, PhD[1]

[1]Joslin Diabetes Center, Harvard Medical School, Boston, MA and [2]Universiti Putra Malaysia, Selangor, Malaysia

INTRODUCTION

Nutrition therapy (NT) is essential in managing patients with type 2 diabetes (T2D) and obesity. While it aims to improve glycemia and induce weight less, it is often associated with depletion of essential micronutrients.

AIM

This study evaluates the effect of NT implemented in 2 different models on macro- and micronutrient dietary intake in patients with T2D and are overweight/obese.

METHODS

We randomized 108 participants (ratio 1:2) to receive individualized dietary plan (IDP) or structured dietary plan (SDP) (fig. 1); that includes specified menus, diabetes-specific meal replacements and snacks (fig. 2). SDP were further randomized to receive additional weekly phone coaching or not. Participants had 3 visits and 2 follow-up phone calls with a registered dietitian (RDN) over 16 weeks. They were asked to provide a 3-day dietary log at each visit. We analyzed data from 81 participants (75%) who completed 16 weeks of follow-up and had completed 3-day dietary records. Their baseline characteristics are listed in Table 1.

Figure 1.

Figure 2.

Table 1. **Baseline Characteristics**

	Individualized Dietary Plan (n=33)	Structured Dietary Plan (n=48)
Age (years)	57 ± 10	60 ± 9
Sex (Female %)	66.7	56.3
Diabetes Duration (years)	10.8 ± 9.3	11.1 ± 6.4
HbA1c (%)	8.19 ± 1.04	7.91 ± 0.97
Body weight (kg)	100.4 ± 21.3	100.1 ± 22.3
BMI (kg/m²)	35.2 ± 7.2	34.2 ± 7.6
Energy intake (kcal/day)	1916 ± 675	1913 ± 596
Carbohydrate intake (g/day)	212 ± 86	215 ± 84
% of energy	43 ± 8	44 ± 7
Fiber intake (g/day)	15 ± 6	20 ± 6
Total fat intake (g/day)	85 ± 39	82 ± 29
% of energy	38 ± 6	38 ± 6
Saturated fat intake (% of energy)	12 ± 2	12 ± 3
Protein intake (g/day)	81 ± 22	86 ± 23
% of energy	17 ± 4	18 ± 4

Values are mean ± SD. Groups were not significantly different at baseline

Figure 3. Change in HbA_{1c} Over 16 Weeks

Figure 4. Change in Body Weight Over 16 Weeks

Values are mean ± SEM. Individualized Dietary Group (n=33), Structured Dietary Group (n=48)

Table 2. Change in Energy, Macronutrient & Fiber Intake Over 16 Weeks

	Individualized Dietary Plan (n=33)		Structured Dietary Plan (n=48)		*P value* difference between groups over time
	Baseline	Week 16	Baseline	Week 16	
Energy intake (kcal/day)	1916 ± 118	1727 ± 83*	1913 ± 104	1624 ± 68***	NS
Carbohydrate intake (g/day)	211.8 ± 14.9	182.1 ± 9.9*	215.0 ± 14.6	175.2 ± 9.0***	NS
% of energy	43 ± 1	42 ± 2	44 ± 1	41 ± 1	NS
Fiber intake (g/day)	15.3 ± 1.0	17.0 ± 1.3*	19.8 ± 1.1	22.9 ± 1.0**	<0.01
Total fat intake (g/day)	84.9 ± 6.8	75.1 ± 5.1	81.8 ± 5.0	66.5 ± 3.2***	NS
% of energy	38 ± 1	38 ± 1	38 ± 1	36 ± 1**	NS
Saturated fat (% of energy)	12 ± 1	12 ± 1	12 ± 1	9 ± 1***	<0.01
Protein intake (g/day)	81.1 ± 3.9	83.2 ± 4.6	86.0 ± 3.9	92.5 ± 3.2*	NS
% of energy	17 ± 1	19 ± 1	18 ± 1	23 ± 1***	NS

Values are mean ± SEM. *p<0.05, **p<0.01, ***p<0.001 compared to baseline. N=68 in each cohort. The Why WAIT cohort was enrolled in a 12-week intensive lifestyle intervention program. The Usual Care cohort received care from an endocrinologist.

Table 3. Change in Dietary Vitamin & Mineral Intake Over 16 Weeks

	Individualized Dietary Plan (n=33)		Structured Dietary Plan (n=48)		*P value* difference between groups over time
	Baseline	Week 16	Baseline	Week 16	
Vitamin A (RAE/dey)	633.9 ± 177.7	461 ± 49.3	487.3 ± 43.7	502.4 ± 88.8	NS
Vitamin B_1 (mg/dey)	0.93 ± 0.08	0.86 ± 0.07	0.93 ± 0.06	1.42 ± 0.06**	<0.001
Vitamin B_2 (mg/dey)	1.3 ± 0.1	1.1 ± 0.1	1.4 ± 0.1	1.7 ± 0.1*	<0.01
Vitamin B_3 (mg/dey)	15.3 ± 1.0	15.5 ± 1.3	16.5 ± 1.3	23.8 ± 1.1	<0.01
Vitamin B_6 (mg/dey)	1.3 ± 0.1	1.3 ± 0.1	2.2 ± 0.3	2.2 ± 0.1*	NS
Vitamin B_{12} (mcg/dey)	4.7 ± 1.4	2.5 ± 0.3	3.9 ± 0.5	5.9 ± 0.4**	NS
Vitamin C (mg/dey)	183.2 ± 108.5	88.9 ± 10.3	84.0 ± 7.3	121.4 ± 8.0	NS
Vitamin D (mcg/dey)	2.3 ± 0.4	2.2 ± 0.3	4.0 ± 1.4	10.3 ± 5.5	NS
Vitamin E (mg/dey)	4.5 ± 0.7	12.3 ± 8.3	4.9 ± 0.5	3.8 ± 0.3	NS
Folate (mcg/dey)	240.3 ± 26.5	228.2 ± 24.9	263.0 ± 24.0	354.8 ± 23.1	<0.05
Vitamin K (mcg/dey)	121.5 ± 31.9	91.7 ± 16.9	122.4 ± 19.2	118.0 ± 18.1	NS
Pantothenic acid (mcg/dey)	3.6 ± 0.3	3.2 ± 0.2	3.9 ± 0.2	10.4 ± 2.0**	<0.01
Calcium (mg/dey)	656.1 ± 50.0	552.3 ± 38.5	681.8 ± 42.8	909.2 ± 31.3***	<0.001
Copper (mg/dey)	0.9 ± 0.3	0.6 ± 0.1	4.9 ± 4.1	4.0 ± 0.1	NS
Iron (mg/dey)	13.5 ± 1.4	33.2 ± 19.7	18.4 ± 5.3	18.8 ± 0.6	NS
Magnesium (mg/dey)	147.9 ± 15.4	139.8 ± 10.5	173.6 ± 12.2	559.0 ± 18.5***	<0.001
Phosphorous (mg/dey)	754.8 ± 53.6	700.7 ± 51.8	754.8 ± 44.4	1087.8 ± 41.7**	<0.001
Potassium (mg/dey)	1680.8 ± 115.5	1607.9 ± 93.9	1852.3 ± 89.5	2286.8 ± 117.3**	<0.01
Selenium (mcg/dey)	62.9 ± 6.3	197.7 ± 136.6	65.8 ± 4.1	172.7 ± 6.0***	NS
Sodium (mg/dey)	3301.1 ± 296.6	2798.7 ± 206.4	2977.6 ± 174.9	2232.4 ± 130.9	NS
Zinc (mg/dey)	6.5 ± 0.6	6.0 ± 0.6	7.5 ± 0.9	40.5 ± 1.3***	<0.001

RESULTS

Both interventions reduced energy, carbohydrate and fat intake compared to baseline with no difference between groups. HbA1C and weight decreased in SDP compared to IDP (HbA1c -0.64±0.13% vs 0.01±0.19%, p<0.01; weight -3.0±0.6 kg vs -0.9±0.5 kg, p<0.05) (fig 3 & 4). Dietary fiber intake increased while saturated fat intake decreased in SDP compared to IDP (p<0.01) (table 2). Energy intake from protein was higher in SDP compared to baseline (p<0.001) (table 2). Participants in the SDP significantly increased intake of vitamins B1, B2, B3, B9, B12, pantothenic acid (B5), dietary calcium, magnesium, phosphorus, potassium and zinc compared to IDP (table 3). No difference in micro- or macronutrients between SDP with or without weekly RDN phone support.

CONCLUSION

For overweight and obese patients with T2D, a structured nutrition plan provided by RD reduces A1C, body weight and improves level of 11 essential nutrients compared to current recommendation of individualized meal plan despite providing similar caloric level and macronutrient composition.

Mohd-Yusof BN, Mottalib A, Salsburg V, et al. Improved intake of essential nutrients following structured nutrition therapy versus individualized dietary plan for overweight and obese patients with type 2 diabetes: A randomized clinical study. Joslin Diabetes Center.

Joslin Study #1: Study Design

- Rigorous, head-to-head comparison of nutrition therapy (NT) methods
- 108 patients (62 female, 46 male; 18-80 years old) with type 2 diabetes (T2D)
- Baseline characteristic (averages):
  - Age: 60, Weight: 101.4 kg, BMI: 35.2, HbA1c: 8.07%
- Patients randomized to 1 of 3 NT lifestyle interventions, for 16 weeks:
  - Group A: Met with RD for individualized dietary plan
  - Group B: Met with RD and followed structured dietary plan, including diabetes-specific nutrition formula (meal replacement)
  - Group C: Same as Group B + increased patient-RD interactions

Mottalib A, Salsberg V, Mohd-Yusof BN, et al. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. *Nutr J.* 2018;17:42.

Summary article

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Joslin Study #1: Results
Changes in HbA1c and Body Weight over 16 Weeks

Figure 3. Change in HbA_{1c} Over 16 Weeks

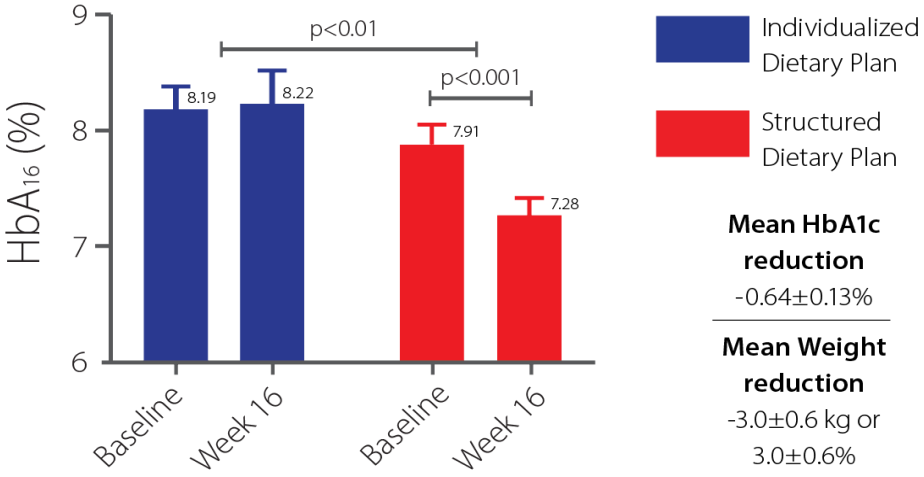
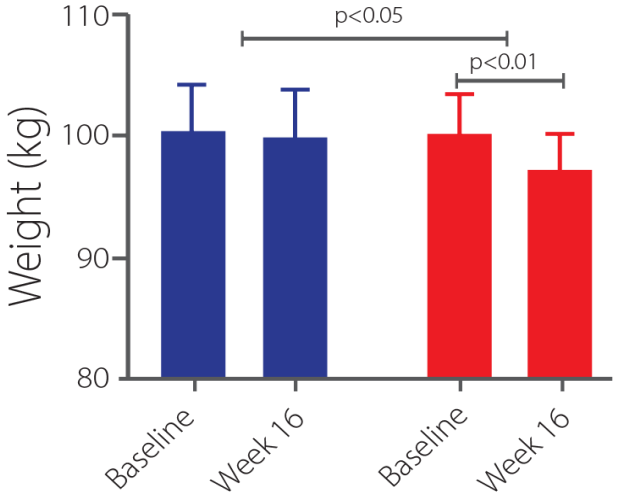


Figure 4. Change in body weight Over 16 Weeks



Values are mean ± SEM. Indivdualized Dietary Group (n=33), Structured Dietary Group (n=48)

Mohd-Yusof BN, Mottalib A, Salsburg V, et al. Improved intake of essential nutrients following structured nutrition therapy versus individualized dietary plan for overweight and obese patients with type 2 diabetes: A randomized clinical study. Joslin Diabetes Center
Mottalib A, Salsberg V, Mohd-Yusof BN, et al. *Nutr J.* 2018;17:42.

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Joslin Study #1: Results (cont.) & Conclusions

Statistically significant results:

- All 3 groups experienced ↓ in energy intake, total carbs, total fat, and saturated fat
- ↓ Body weight, ↓ % body fat, and ↓ waist circumference in Groups B and C
- ↓ Visceral fat levels in Group B only
- Significant ↓ in HbA1c for Groups B and C

Conclusions:

- RDs play a critical role in partnering with patients with T2D to develop and implement NT interventions
- Structured NT (Groups B and C) were superior to individualized eating plan (Group A) in helping patients improve glycemic control and CVD risk factors
- The diabetes-specific nutrition formula (meal replacement) was an important, differentiating feature of the structured meal plan approach (Groups B and C) and success

Mottalib A, Salsberg V, Mohd-Yusof BN, et al. Effects of nutrition therapy on HbA1c and cardiovascular disease risk factors in overweight and obese patients with type 2 diabetes. *Nutr J.* 2018;17:42.

Summary article

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Joslin Study #2: Three-Way, Cross-Over Clinical Study

Study Objective:
Compare the post-prandial glycemic response to a single serving of 2 nutritional formulas (novel vs. standard) vs. oatmeal breakfast of equal calories in patients with type 2 diabetes

Patients with type 2 diabetes (N=22)

Diabetes duration (yrs): 9.5 ± 9.8

Open-label, 3-way, cross-over randomized study conducted at the Joslin Diabetes Center

Visit 1 → **Patient consumed : 1 serving/day 200 kcal**

Visit 2 → **Patient consumed : 1 serving/day 200 kcal**

Week 3 → **Patient consumed : 1 serving/day 200 kcal**

- Subjects enrolled in this study came for 3 visits on 3 separate days. All 3 visits had to be completed in a 3-week period with at least 2 days between each visit.
- On each visit, subjects were fasting overnight and then served a food product with a caloric value of 200 kcal
- The food product consumed was either a novel nutritional formula, standard nutritional formula, or regular oatmeal

Mottalib A, Mohd-Yusof BN. *Nutrients.* 2016;8(7):E443.

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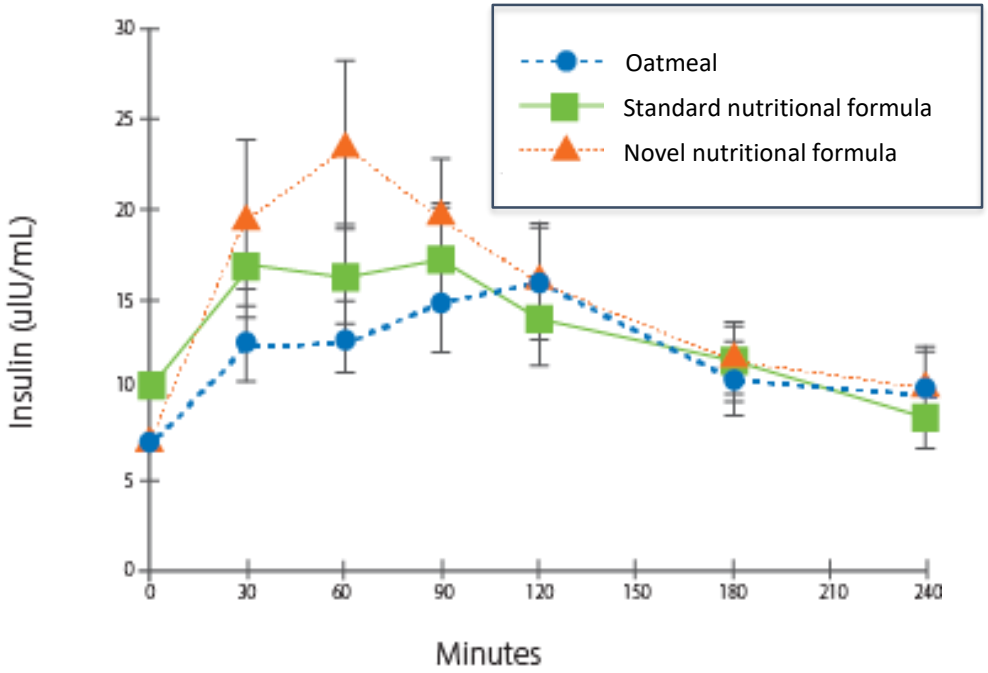
Joslin Study #2: Insulin Results

A novel nutritional formula resulted in a more pronounced secretion of insulin, resulting in a more sustained and balanced glucose response curve



Adapted from: Mottalib A, Mohd-Yusof BN. *Nutrients.* 2016;8(7):E443.

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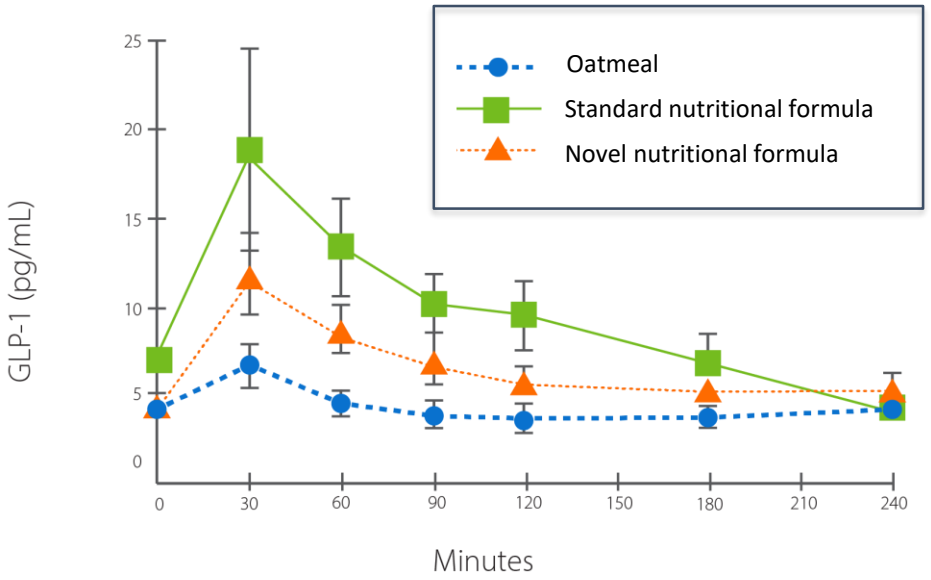
Joslin Study #2: GLP-1 Results

The novel nutritional formula resulted in a more pronounced secretion of glucagon-like peptide-1 (GLP-1), resulting in a more sustained and balanced glucose response curve



Adapted from: Mottalib A, Mohd-Yusof BN. *Nutrients.* 2016;8(7):E443.

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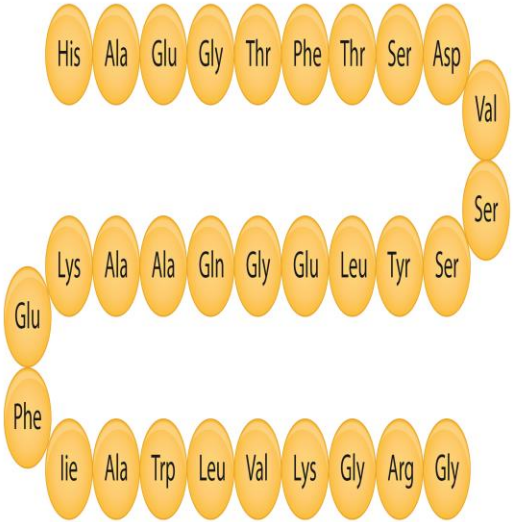
What is GLP-1?

- Glucagon-like peptide-1 (GLP-1) is a gut-derived peptide secreted from intestinal L-cells and is released in response to food consumption
- Main action- stimulates insulin secretion and inhibits glucagon secretion, thereby promoting postprandial glucose homeostasis
- Slows gastric emptying and induces satiety



Holst JJ. *Physiol Reviews*. 2007;87(4):1409-1439.

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Summary of Joslin Study Findings with Targeted NT for T2D

- Reductions in **weight, body fat, waist circumference, and HbA1c**
- Improvements in **diet quality**; reduction in **energy intake**
- More pronounced **GLP-1 production**, which can help regulate appetite and post-prandial glucose levels
- **A more sustained and balanced glucose control without a hypoglycemic effect**

1. Mohd-Yusof BN, Mottalib A, Salsburg V, et al. Improved intake of essential nutrients following structured nutrition therapy versus individualized dietary plan for overweight and obese patients with type 2 diabetes: A randomized clinical study. Joslin Diabetes Center.
2. Mottalib A, Mohd-Yusof BN. *Nutrients* 2016:8(7):E443

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Summary of Study Findings with NT in T2D

- Previous studies have shown that intensive diet and lifestyle interventions have resulted in **delaying the onset of diabetes by 58% compared to placebo**, statistically significant reductions in HbA1c, fasting plasma glucose, CVD risk factors, and weight loss[1]
- In clinical practice, combining an innovative nutritional formula with dietary and lifestyle recommendations may provide clinical benefit. This combination can form an important part of a medical nutrition therapy program for blood glucose management.

1. Delahanty LM, Nathan DM. Implications of the Diabetes Prevention Program (DPP) and Look AHEAD clinical trials for lifestyle interventions. *J Am Diet Assoc.* 2008;108(4):S66-S72.

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Practice-Based Research with Innovative Nutritional Formula for Dyslipidemia

IRB-approved, open-label, case observation series

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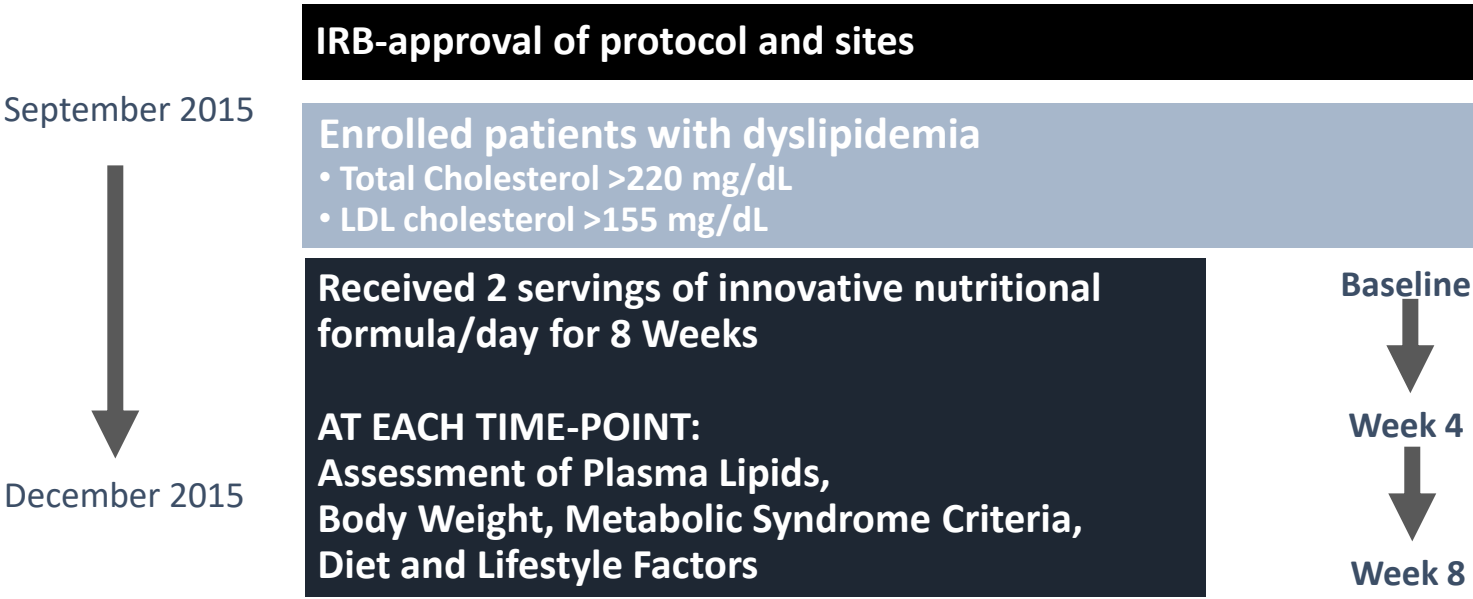
Case Study Design



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Practice-Based Research Results with UMC Medical Food: Effects on Plasma Lipid Profile and Selected Clinical Biomarkers for Metabolic Syndrome, Sept- December 2015.

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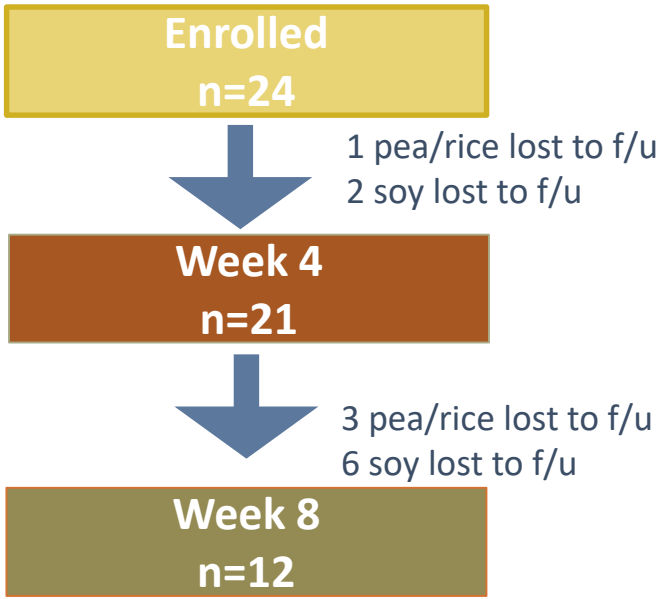
Flow Chart of Participation



Pea/Rice (n)	Soy (n)
13	11

Pea/Rice (n)	Soy (n)
12	9

Pea/Rice (n)	Soy (n)
9	3

Analysis Plan

Differences from baseline at 4 weeks and 8 weeks assessed by paired t-test

Mean data presented on following slides calculated for completers of that variable

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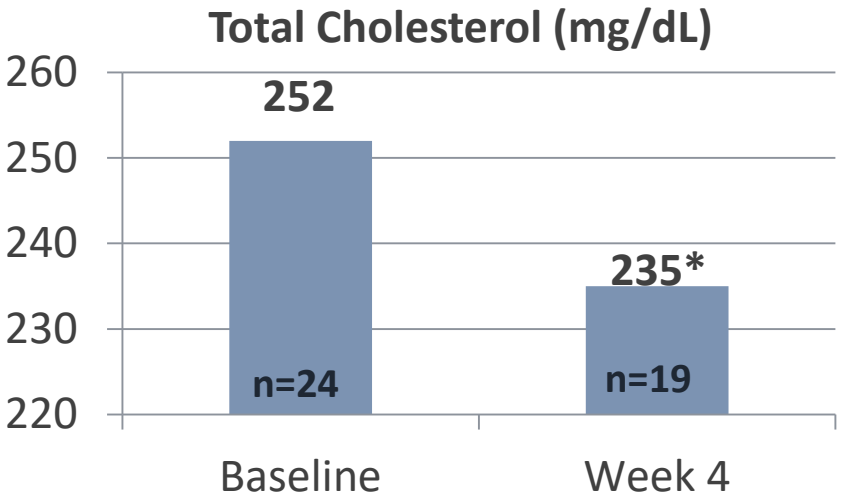
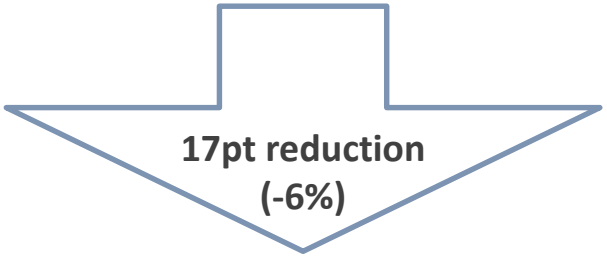
Total Cholesterol
Significantly Reduced at 4 Weeks



* denotes p-value = 0.01, as assessed by paired t-tests between baseline and 4-week data



- Group moved from high down to borderline high total cholesterol
- 47% of subjects re-classified into a lower TC risk category
- Up to 27.6% reduction at 4 weeks
- No significant difference between soy and pea group

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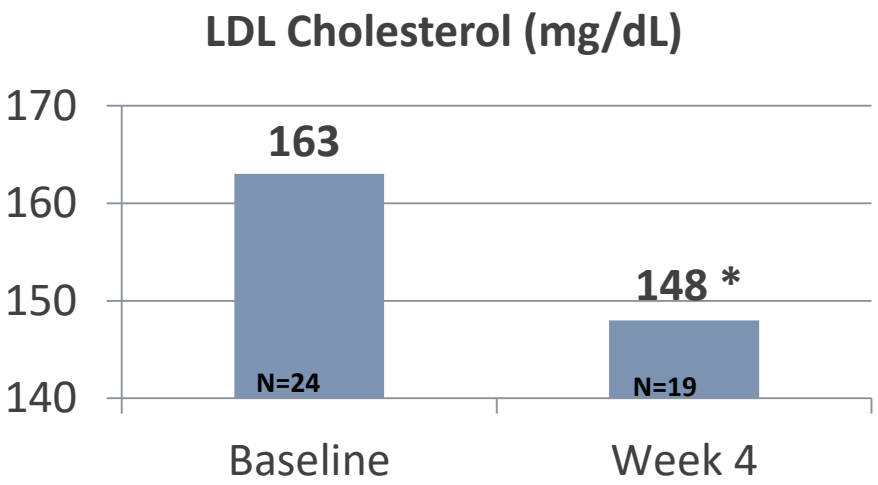
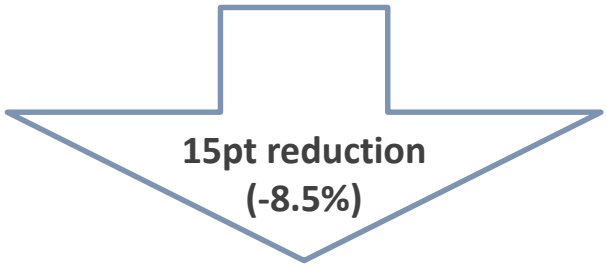
LDL Cholesterol
Significantly Reduced at 4 Weeks



* denotes p-value = 0.01, as assessed by paired t-tests between baseline and 4-week data



- Group moved from high down to borderline high LDL in 4 weeks
- 56% of subjects re-classified into a lower LDL cholesterol risk category
- Up to 35.9% reduction at 4 weeks
- No significant difference between soy and pea group

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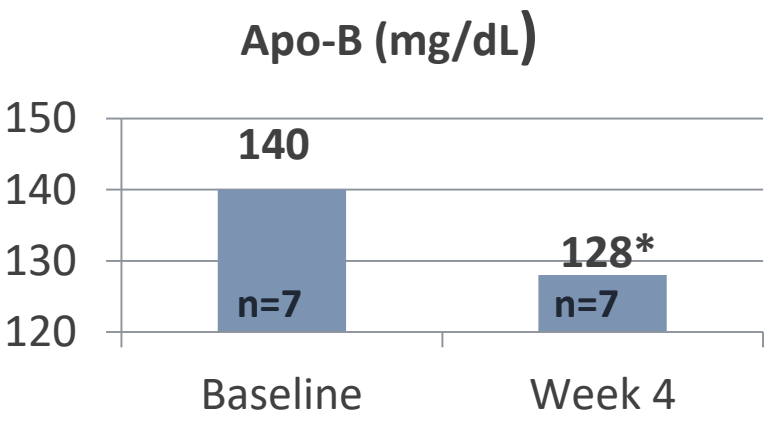
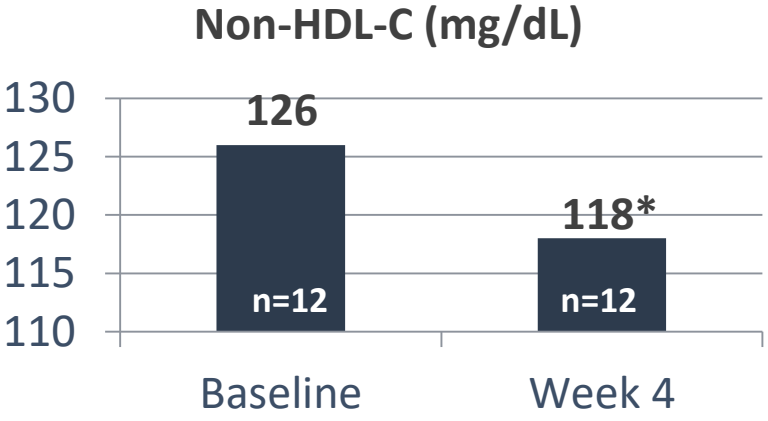
Other Atherogenic Lipid Biomarkers
Significantly Reduced Within 4 Weeks



8.2% reduction within 4 weeks



8.6% reduction within 4 weeks

* denotes p-value < 0.05, as assessed by paired t-tests between baseline and 4-week data

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Metabolic Syndrome Criteria
Improvement Noted at 4 Weeks

n=21

	Waist (inches)	SBP (mmHg)	HDL-C (mg/dL)	TG (mg/dL)	Glucose (mg/dL)
Ref. range	***<40/35 (M/F)***	***<135***	***<40/50 (M/F)***	***<150***	***<100***
Baseline	40.5	125.8	60.0	144.7	95.7
4 Weeks	***39.7***	***117.7***	***60.5***	***136.0***	***96.8***
	- 1 in.	- 6%			
	4% reduction in CVD risk[1]	12.8% reduced CVD risk[2]	No clinical change	Remained WNL	No clinical change

* Significant reduction ($p<0.05$) from baseline as assessed by paired t-tests between time-points

1. de Koning L, Merchant AT. *Eur Heart J.* 2007;28(7):850-856.
2. Scott R, Donoghoe M, Watts GF, et al. *Cardiovasc Diabetol.* 2011;10:102.

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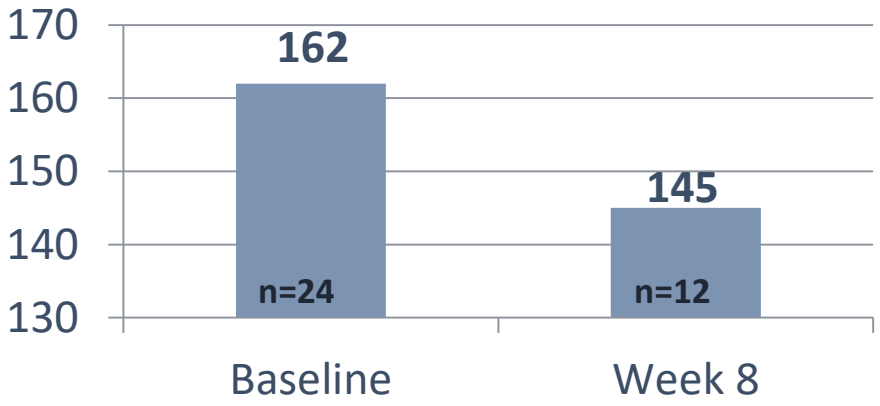
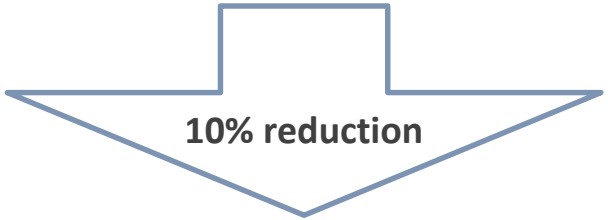
Continued Reduction
LDL Cholesterol in Group that Completed 8 Weeks



‡ mean data from sub-group completing 8-week time-point only



- Up to 21% reduction
- 67% of subjects re-classified to lower risk category
- 6.4% reduction in total cholesterol (up to 16% reduction)
- No further improvements in other metabolic syndrome criteria

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Study summary and conclusions[3]

- Significant reductions in the atherogenic lipid profile (LDL-C, apoB, non-HDL cholesterol), and risk reclassification into lower risk group
- Improvements in particle size in select cases where measured
- Improvements in metabolic syndrome-related variables seen, and waist circumference and systolic blood pressure reductions at a magnitude previously associated with a lowering of CVD risk[1,2]

1. de Koning L, Merchant AT. *Eur Heart J.* 2007;28(7):850-856.
2. Scott R, Donoghoe M, Watts GF, et al. *Cardiovasc Diabetol.* 2011;10:102.
Stagg, J, Change, N, Whole Health Chicago. Practice-Based Research Results with UMC Medical Food: Effects on Plasma Lipid Profile and Selected Clinical Biomarkers for Metabolic Syndrome, Sept- December 2015.

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Study summary and conclusions

- Previous studies have shown that intensive diet and lifestyle interventions have resulted in LDL lowering benefits of 10.8% in 8 weeks, with an added benefit of a nutritional formula of 8.1% in these studies.[1] This study showed a 10% reduction in LDL cholesterol in 8 weeks, with additional positive changes in atherogenic lipid profile and cardiometabolic risk biomarkers within 4 weeks
- In clinical practice, an additional emphasis on combining an innovative nutritional formula with dietary and lifestyle recommendations can bring broad benefit. This combination can form the basis of a medical nutrition therapy program for longer-term management of dyslipidemia.

1. Jones DL, Fernandez ML, McIntosh MS. *J Clin Lipidol.* 2011;5(3):188-196.

Practice-Based Research with Innovative Nutritional Formula for Gastrointestinal (GI) Function

Single Arm, Open-Label Study

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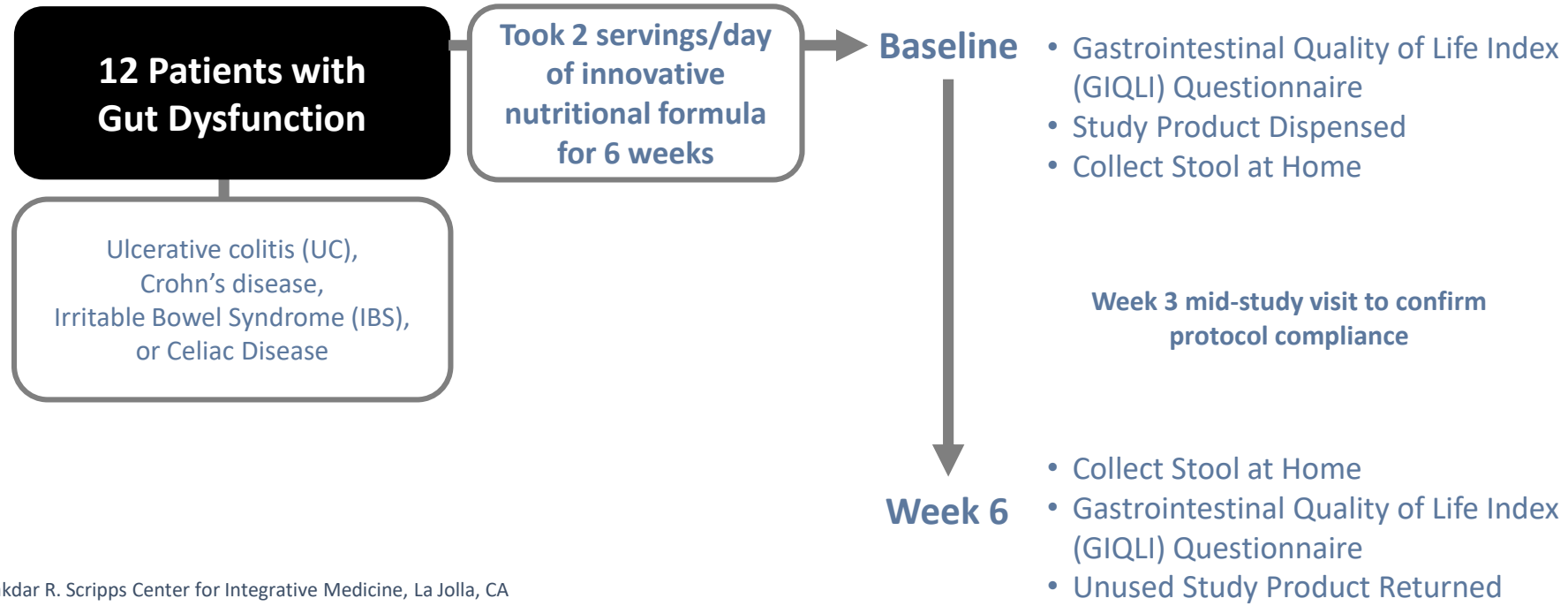
Clinical Study Design



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Results

GIQLI	Score Range	Results (Mean)	% Change	P-value (Paired T-test)
Total Score	0-144	Baseline: 94.5 +/- 25.5 Study End: 109.4 +/- 19.2	+ 20.8%	**0.020**
GI Symptoms Domain	0-76	Baseline: 53.3 +/- 10.3 Study End: 61.4 +/- 7.7	+ 18.1%	**0.022**
Social Function Domain	0-16	Baseline: 10.7 +/- 3.8 Study End: 12.3 +/- 3.7	+ 18.4%	**0.004**

- Total score, GI symptom domain, and Social function domain scores improved
- Higher scores are consistent with better quality of life
- Additional domain (physical function and emotional function) scores were improved, but did not reach statistical significance

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Results: Significantly Increased Bifidobacterium

	Reference Range	Results (mean +/- SD)	Mean % Change	p Value (Paired t-test)
Bifidobacterium spp.	≤6.4E9	Baseline: 1.2E9 +/- 1.5E9 6 Weeks: 5.4E9 +/- 5.1E9	**+ 1890.1% (19-fold increase)**	**0.026**

2’-FL and IMO are key nutritional bioactives that are likely responsible for the increases in butyrate, SCFAs, and *Bifidobacterium* levels

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Results: Significantly Enhanced Production of SCFAs Including Butyrate

	Reference Range	Results (mean +/- SD)	Mean % Change	P-value (Paired T-test)
n-Butyrate Concentration	≥ 3.6 micromol/g	Baseline: 8.1 +/- 4.8 6 Weeks: 16.7 +/- 9.6	+ 594.0 %	0.040
SCFA (Total)	≥ 23.3 micromol/g	Baseline: 46.3 +/- 13.3 6 Weeks: 76.4 +/- 37.0	+ 72.2 %	0.026

(Total SCFAs = Butyrate + Acetate + Propionate)

- Levels of bacterial strains known to produce butyrate also increased
  - *F. prausnitzii* levels increased 20-fold (p=0.029)
  - *Roseburia* spp. levels increased 13-fold (p=0.091, non-significant)
- The increased production of butyrate in the gut is a potential mechanism for the reduction in GI symptoms demonstrated in this study

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Study Summary

GI symptoms and quality of life scores improved significantly

Significantly increased *Bifidobacterium* (19-fold)

Significantly enhanced production of SCFAs, including butyrate by 594.0% (on average)

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