A Pilot Trial Comparing the Effects of Identical Weight Loss Diet Programs with or without Additional Nutrient Supplementation in Subjects with Insulin Resistance and Hyperinsulinemia

FUNCTIONAL MEDICINE
RESEARCH CENTER

Research Report Number 105

May 15, 2000

Rev 05/00

A Pilot Trial Comparing the Effects of Identical Weight Loss Diet Programs with or without Additional Nutrient Supplementation in Subjects with Insulin Resistance and Hyperinsulinemia

Dan Lukaczer, ND, Robert Lerman, MD, PhD, Barbara Schiltz, MS, RN, CN, and Gary Darland, PhD.
Functional Medicine Research Center, HealthComm International, Inc., Gig Harbor, WA, 98335.

Abstract

Insulin resistance and hyperinsulinemia are significant risk factors for the development of Type II diabetes mellitus, hypertension (HTN), and coronary artery disease (CAD). We report the results of a study comparing the effects of a standard calorie-restricted dietary program with or without additional nutrient supplementation in subjects with insulin resistance. Forty-nine hyperinsulinemic individuals were randomly assigned to one of two treatment groups. All subjects were instructed to follow a weight loss program. In addition, half the subjects were instructed to consume a specific combination of macro- and micronutrients in a powdered beverage drink mix and an encapsulated supplement; the other half were given a calorically similar powdered beverage drink mix and a placebo capsule. Over the course of eight weeks, subjects were evaluated for changes in weight, body mass index, waist circumference, hip circumference, percent body fat, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting and 2-hour postprandial insulin and glucose. Both groups showed weight loss and improvements in lipid and insulin values. Subjects on the treatment arm consuming the macro/micronutrient combination designed specifically to improve insulin sensitivity showed a greater improvement in triglycerides, total cholesterol and insulin values, suggesting that the presence of these nutrients was of additional benefit in these people. Further investigations are needed to confirm these results.

Introduction

There is now a substantial body of evidence suggesting that the ability of insulin to mediate glucose disposal varies widely from person to person. Research over the past 20 years has shown that differences in the secretion and action of insulin can have profound health consequences. Individuals with impairments in insulin action may develop a cluster of symptoms that have been termed Syndrome X. Syndrome X, which includes insulin resistance, glucose intolerance, hyperinsulinemia, hypertension, and decreased HDL cholesterol, is now recognized as a significant risk factor in the etiology of Type II diabetes mellitus and coronary artery disease (CAD).[1]

Binding of insulin to its receptor in the cell membrane is the first step of a metabolic cascade leading to glucose uptake and metabolism in insulin-sensitive tissues.[2] While genetics plays a role in the development of insulin resistance, environmental factors such as diet and physical activity also appear to be important contributors in this process. Extensive research has been conducted on the use of specific macro- and micronutrients in improving cellular sensitivity to insulin. Various studies on macronutrients such as protein[3], fiber,[4,5,6] and specific starch carbohydrates [7,8] have all shown a significant impact on insulin and glucose response. Micronutrients also appear to play an important role in glucose homeostasis through their effects on insulin secretion and action.

CORRESPONDENCE: Functional Medicine Research Center, HealthComm International, Inc., P.O. Box 1729, Gig Harbor, WA 98335, USA, www.healthcomm.com

Vitamin E,[9,10] biotin,[11] chromium,[12,13] alpha-lipoic acid[14,15] and the minerals magnesium[16,17] and vanadium[18,19] all appear to improve insulin responsiveness, insulin sensitivity, insulin-mediated glucose uptake, and/or glucose response.

While a variety of studies have looked at these specific nutrients independently, little work has been done using a combination of these macro- and micronutrients incorporated into a dietary program. The aim of the present study was to investigate the additive effect of a combination of these nutrients to a weight loss dietary program in individuals presenting with insulin resistance and hyperinsulinemia.

METHODS

Subjects

Forty-nine subjects were selected for this trial on the basis of a fasting glucose/insulin ratio of less than or equal to 6. In our experience, this ratio correlates well with hyperinsulinemia 2 hours after a 75-gram glucose load. Subjects were males and females between the ages of 21 and 64, with an average age of 46. Prior to initiating the study, subjects were evaluated by blood chemistry panels, medical history, and physical examination. Subjects diagnosed with Type I diabetes, AIDS (Acquired Immune Deficiency Syndrome), a history of ketoacidosis, heart disease, liver disease, kidney disease, or severe mental illness were excluded from the study. Additionally, subjects currently pregnant or lactating, using insulin to control Type II diabetes, or who had used prescription weight loss medication or oral corticosteroids in the preceding four weeks were excluded from the study.

Dietary Products

Two different nutritional product combinations were used in the study, "Combination A" and "Combination B." Each combination consisted of a powdered product and a supplemental capsule. Subjects prepared the powdered product as a drink mix at the time of use, by mixing 2 measuring scoops of powder (50 g) in 8 to 12 ounces of water. The capsules were taken with water. Subjects were asked to discontinue other non-prescription nutritional supplements. All subjects participating in the study were also given the same daily dose of a dietary multivitamin and mineral supplement (Multigenics™ Without Iron, Metagenics, Inc., San Clemente, CA).

The daily nutrient profile provided by the powdered product and capsule in both combinations is shown in Table 1. Within each combination, the amounts of common ingredients to the vitamin-mineral supplement and the nutritional products were added, and are presented as a single figure. The primary carbohydrate sources in the powdered product for Combination A were a rice extract that has been shown to have a low glycemic index (GI) (unpublished data) and two sources of high-amylose cornstarch that also have been shown to have a low GI.[20,21] Specific fibers that display a beneficial effect on insulin secretion and action were also chosen for inclusion in the powdered product in Combination A.[22,23] The multivitamin and mineral supplement provided minimal levels of vitamins A, C, D, B_6, B_{12}, thiamin, riboflavin, niacin, folic acid, manganese, molybdenum, quercetin, betaine hydrochloride, pantothenic acid, calcium, and iodine. These ingredients are not shown in Table 1.

Table 1. Daily nutrient profiles of Combination A and B nutritional powders, capsules, and vitamin/mineral supplements received by Protocol A and Protocol B subjects.

Ingredient	Combination A	Combination B
Protein (soy)	16 g	—
Protein (rice)	—	20 g
Carbohydrates	44 g	37 g
Fat	6.0 g	4.0 g
Fiber	10 g	2.5 g
Holy basil	1.0 g	—
Alpha-lipoic acid	400 mg	—
Glutamine	1.0 g	—
Biotin	3.1 mg	100 mcg
Vitamin E	433 IU	33 IU
Copper lysinate	3.7 mg	0.7 mg
Chromium (picolinate, dinicotinate glycinate)	1.1 mg	67 mcg
Magnesium (citrate, glycinate)	483 mg	83 mg
Selenium (methionine, aspartate)	467 mcg	67 mcg
Vanadyl sulfate	5.0 mg	—
Zinc (picolinate, aspartate)	52 mg	6.7 mg

Diet

The diet prescribed for the subjects was designed based on the standard guidelines recommended by The American Diabetes Association and The American Dietetic Association for management of diabetes.[24] At the beginning of the study, subjects' weights and heights were recorded. Basal metabolic rates (BMRs) were estimated from weight, gender, and age, and multiplied by a factor according to each subject's self-described level of physical activity: 1.0 for no activity, 1.3 for mild physical activity, 1.5 for moderate physical activity, and 1.7 for strenuous physical activity. Five hundred calories were then subtracted from this figure to put each subject at a daily caloric deficit. Caloric intake was rounded down to 1000, 1200, 1500, 1800, 2100, or 2400 calories. This approach was intended to standardize the expected weight loss of all participants and achieve a decrease of one to two pounds per week. Specific dietary handouts and exchange program information were then supplied to each participant for his/her specific caloric intake.

Study design

The study was a randomized, double-blind clinical trial. After a screening exam, subjects were randomly assigned to one of two protocols:

1. Protocol A: the twenty-five subjects assigned to this Protocol consumed Combination A products. Each subject also followed his/her prescribed individual diet.
2. Protocol B: the twenty-four subjects assigned to this Protocol consumed Combination B products. Each subject also followed his/her prescribed individual diet.

Both protocols were followed for an 8-week period. Subjects were instructed to make no changes in their medication or exercise routine, and to stop vitamin/mineral supplements (other than those prescribed with the diet) during the course of the study. Compliance to the respective protocol, exercise, and medication use was documented at each office visit.

Clinical Assessment

Evaluation of the subjects' progress during the course of the trial was done using a variety of criteria, including measurements performed during physical examination (weight and shape analysis), percent body fat, questionnaire responses and results of laboratory tests.

Physical examination was performed during the initial visit to the clinic, and after 1 week, 2 weeks, 4 weeks, and 8 weeks. Physical exams included measurements of blood pressure, pulse, height, weight, and waist and hip circumferences. Body mass indices (BMIs) and waist-to-hip ratios (WHRs) were calculated from these data.

Body composition was evaluated as percent body fat using a bioelectrical impedance analyzer (ElgII-ElectroLipoGraph, Bio/Analogics, Beaverton, OR). This measurement was taken at the initial visit for the trial and at the end of the 8-week period. Electrodes were placed on the right foot and ankle, as well as the right hand and wrist of a subject while lying supine, allowing for the measurement of the resistance offered by the body to the current. Utilizing this measurement, a special calculator (Hewlett Packard 48G) connected to the analyzer calculated the total amount of body water, percent body fat, and lean muscle mass.

Subjects' compliance to the program was monitored by response to 24-hour diet recall surveys, weekly food logs, and taste and tolerance questionnaires. Additionally, subjects were asked to complete the Medical Symptoms Questionnaire© (MSQ, HealthComm Intl.) during their initial visit for the trial and after 1 week, 2 weeks, 4 weeks, and 8 weeks. The MSQ evaluates general physical symptoms. A high score on the MSQ suggests a higher or more substantial amount of overall symptoms in terms of duration, frequency, and intensity. MSQ scores that total above 75 are generally associated with substantial symptomatology and disability. MSQ scores below 30 generally indicate few symptoms or symptoms of low intensity (unpublished observations).

Laboratory evaluation was done at the initial visit for the trial, and again at the 4-week and 8-week points; the specimens were collected on site and tested by Laboratories Northwest, Tacoma, WA. Tests performed on serum specimens collected at each of the three visits were: fasting insulin (solid-phase radioimmunoassay); glucose, triglycerides, HDL cholesterol, and total cholesterol (photometric methods on a Vitros 950 IRC analyzer, Ortho Clinical Diagnostics); calculated LDL cholesterol. Two-hour

postprandial measurements of glucose and insulin following ingestion of 75-gram dextrose (Trutol® 100, Custom Laboratories, Baltimore, MD) were done at the time of the initial visit and at the ending of the 8-week trial period. Routine serum liver and kidney profile tests were also included: bilirubin, SGOT, SGPT, urea nitrogen, and creatinine (Vitros 950 IRC analyzer, Ortho Clinical Diagnostics).

Data Analysis

The majority of the data was analyzed by standard statistical methods using a one-tailed, paired t-test analysis (Microsoft® Excel) for comparison of baseline values with those at the end of the 8-week trial. Mean values and standard errors are reported. The parameters included in this analysis were: BMI, body weight, WHR, percent body fat, fasting glucose, fasting insulin, glucose/insulin ratio, 2-hour postprandial glucose, 2-hour postprandial insulin, and lipid profile parameters (triglycerides, total cholesterol, HDL cholesterol, cholesterol/HDL cholesterol ratio, and LDL cholesterol).

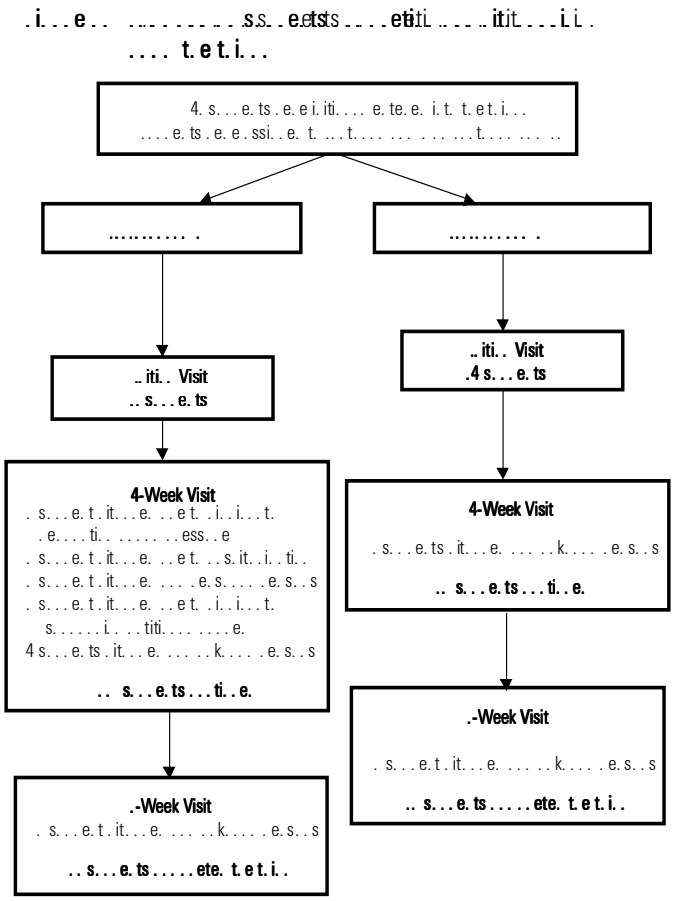
Parameters that were measured as concentration (e.g., fasting glucose) and body weight were transformed to logarithms prior to the analysis. Data shown in the table are the arithmetic means. For the MSQ questionnaire data, percent change was determined as follows: Percent MSQ Change = [(initial MSQ score – final MSQ score)/ initial MSQ score] x 100. Individuals for whom both initial and final data were not recorded were excluded from the data analysis.

RESULTS

Subjects completing and withdrawing from the trial

Sixteen of the twenty-five subjects who started Protocol A completed the 8-week program. Of the nine subjects who did not complete the trial, six chose to withdraw for unknown reasons, one due to hospitalization for an unrelated condition, one due to unusual blood pressure variations, and one due to intolerance of the powdered product.

Twenty-one of the twenty-four subjects who started Protocol B completed the 8-week program. Three subjects chose to withdraw from the trial without offering an explanation. There was no significant statistical difference between the number of withdrawals for each protocol. Figure 1 summarizes this information.



Weight, Shape, and Body Fat Analysis

Table 2 presents the results of the data analysis for both protocol arms related to BMI, body weight, percent body fat, waist and hip measurements, and WHR. While moderate improvement was seen in the measured parameters for subjects in both groups, the calculated WHR remained virtually unchanged for both protocol arms. These results were not unexpected given the limited duration of the study.

Table 2. Weight, Shape, and Body Fat Analysis. Values shown are the arithmetic means and the standard errors obtained in each category for N number of individuals in Protocol A or B.

Category	N	Protocol A mean ± SE		N	Protocol B mean ± SE	
		baseline	week 8		baseline	week 8
BMI	16	40.5 ± 1.9	39.5 ± 2.1**	21	38.5 ± 1.3	32.0 ± 1.3**
body weight (lbs)	16	251.4 ± 14.3	245 ± 14.8**	21	235 ± 10.4	225.7 ± 9.9**
percent body fat	16	42.7 ± 1.7	40.3 ± 1.6*	21	39.6 ± 1.6	38.2 ± 1.5**
waist (in)	15	43.9 ± 1.4	42.6 ± 1.4**	21	43.5 ± 1.3	41.2 ± 1.1**
hips (in)	15	51.5 ± 1.4	49.6 ± 1.5**	21	50.1 ± 1.3	47.5 ± 1.2**
WHR	15	0.85 ± 0.02	0.86 ± 0.02	21	0.87 ± 0.02	0.87 ± 0.02

*- 0.01□p<0.05 ** p<0.01

Questionnaire Results

The average MSQ value for subjects on Protocol A was 48 at the start of the trial and decreased to 17 by the eighth week. Subjects in Protocol B started at an average of 34 and ended at an average of 12. This represents an equal and statistically significant 64 percent improvement in symptoms for both groups, indicating that both trial arms had a positive effect on the subjects' perceived quality of life, as experienced through intensity, duration, and frequency of symptoms. The other questionnaires, used primarily to assess subjects' compliance to the program and tolerance to the product, did not show differences between the two groups. Subjects generally tolerated the products well (data not shown).

Laboratory Analysis

Table 3 summarizes the results of the statistical analysis of the laboratory parameters. To qualify for the trial, subjects were screened to fit the inclusion criteria on the basis of a glucose/insulin ratio of less than or equal to six (data not shown). Baseline values were again measured at the commencement of the trial for fasting insulin and glucose. Assessment of these lab parameters through the course of the trial was done in batch at the end of the trial, on frozen specimens.

Fasting glucose did not change for subjects in either protocol. Fasting insulin and postprandial insulin, as well as glucose and the glucose/insulin ratio, were significantly improved in the 8-week period for subjects in both protocols. However, although both improvements were statistically significant, percent decline in fasting insulin was greater in Group A.

Interesting differences were seen between the groups with respect to the lipid parameters. Although total cholesterol decreased in both groups A and B, the changes did not reach statistical significance for either. A modest increase in HDL cholesterol was observed for Group A, while a decline was shown by Group B. Additionally, both the LDL cholesterol and the total cholesterol/ HDL cholesterol ratio decreased in Group A but did not change in Group B. Lastly, although a substantial decrease was observed for the triglycerides in Group A (14 percent), statistical significance could not be demonstrated due to the high inter-subject variability; no meaningful change was seen in Group B subjects.

It should be noted that LDL cholesterol calculations were not performed if triglycerides were out of range, and one subject was excluded from the analysis for HDL cholesterol due to an insufficient serum sample. Liver and kidney function tests performed at the beginning and at the conclusion of the trial showed no significant changes; therefore these results are not reported.

Table 3. Analysis of Biochemical Parameters. Values shown are the arithmetic means and the standard errors obtained in each category for N number of individuals in Protocol A or B.

Parameter	N	Protocol A mean ± SE baseline	Protocol A mean ± SE week 8	N	Protocol B mean ± SE baseline	Protocol B mean ± SE week 8
fasting glucose (mg/dL)	16	104.1 ± 9.9	102.3 ± 7.3	21	100.0 ± 4.0	96.9 ± 2.4
fasting insulin (□U/mL)	16	22.7 ± 4.1	16.3 ± 2.1 **	21	18.8 ± 1.5	15.1 ± 1.5**
glucose/insulin (mg/□U)	16	6.3 ± 0.8	8.5 ± 1.8*	21	6.2 ± 0.6	8.3 ± 1.0**
glucose (mg/dL) **2-hr postprandial**	16	134.3 ±16.0	125.6 ± 15.3	21	140.8 ± 9.3	131 ± 8.4
insulin (□U/mL) **2-hr postprandial**	16	111.0 ± 25.8	71.5 ± 18.3**	21	133.7 ± 19.9	100.7 ± 7.2**
cholesterol (mg/dL)	16	216.7 ± 13.0	203.0 ± 9.6	21	203.1 ± 6.0	184.8 ± 7.5
HDL cholesterol (mg/dL)	16	41.2 ± 2.5	44.4 ± 2.9	20	48.2 ± 2.4	42.8 ± 2.
cholesterol/ HDL cholesterol	16	5.5 ± 0.5	4.9 ± 0.4*	20	4.3 ± 0.2	4.1 ± 0.2
LDL cholesterol (mg/dL)	12	119.8 ± 8.5	112.4 ± 8.6*	17	117.8 ± 7.2	111.9 ± 8.4
triglycerides (mg/dL)	16	323.8 ± 63.1	277.9 ± 53.1	21	243.0 ± 58.1	250.9 ± 61.5

*- 0.01□p<0.05 ** p<0.01

DISCUSSION

Insulin resistance may be defined as a state in which greater than normal amounts of insulin are required to elicit a quantitatively normal response.[25] Adequate insulin secretion is necessary for proper glucose disposal and management. However, excessive secretion occurs under conditions in which normal insulin action is impaired. Secondary to this insulin resistance, the compensatory hyperinsulinemia causes a cascade of biochemical events, as mentioned in "Introduction."[26] This dysregulation is surprisingly common, and may be seen in as many as 25 percent of a normal non-diabetic population.[27] Unfortunately, this compensatory hyperinsulinemia results in increased risk of diabetes, heart disease, and stroke.[28] The economic costs of treating these end-stage disorders are obviously enormous. Recognition and early treatment are, therefore, essential.

Direct measurement of insulin resistance can be performed using infusions of somatostatin, insulin and glucose.[29] While exacting, this is an unrealistic way to assess insulin resistance in clinical practice. Laboratory parameters can be key screening tools to indirectly measure insulin resistance.[30] Triglycerides and HDL cholesterol are particularly valuable indicators within the lipid profile since they are significantly impacted by hyperinsulinemia, with triglycerides elevated and HDL cholesterol depressed in the insulin-resistant individual.[31] In the individual who has adequately compensated with increased insulin secretion, glucose measurements are not useful prognosticators of the degree of insulin resistance. Serum insulin measurements can offer useful information.[32,33]

Our experience suggests that the best practical measures of insulin resistance and hyperinsulinemia are fasting and 2-hour postprandial (following a 75-gram glucose challenge) serum insulin values. Elevations of serum insulin above 15 □U/mL fasting and/or 50 □U/mL postprandial signify increased insulin secretion secondary to insulin resistance (unpublished observations).

Other additional clinical assessments of the insulin-resistant patient can be performed easily. Measurements of physical parameters such as weight, BMI and WHR are useful to predict the individual's risk to insulin resistance. While obesity may not itself cause insulin resistance, it can exacerbate it; and individuals with BMIs over 30 are at increased risk. Central obesity, with a WHR greater than 1 for men and 0.8 for women, is a predictor of increased insulin resistance. A

combination of increased BMI and elevated WHR is correlated even more strongly with insulin resistance.[34] Assessment of percent body fat by in-office bioelectrical impedance analysis offers a specific and often useful measure of adiposity.

It appears that at the core of this insulin resistance is a defect in cellular sensitivity to insulin. As more light has been shed on this disturbance, it is suggested that direct focus be placed on this underlying metabolic dysregulation.[35] Although the cellular disturbance is not completely understood, modifiable factors such as obesity, exercise and nutrition appear to have significant effects. While genetic background may determine propensity to the disorder, these aforementioned factors should be part of any comprehensive clinical management strategy to reduce its phenotypic expression.

A variety of macro- and micronutrients have been shown to have an effect on insulin and glucose regulation. For our trial, we combined some of these nutritional factors into a powder and supplement combination to assess the degree of improvement above a standard weight-loss program. The powdered beverage used closely matched a similar reported beverage in terms of calories and protein/carbohydrate/fat ratio. We concluded that since the calories and ratios were similar, the only other factor that could account for the results were the specific types of macronutrients that were used in the tested products.

Both groups experienced expected weight loss. Our findings suggest that over eight weeks there was a significant positive trend in both lipid and insulin values of the subjects following Protocol A. We observed a statistically significant improvement in triglycerides and total cholesterol in Protocol A but not in Protocol B. Additionally, triglyceride/HDL cholesterol ratio, which may be a useful indicator of insulin resistance, also showed a statistically significant decrease in those individuals who exhibited elevations (> 5.0) at the beginning of the trial. Nine subjects in group A exhibited an elevated triglyceride/HDL cholesterol ratio. In this group, the average value at week 0 was 14.6. After 8 weeks of therapy, the ratio dropped to 11.0 ($p < 0.05$). Eight subjects in group B exhibited an elevated triglyceride/HDL cholesterol ratio. The average value at week 0 was 10.5 in this group. After 8 weeks of the program the ratio was 10.3 ($p > 0.05$). While there was statistically significant improvements in both groups in terms of fasting insulin and 2-hour postprandial insulin, the percent decrease in the former was greater in the nutrient-supplemented group.

In conclusion, our findings suggest that, in accordance with previous studies, weight loss has a salutary effect on insulin resistance. The addition of specific macro- and micronutrients consumed by the subjects in Group A appeared to increase the improvement over the eight-week trial. While the effect was modest, it was statistically significant and suggests a benefit is derived from this combination of macro- and micronutrients. Larger and longer trials may be necessary to further assess the effects of such an approach.

Acknowledgements

We thank Julie Triggs for clinical assistance; Tracey Irving for preparation of the investigational products; and Mabel Lorenzi-Albé for assistance in preparation of the manuscript. We also thank DeAnn Liska, PhD, for technical review of the manuscript, and Jeffrey S. Bland, PhD, for critical comments and support of this project.

References

1 Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37:1495-1507.
2 Adamo M, LeRoith D, Simon J, Roth J. Effect of altered nutritional states on insulin receptors. Ann Rev Nutr. 1988;8:149-166.
3 Krezowski PA, Nuttall FQ, Gannon MC, Bartosh NH. The effect of protein ingestion on the metabolic response to oral glucose in normal individuals. Am J Clin Nutr. 1986;44: 847-856.
4 Philipson H. Dietary fibre in the diabetic diet. Acta Med Scand. 1983;671(suppl):91-93.
5 Landin K, Holm G, Tengborn L, Smith U. Guar gum improves insulin sensitivity, blood lipids, blood pressure, and fibrinolysis in healthy men. Am J Clin Nutr. 1992;56:1061-1065.
6 Chait A. Dietary management of diabetes mellitus. Contemp Nutr. 1984:9:2.
7 Howe JC, Rumpler WV, Behall KM. Dietary starch composition and level of energy intake alter nutrient oxidation in "carbohydrate-sensitive" men. J Nutr. 1996;126:2120-2129.

[8] Behal KM, Howe JC. Effect of long-term consumption of amylose vs. amylopectin starch on metabolic variables in human subjects. Am J Clin Nutr. 1995;61:334-340.
[9] Paolisso G, D'Amore A, Giugliano D. Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. Am J Clin Nutr. 1993;57:650-656.
[10] Paolisso G, Gambardella A, Giugliano D, et al. Chronic intake of pharmacological doses of vitamin E might be useful in the therapy of elderly patients with coronary heart disease. Am J Clin Nutr. 1995;61:848-852.
[11] Zhang H, Osada K, Maebashi M, et al. A high biotin diet improves the impaired glucose tolerance of long-term spontaneously hyperglycemic rats with non-insulin-dependent diabetes mellitus. J Nutr Sci Vitaminol. 1996;42:517-526.
[12] Anderson R, Cheng N, Bryden, et al. Beneficial effects of chromium for people with type II diabetes. Diabetes. 1996;45:124A.
[13] Evans GW, Bowman TD. Chromium picolinate increases membrane fluidity and rate of insulin internalization. J Inorg Bio. 1992;46:243-250.
[14] Jacob S, Henriksen EJ, Schiemann AL, et al. Enhancement of glucose disposal in patients with type 2 diabetes by alpha-lipoic acid. Arzneim-Rorsch Drug Res. 1995;45(8):872-874.
[15] Jacob S, Streeper RS, Fogt DL, et al. The antioxidant a-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle. Diabetes. 1996;45:1024- 1029.
[16] Paolisso G, Sgambato S, Gambardella A, et al. Daily magnesium supplements improve glucose handling in elderly subjects. Am J Clin Nutr. 1992;55:1161-1167.
[17] Paolisso G, Barbagallo M. Hypertension, diabetes mellitus, and insulin resistance: the role of intracellular magnesium. Am J Hypertens. 1997;10:346-355.
[18] Shechter Y, Li J, Meyerovitch J, et al. Insulin-like actions of vanadate are mediated in an insulin-receptor-independent manner via non-receptor protein tyrosine kinases and protein phosphotyrosine phosphatases. Mol Cell Biochem. 1995;153:39-47.
[19] Halberstam M, Cohen N, Shlimovich P, et al. Oral vanadyl sulfate improves insulin sensitivity in NIDDM but not in obese nondiabetic subjects. Diabetes. 1996;45:659-666.
[20] Behall KM, Howe JC. Effect of long-term consumption of amylose vs. amylopectin starch on metabolic variables in human subjects. Am J Clin Nutr. 1995;61:1334-1340.
[21] U.S. Patent # 5,695,803.
[22] Feldman N, Norenberg C, Voet H, Manor E, Berner Y, Madar Z. Enrichment of an Israeli ethnic food with fibres and their effects on the glycaemic and insulinaemic responses in subjects with non-insulin-dependent diabetes mellitus. Br J Nutr. 1995;74:681-688.
[23] Zavoral JH, Hannan P, Fields DJ, et al. The hypolipidemic effect of locust bean gum food products in familial hypercholesterolemic adults and children. Am J Clin Nutr. 1983;38:285-294.
[24] American Diabetes Association, Inc., The American Dietetic Association. Exchange lists for meal planning. 1986.
[25] Flier J. An overview of insulin resistance. In: Moller DE, ed. Insulin Resistance. Chichester, U.K.; Wiley: 1993.
[26] Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37:1495-1507.
[27] Reaven, GM. Pathophysiology of insulin resistance in human disease. Physiological Reviews. 1995;75(3):473-485.
[28] Reaven. GM. Role of insulin resistance in human disease. Diabetes. 1988;37:1495-1507.
[29] Facchini F, Humphreys MH, Jeppesen J, Reaven GM. Measurements of insulin-mediated glucose disposal are stable over time. J Clin Endocrinol Metab. 1999; 84(5):1567-1569.
[30] Reaven, GM. Pathophysiology of insulin resistance in human disease. Physiol Rev. 1995;75(3):473-485.
[31] Tobey TA, Greenfield M, Kraemer F, Reaven GM. Relationship between insulin resistance, insulin secretion, very low-density lipoprotein kinetics and plasma triglyceride levels in normal triglyceridemic men. Metabolism. 1981;30:165-171.
[32] Flier J. An overview of insulin resistance. In: Moller DE, ed. Insulin Resistance. Chichester, U. K.; Wiley: 1993.
[33] Zavaroni I, Mazza S, Dall'aglio E, et al. Prevalence of hyperinsulinaemia in patients with high blood pressure. J Int. Med. 1992;231:235-240.
[34] Vanhala MJ, Pitkajarvi TK, Kumpusalo EA, Takala JK. Obesity type and clustering of insulin resistance-associated cardiovascular risk factors in middle aged men and women. Int J Obes Relat Metab Disord. 1998;22(4):369-374.
[35] Ruderman, N, Chisholm D, Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. Diabetes 1998;47:699-713.