



RESEARCH ARTICLE

Incretins and Cardiovascular Effects of Weight Loss and Remission of Prediabetes

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Abstract

Aim and Background: The incretins GLP-1 and GIP have important roles in insulin sensitivity and have been shown to be effective in pharmacological treatment of Type 2 Diabetes and improvement in Cardiovascular Risk Factors (CVRF). Ghrelin has been shown to be associated with satiety. Therefore, we studied the GLP-1, GIP, Ghrelin and BNP changes with weight loss and remission of prediabetes.

Methods and Results: 24 obese women and men with prediabetes were recruited and randomized to either a High Protein (HP) (n=12) or High Carbohydrate (HC) (n=12) diet for 6 months with all food provided. OGTT and MTT were performed and GLP-1, GIP, Ghrelin, BNP, insulin and glucose were measured at baseline and 6 months on the respective diets.

Author's studies showed that subjects on the HP diet had 100% remission of prediabetes compared to only 33% on the HC diet with similar weight loss.

HP diet subjects had a greater increase in (1) OGTT GLP-1 AUC (p=0.001) and MTT GLP-1 AUC (p=0.001), (2) OGTT GIP AUC (p=0.005) and MTT GIP AUC (p=0.005), and a greater decrease in OGTT ghrelin AUC (0.005) and MTT ghrelin AUC (p=0.001) and BNP (p=0.001) compared to the HC diet at 6 months.

Conclusions: This study demonstrates that the HP diet increases GLP-1 and GIP which may be responsible in part for improved insulin sensitivity and β cell function compared to the HC diet. HP ghrelin results demonstrate the HP diet can induce satiety more effectively than the HC diet. BNP and other CVRF, metabolic parameters and oxidative stress are significantly improved compared to the HC diet.

Keywords: Incretins, BNP, Cardiovascular Risk Factors (CVRF), Weight loss, High protein diet, High carbohydrate diet, Insulin sensitivity, Remission of prediabetes, Oxidative stress

Introduction:

The incretins, Glucose-dependent Insulinotropic Peptide (GIP) and Glucagon Like Peptide -1 (GLP-1) are potent glucose-dependent stimulators of insulin secretion at physiological levels [1]. In addition to secreting insulin in response to ingestion of glucose or fat, GLP-1 and GIP are also involved in fat metabolism and promotion of β -cell proliferation and survival [2,3]. Studies have shown that Type 2 Diabetes subjects have impaired regulation of incretins [4]. Because of the central role of β -cell function in the pathophysiology of Type 2 Diabetes, one of the goals of therapy for Type 2 Diabetes Mellitus should be preventing the deterioration of β -cells that leads to more serious complications. GLP-1 receptor agonists have been shown to have positive effects on the B-cells of the pancreas [2,5-8] and are beneficial drugs for the treatment of Type 2 Diabetes [9, 10]. Treatments with GLP-1 agonists have also been shown to have beneficial cardiovascular effects [11-14]. However, treatment with these incretin drugs has not been without side effects and poor adherence in some cases [15,16]. Therefore, methods of increasing secretion of incretins rather than pharmaceutical means could be beneficial to the patients.

GLP-1, GIP and gastrin have been shown to be significantly increased with a high protein (HP) diet (30% protein, 30% fat and 40% carbohydrate) compared to a high carbohydrate (HC) diet (15% protein, 30 % fat and 55% carbohydrate) in obese premenopausal women [17]. Additionally, hunger suppression and increased satiety have been observed with a high protein diet [18-21]. Ghrelin has been shown to be associated with satiety and HP diets are thought to provide greater satiety [22]. Any diet that leads to an increase in secretion of GLP-1 or GIP could be beneficial in preventing the progression of Type 2 Diabetes Mellitus and/or remission of prediabetes.

The increase in the number of overweight and obese individuals is an alarming trend that has far-reaching health consequences for the US. Obesity has been related to increased risk for diabetes, cardiovascular disease, and a host of other medical problems

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Received: Aug 19, 2020; **Accepted:** Sept 02, 2020; **Published:** Sept 04, 2020

[23]. Behavioral changes in diet and exercise have been shown to be very effective in reduction of obesity. However, these changes often can be difficult for patients, leading to a lack of compliance [24]. In addition, there is an absence of evidence for the superiority of one diet over another. Also, the long-term adherences to such weight loss regimens in general have been poor [25]. Thus, a palatable diet providing satiety as well as essential nutrients may go a long way in treating overweight individuals. Studies comparing a moderately High Protein diet (HP) vs. a High Carbohydrate (HC) diet have shown the HP diet provides greater improvement in insulin sensitivity, cardiovascular risk factors, oxidative stress, and inflammatory cytokines than the high carbohydrate (HC) diet where all food was provided for the 6 month studies [18,21].

The purpose of this study is to evaluate the effects of a moderately high protein (HP) diet compared to a high carbohydrate (HC) diet for 6 months on metabolic parameters in obese, prediabetes subjects with 500 kcal intake/day restriction based on each subjects resting metabolic rate (RMR). In particular, the effects of both diets on glucose metabolism, insulin sensitivity, which we previously have reported [18], and effects on the incretins (GLP-1 and GIP), satiety (ghrelin) and cardiovascular factors including Brain Natriuretic Peptide (BNP). GLP-1, GIP and ghrelin responses to Oral Glucose Tolerance Test (OGTT) and Meal Tolerance Test (MTT) using a HP or HC meal at baseline and after 6 months on the HP or HC diets were compared.

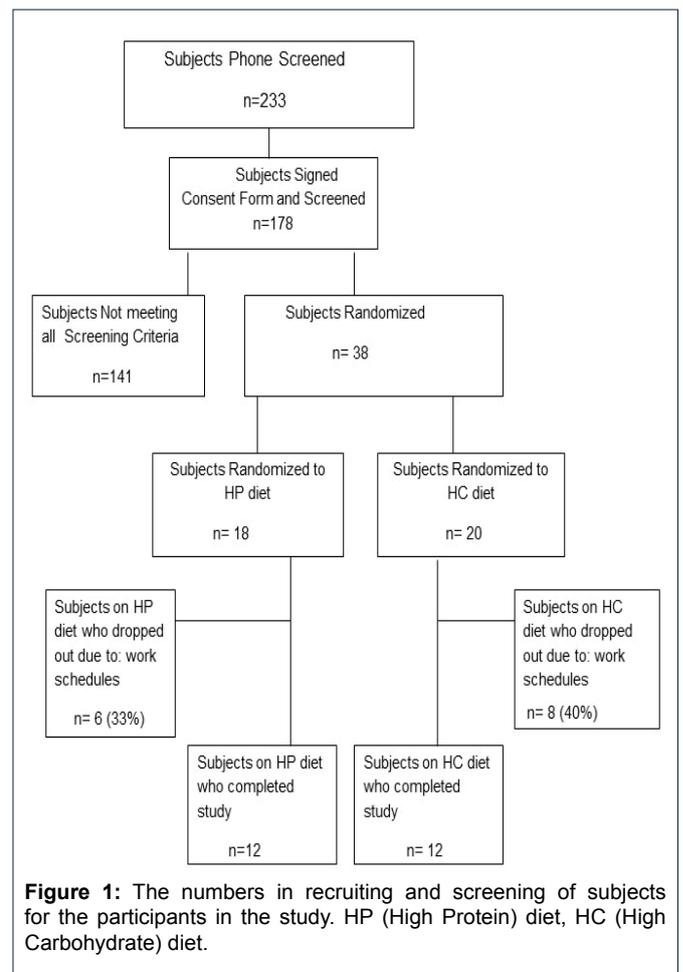
Dr. Stentz et al. hypothesized that: a moderately high-protein (HP) diet (30% protein, 30% fat, and 40% carbohydrate) would result in different incretin and satiety responses than a high-carbohydrate (HC) diet (55% carbohydrate, 30%fat, 15% protein); and the GLP-1 response may improve cardiovascular factors (CFs) such as BNP, a polypeptide released by the ventricles in the heart after excessive stretching of cardiomyocytes.

Methods:

Study population

Twenty four prediabetes female and male subjects ages 20 to 50 years with BMI ≥ 30 to ≤ 55 kg/m² were randomized to the HP or HC diet for 6 months and monitored at weekly intervals. Inclusion criteria included age, BMI, fasting glucose <126 mg/dl and 2 hr Oral Glucose Tolerance Test (OGTT) glucose <200 mg/dl. A 75 gm OGTT and MTT (HP or HC diet) were done at baseline and 6 months. Exclusion criteria consisted of surgical or premature menopause, history of liver disease, abnormal liver function tests, thyroid disease, diabetes, elevated creatinine (>1.5 mg/dl), weight >350 lbs, triglycerides >400 mg/dl, medications known to affect lipid or glucose metabolism, pregnancy or plan on pregnancy in next 6 months, history of cancer undergoing active treatment, smoking, as previously described [18]. Figure 1 shows the recruiting process.

The study was a prospective randomized trial of an HP diet versus HC diet with all food provided for the 6 months. The study was



approved by the University of Tennessee Health Science Center (UTHSC) Institutional Review Board. All participants were studied at the Clinical Research Center at UTHSC. After signing the consent form a history and physical examination, weight, height, blood pressure and waist circumference were performed. Study participants underwent a 75 gm OGTT and Mixed Meal Test (MMT) (HP or HC diet) with glucose, insulin and other metabolites measured at 30 minute intervals for 2 hours. These tests were performed after a 12 hour fast at baseline and after the 6 month diet intervention. Chemistry profile, complete blood count, lipid profile, dual energy X-ray absorptiometry (DXA) scan, and Resting Metabolic Rate (RMR) were performed at baseline and 6 months. Creatinine Clearance, microalbumin and urinary urea nitrogen (UUN) were done on 24 hour urine collection at baseline and 6 months.

Diets

These diets were as we previously have described [18] and consistent with the guidelines of the Institute of Medicine and American Diabetes Association [10]. Briefly, the diets were designed as a 500 Kcal reduction from each subject's RMR as determined using a Cardio Coach (Koor Medical Technologies) for weight loss. Meals were provided by pre-packaged foods on a weekly basis with daily meal plans for enhanced diet compliance. Participants were required to return their weekly meal plan record when they returned for the next week food pick up for compliance of diet adherence.

Weight loss of 1-2 lbs per week was targeted over the 6 month duration of diet intervention in each group.

Both diets were designed to minimize participants' health risks. Recommended daily intake of vitamins and minerals were met with both the HP and HC diet. Nutrition adequacy was assessed using nutrition software of the University of Minnesota Nutrition Data System for Research. Both diets provided more than the recommended amount of calcium (1,000 mg/day) [26]. Monounsaturated and polyunsaturated fats were the main fats types, i.e. nuts and plant oils, and dietary carbohydrates included mostly whole grains, fruits and vegetables. Sources of dietary protein included fish, lean meats, chicken, eggs and low fat dairy foods. All foods were readily available at local grocery stores.

The HP diet consisted of Cedarlane™ “The Zone” frozen meals as well as tuna, salmon, and mahi mahi burgers served with Rudi's whole wheat organic bun. In between meal snacks included high protein shakes and Zone Perfect Bars.

The HC diet entrees consisted of Lean Cuisine (LC) pizzas, five cheese rigatoni; Weight Watcher's chicken enchilada, chicken parmesan; and Amy's organic bean and cheese burrito. Between meal snacks included Slim Fast Optima shakes and Slim Fast meal bars.

Both diets included 1 cup of frozen vegetables for lunch and dinner with choice of broccoli, cauliflower, carrots, green beans, Brussels sprouts, or “California” blend vegetables. Each breakfast had a variety of cold and hot cereals with 2% milk or eggs and toast and canned peaches, mixed fruit or apple sauce.

Determination of plasma metabolic hormones and cardiovascular risk factor markers

Blood samples for GLP-1 and GIP were collected in EDTA tubes containing DPP4 inhibitor. Ghrelin was collected in citrate tubes. BNP, hsCRP and insulin were collected in EDTA and heparin tubes, respectively. All tubes were immediately put on ice and centrifuged at 4°C. The plasma was then immediately removed, aliquoted into tubes and frozen at -80°C until the respective assays performed. Active GLP-1, GIP, ghrelin, and BNP were performed by immunoassays using EMD Millipore Multiplex reagents on the Multiplex/Luminex instrument (Billerica, MA). Insulin and hsCRP were assayed by immunoassay using the Siemens Immulite (Deerfield, IL). Glucose was determined using the glucose oxidase method and inflammation markers and oxidative stress markers were assayed as we have previously reported [18,21,27]. All assays were by established procedures in the UTHSC Endocrinology/Lipoprotein laboratory, a CMS, CAP and State of Tennessee licensed laboratory.

GLP-1, GIP, Ghrelin, insulin, and glucose levels were measured for the 2 hr OGTTs and 2 hr MTTs for the 0, 30, 60, 90, and 120 minute plasma samples at baseline and after 6 months on the diets and areas under the curve (AUC) were calculated using the Trapezoidal rule. BNP levels were measured at baseline and at 6 months.

Insulin Sensitivity and B-cell function

Insulin resistance was determined by HOMA-IR [28]. Plasma glucose and insulin measurements of the 2 hour OGTT were used to determine the insulin sensitivity (ISI) using by the Matsuda index [29]. Beta-cell function was calculated as the index of insulin secretion factored by insulin resistance ($\Delta I_{0-120}/\Delta G_{0-120} \times \text{Matsuda index}$) during the OGTT as preciously described [18,30].

Statistical Analysis:

Statistical Analysis was as described in our previous paper [18]. Changes between the two arms (HP vs. HC diets) were compared using Wilcoxon rank-sum test to compare the effects of the two diets. Also, Wilcoxon signed-rank test was used to compare baseline and 6 month data to assess the effects of the diets.

Effectiveness of randomization was assessed with the Wilcoxon rank-sum test to compare baseline variables between the two arms. A p value of <0.05 was considered statistically significant. If important baseline differences were identified they were included in analysis using generalized linear models. The Mean + SE were calculated and Wilcoxon rank sum tests used to compare variables between the two diet groups and Wilcoxon Signed Rank Test to compare baseline and 6 months where $p < 0.05$ was considered statistically significant.

Results:

At baseline there were no statistically significant differences between the 24 subjects with respect to age, sex, ethnicity, BMI, HbA1c, fasting insulin and glucose (all p-values > 0.05). Table 1 show the mean \pm SE for the various parameters monitored at baseline (BL) and after 6 months on the respective HP or HC diets. The HP and HC groups were not statistically different at baseline. However, of important significance, after 6 months on the HP diet, the HP diet group had 100% or remission of prediabetes; whereas, only 33% of the HC diet group had remission of prediabetes as we have reported in our previous publication [18]. Compliance to the HP or HC diets for the 6 months was 93 ± 1.6 and 94 ± 2.1 % respectively, not statistically different. Both diet groups had significant weight loss at 6 months from baseline HP ($9.8 \pm 1.4\%$) and HC (11.3 ± 1.8 %) but were not significantly different between the HP and HC groups at 6 months. The glucose area under the curve (AUC) for the OGTT for the HP and HC groups was not statistically different at baseline and decreased significantly in both the HP and HC groups. However, the OGTT AUC decreased significantly more at 6 months in the HP diet than the HC diet group. Insulin sensitivity (HOMA IR), Beta cell function and HbA1c were all significantly improved at 6 months in both diet groups; however, the HP diet group had significantly greater improvement in these parameters at 6 months compared to the HC diet group. Lean Mass (LM) percent was significantly increased in the HP diet group at 6 months; whereas, the HC diet group lost significant LM. Both diet groups lost significant Fat Mass (FM) after 6 months on the diets.

Table 1: Effects of HP or HC Diets on Insulin Sensitivity, B Cell Function, Cardiovascular Risk Factors including BNP, Oxidative Stress, Weight Loss and Remission of Prediabetes.

Parameters	High Protein Diet (n=12)			Carbohydrate Diet (n=12)			p**
	Baseline	6 months	p*	Baseline	6 months	p*	
% Remission		100			33.3		0.001
Age	43.1 ± 1.3			41.1 ± 1.7			0.96
Ethnicity AA/C	10/2			9/3			
Female/Male	9/3			10/2			
BMI (kg/m ²)	40.5 ± 1.8	37.3 ± 1.9	<0.001	37.4 ± 1.7	33.8 ± 1.6	0.002	0.391
% LM change		+ 2.55 ± 0.3	0.001		- 3.02 ± 0.4	0.005	<0.001
% FM change		- 2.49 ± 0.3	0.006		- 3.55 ± 0.4	0.005	0.01
Waist (cm)	112.5 ± 3	105.2 ± 2.6	0.001	110.7 ± 3.4	103.5 ± 4	0.001	0.24
Insulin Sensitivity							
HbA1c %	6.0 ± 0.015	5.46 ± 0.12	0.0005	5.93 ± 0.12	5.73 ± 0.17	0.005	<0.0001
HOMA IR	4.79 ± 0.71	1.58 ± 0.38	0.0005	4.74 ± 0.72	3.34 ± 0.78	0.005	<0.0001
ISI (Matsuda index)	2.3 ± 0.3	6.5 ± 1.1	0.0005	2.3 ± 0.3	3.2 ± 0.4	0.005	0.003
B-cell Function	3.74 ± 0.3	11.24 ± 2.1	0.0005	3.79 ± 0.3	5.68 ± 0.6	0.005	0.001
Glucose AUC-OGTT	20715 ± 529	14745 ± 386	0.0005	20685 ± 541	18720 ± 422	0.001	0.0001
Insulin AUC-OGTT	14160 ± 314	5575 ± 210	0.0005	14145 ± 326	10590 ± 289	0.005	0.0001
Glucose AUC-MTT	13275 ± 286	11775 ± 210	0.0005	15545 ± 297	14505 ± 273	0.01	0.0001
Insulin AUC-MTT	5325 ± 164	2970 ± 135	0.001	7801 ± 219	7035 ± 215	0.02	0.0001
Cardiovascular Risk Factors							
BP (sys/diast)	130/81 ± 3/2	116/72 ± 2/2	0.01/0.01	126/81 ± 3/2	118/74 ± 3/3	0.01/0.01	0.73/ 0.77
hsCRP (mg/L)	7.9 ± 0.4	3.9 ± 0.3	0.001	7.5 ± 0.4	5.7 ± 0.3	0.02	0.001
FFAs (mmol/L)	0.60 ± 0.04	0.47 ± 0.03	0.002	0.61 ± 0.03	0.78 ± 0.06	0.038	0.001
BNP (pg/ml)	149.2 ± 2.3	55.9 ± 2.8	0.003	148.6 ± 2.9	89.6 ± 3.1	0.02	0.001
Oxidative Stress and Inflammation							
MDA (umol/L)	1.9 ± 0.08	0.8 ± 0.06	0.0005	1.8 ± 0.06	1.3 ± 0.05	0.01	0.001
IL-1β (pg/ml)	10.8 ± 0.7	2.9 ± 0.4	0.001	10.9 ± 0.08	7.4 ± 0.07	0.01	0.002

P* indicates Wilcoxon Signed Rank Test for comparison of Baseline to 6 months; P** indicates Wilcoxon Rank Sum Test for 6 months comparison of HP vs. HC. HP, High Protein; HC High Carbohydrate; AA, African American; C, Caucasian; BMI, Body Mass Index; BP, Blood Pressure; HbA1C, Hemoglobin A1C; IL-1 β, Interleukin 1β; MDA, Malondialdehyde; hsCRP, high sensitivity CRP; FFA, Free Fatty Acids; BNP, Brain Natriuretic Peptide.

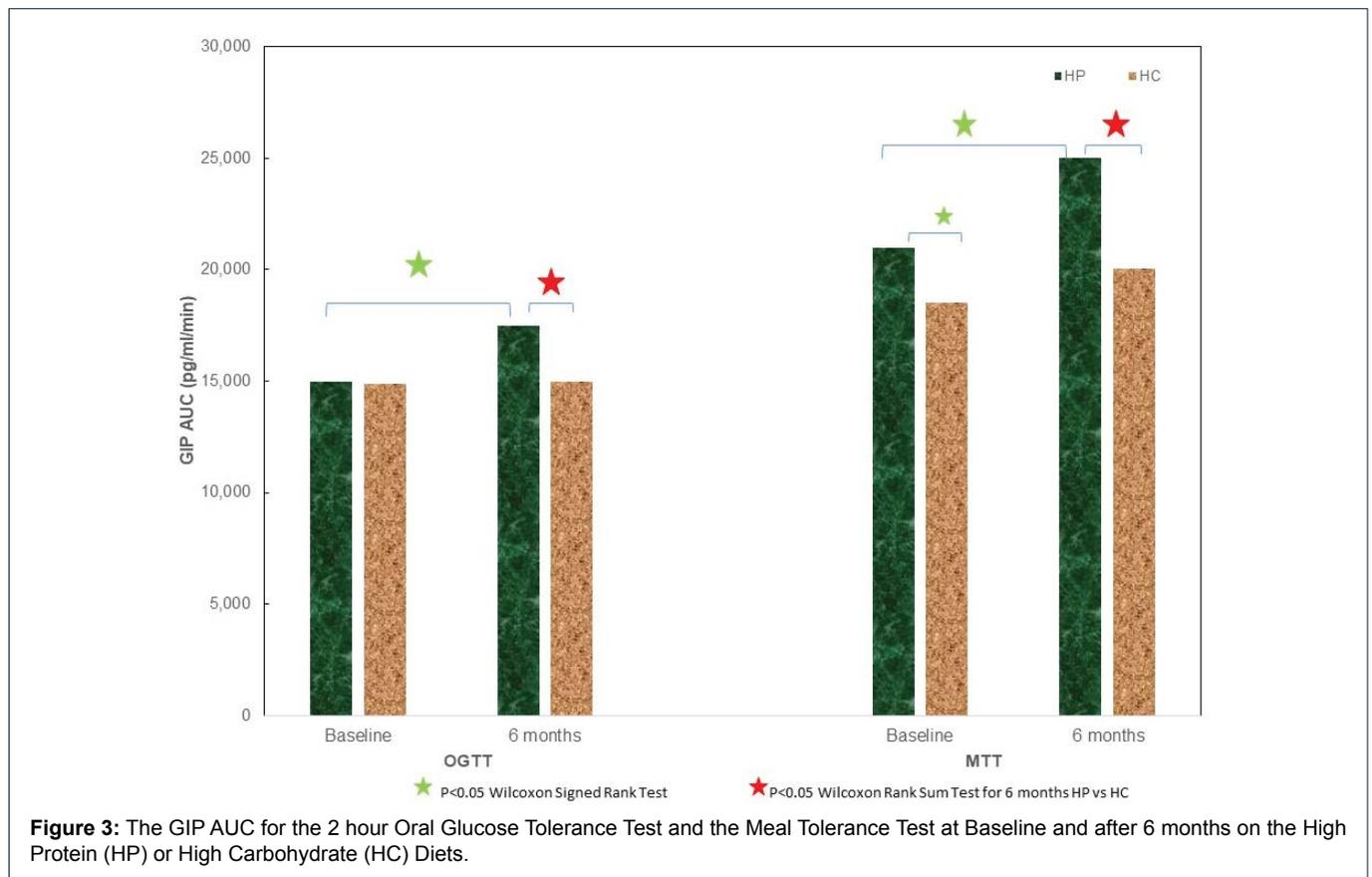
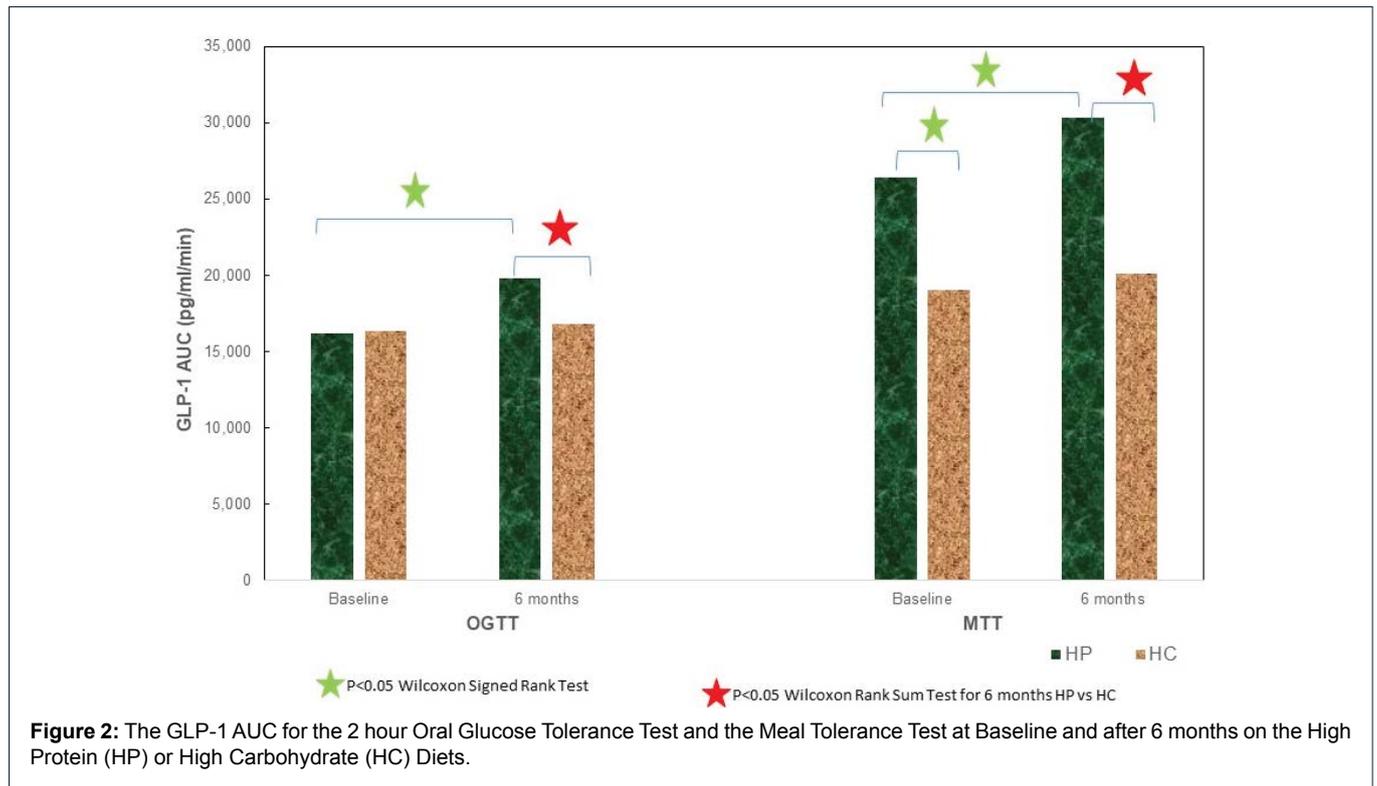
Both the HP and HC diet groups had a significant decrease in waist measurements but not significantly different between diet groups after six months on the diets. The HP diet subjects had a significant decrease in oxidative stress as measured by lipid peroxidase (malondialdehyde) and inflammation (IL-1B) at 6 months compared to the HC subjects.

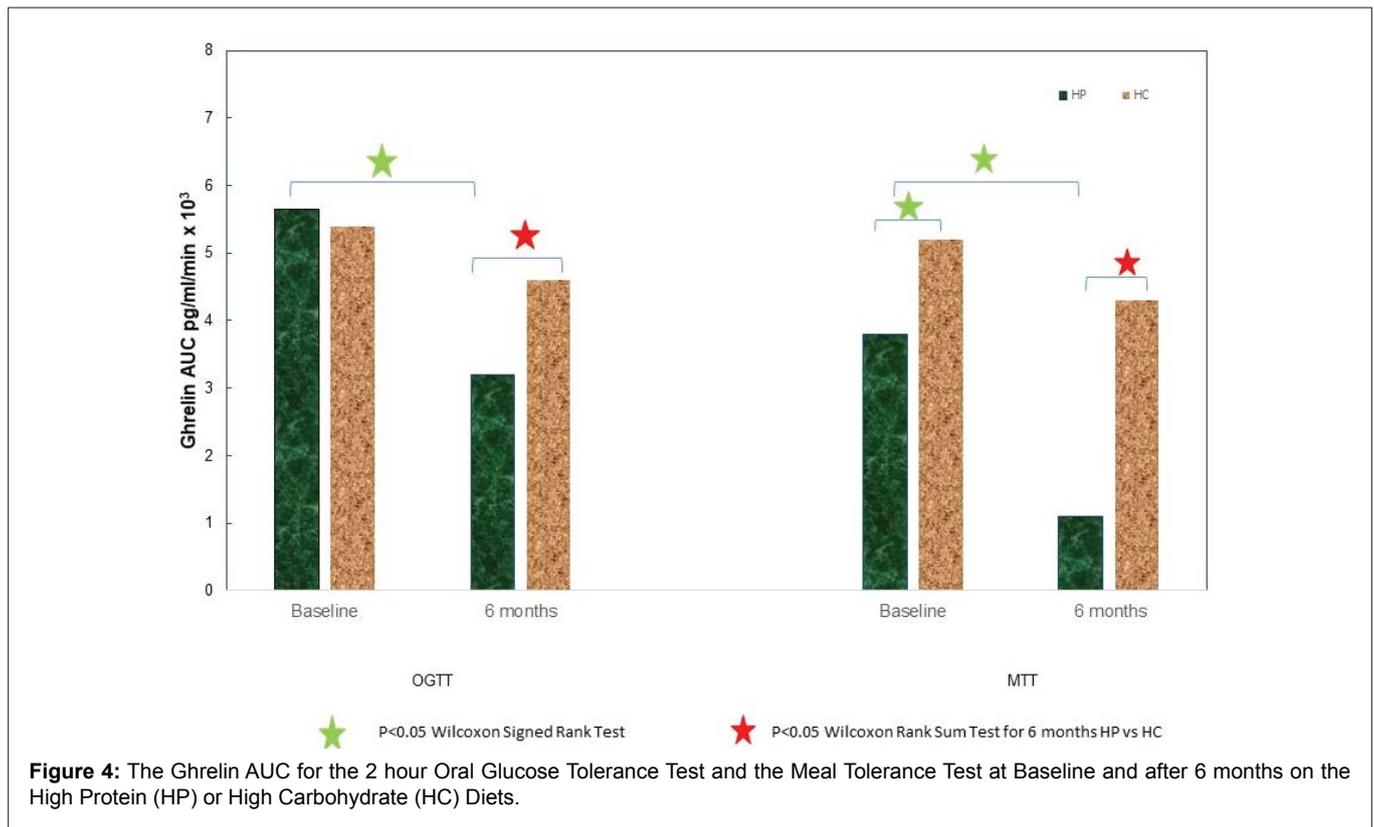
The Cardiovascular Risk Factors (CVR) Brain Natriuretic Peptide (BNP) and hsCRP were significantly decreased in the HP diet group compared to the HC group at 6 months. Other CVR factors including BP, cholesterol, triglycerides, LDL and were significantly decreased in both diet groups; however, the HP diet group had significantly more reduction than the HC diet group at 6 months as we have previously reported. Free fatty acids levels were not significantly different at baseline but the HP group had significantly lower FFAs at 6 months while the HC group had significantly higher FFAs level at 6 months.

Figure 2 shows the AUC of the incretin, GLP-1, during the 2 hr OGTT using the 0, 30, 60, 90 and 120 minute GLP-1 plasma values and the 2 hr MTT using the 0, 30, 60, 90 and 120 minute GLP-1 plasma values at baseline and after 6 months on the HP

and HC diets. At Baseline the AUC GLP-1 was not significantly different between the HP and HC diets for the OGTT. However, after 6 months on the HP or HC diet the GLP-1 AUC for the OGTT of HP diet subjects was significantly greater than the HC group. The GLP-1 AUC of the HP diet MTT was greater at baseline and also significantly greater after 6 months on the HP diet than the HC diet group, demonstrating that the HP diet had a greater effect on the release of the incretin, GLP-1, than the HC diet. Figure 3 shows that similar results of the GIP AUC of the 2 hr OGTT and 2 hr MTT of the HP diet group compared to the HC diet group. The HP diet group had increased GIP AUC compared to the HC diet group with both the OGTT and MTT after 6 months on the diets.

As a measure of satiety the Ghrelin levels were measured for the HP and HC diet groups as shown in Figure 4. At baseline the Ghrelin AUC for the OGTT was not significantly different; however, at 6 months the HP diet group had significantly lower Ghrelin AUC for the OGTT than the HC diet group. At baseline and at 6 months the HP diet group had significantly lower Ghrelin AUC than the HC diet with the MTT. This indicates that the HP diet is more effective in decreasing hunger than the HC diet.





Discussion:

Important findings in this study which have not previously been reported include: (1) The HP diet subjects exhibited greater increase in GLP-1 and GIP along with improvement in insulin sensitivity and B cell function and a decrease in insulin and glucose AUC than the HC diet subjects after 6 months of diet. (2) Although both HP and HC diets resulted in significant but similar improvement at 6 months compared to baseline with respect to BMI, weight loss, and BP; the HP diet group had 100% remission of prediabetes to normal glucose tolerance, whereas, only 33% of the HC diet group had remission. (3) The HP diet caused a reduction in the ghrelin levels compared to the HC diet which indicates the HP diet may have a greater effect on satiety. Other studies have also reported a greater satiety effect of HP meals than HC meals [22] as well. (4) BNP has been shown to be a marker for cardiovascular function [31] and studies have shown natriuretic peptide receptor is related to insulin sensitivity and obesity [32]. The BNP decrease in both diet groups demonstrates that improvement in BP, weight loss, lipids and insulin sensitivity have a positive effect on the heart as measured by the CVR factor, BNP, even though the subjects had no prior history of cardiovascular events or during the study. Additionally, the HP diet had a significantly greater effect than the HC diet as demonstrated by the significantly lower BNP and hsCRP at 6 months in the HP diet group than the HC diet group.

The GLP-1 increase with HP diet may have a positive effect on the heart as measured by BNP. This is corroborated by studies that have shown that treating diabetic subjects with a GLP-1 agonist or DPP4 inhibitors has improvement in cardiovascular risk factors [13,33-36].

The percent Lean body mass (LM) increased with the HP diet group while the percent Fat Mass (FM) decreased, unlike the HC diet group which lost both percent LM and FM. There was no modification in physical activity from baseline during the 6 months on the diets; and, since all subjects were minimally active, this change in LM and FM is the direct effect of the HP and HC diets. Other studies have also shown the importance of maintaining LM in weight loss diets [37,38].

An important factor in macronutrient composition studies is compliance. While most studies rely on patient's recall of the meals they ate days to weeks in the past, in this study all diet meals along with a survey of food consumption were provided weekly to each patient at our UTHSC Clinical Research Center which resulted in greater than 90% compliance in both diet groups.

This study shows a positive correlation with B-cell function and GLP-1 with increase in B-cell function and also increase in GLP-1 with the HP diet. Other studies have also shown improvement in B cell function with treatment with GLP-1 agonists [1,39].

Although several studies have shown improvement in insulin sensitivity and B cell function with weight loss or pharmaceutical intervention in obese subjects [24,30,40,41], to our knowledge, this is the first study to investigate the effects of certain macronutrients composition on weight loss, insulin sensitivity, B cell function [18] and incretin effects in obese prediabetes subjects. The metabolic environment of obesity causes B-cell dysfunction [42,43] is supported by our study as shown by the improvement in insulin sensitivity and B-cell

function with weight loss and change in metabolic parameter with the macronutrients of the HP diet.

This study is important in that it demonstrates that high efficacy can be obtained with a weight loss diet life style intervention when rigorously monitored using a HP diet using foods obtainable from local groceries stores. The diet plans provides a large variety of food choices adjustable according to the subjects likes and dislikes. This weight loss HP diet can be used by primary care physicians and with consultation via emails and phone calls.

In summary, this study demonstrates that the HP diet can provide significant improvement in numerous metabolic parameters, remission of prediabetes and increased incretin levels and B cell function in obese, prediabetes females and male subjects.

Acknowledgements: The authors thank A. Ammons at UTHSC for the lab and hormone assays, all the nursing, nutritionist, and recruiting staff at the UTHSC Clinical Research Center for their efforts. The authors also thank all the study volunteers for their participation in the study. The Medical Student Research Fellowship Program from the National Institutes of Health/ National Institute of Diabetes and Digestive Diseases (C5T35DK007405-28) S. Dagogo-Jack, principal investigator (PI) at the University of Tennessee Health Science Center funded participation of second year medical students, David Wheeler, Andrew Mikhael and Omer Kineish of this research study.

Funding: The study was funded by the American Diabetes association (7-12-CT-41) and the AD Baskin Research Fund (PI FS).

This study was registered at ClinicalTrials.gov. The identifier is: NCT01642849

Competing Interest: The authors have nothing to disclose.

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Citation: Stentz FB, Mikhael A, Kineish O, Christman J, Sands C (2020) Incretins and Cardiovascular Effects of Weight Loss and Remission of Prediabetes. *J Diab Clin Stud* 4(1): 001-008.

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