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R1 - Eight Weeks of Dietary Overfeeding Increases Renal Filtration Rates in Humans: Implications for the Pathogenesis of Diabetic Hyperfiltration

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Abstract

Objective—Diabetic nephropathy is characterized at its onset by glomerular hyperfiltration. Prospective studies in humans measuring filtration rates with weight gain are lacking. We investigated renal filtration following weight gain induced by overfeeding.

Design—Eight week of overfeeding (40 percent above energy requirements; 44 percent fat, 15 percent protein and 41 percent carbohydrate) as well as a six month follow-up after the overfeeding intervention.

Subjects—Thirty-five participants (age: 26.7 ± 5.3 yrs; BMI: 25.5 ± 2.2 kg/m²; 29m/6f).

Measurements—Creatinine clearance rate (Ccr) from 24-hour urine collection, estimated glomerular filtration rate (eGFR) from the modification of diet in renal disease (MDRD), insulin sensitivity/glucose disposal rate (GDR) by a euglycemic-hyperinsulinemic clamp, components from basic metabolic panels, and serum lipid panels

Results—Both eGFR and Ccr increased with overfeeding ($p = 0.04$) and serum lipids (all $p < 0.05$), along with a decrease in insulin sensitivity ($p = 0.003$). Fasting glucose concentration was not affected ($p = 0.98$), but the percent change in Ccr correlated positively with the change in GDR with overfeeding ($r = 0.39$, $p = 0.02$). Six months following overfeeding, serum glucose was maintained, and no evidence of urinary glucose was observed at any time point.

Conclusions—This data suggests that renal hyperfiltration may act as a mechanism to preserve insulin sensitivity through maintenance of systemic glucose homeostasis with caloric excess.

Keywords

Glomerular Filtration Rate; End stage renal disease; type 2 diabetes; insulin resistance

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The authors have nothing to disclose.

Introduction

Diabetic nephropathy is the most common cause of end-stage renal disease¹ in the US leading to reduced quality of life² and affecting patients with both uncontrolled type 1³ and type 2 diabetes⁴. In the early years of diabetes⁵, diabetic nephropathy is characterized by renal hyperfiltration. As the duration of diabetes progresses, this eventually leads to a gross reduction in glomerular filtration rate (GFR)⁶ and increased albuminuria⁷. Several studies have linked the development of diabetic nephropathy to dysglycemia⁸, lipotoxicity⁹, and oxidative damage¹⁰, which similarly has been conjectured to be exacerbated when accompanied with hyperfiltration^{11, 12}.

Epidemiological studies as well as studies in mice suggest that characteristics of the obesogenic environment, such as high fat diet^{13, 14}, caloric excess¹⁵, and high fructose diets¹⁶ lead to the development of renal hyperfiltration. However, few studies have prospectively investigated changes in renal parameters in humans during periods of caloric excess. Therefore, we investigated measures of renal function along with contributing factors relating to dysglycemia and lipotoxicity in response to an 8-week hypercaloric (40 percent caloric excess) in 35 volunteers.

Methods

We recruited 35 participants (29 males, 6 females; 20 Caucasian, 14 African American, and 1 other race; age: 26.7 ± 5.3 yrs; body mass index (BMI): 25.5 ± 2.2 kg/m²) into our overfeeding study. All participants provided informed consent. Study parameters were approved of by the Institutional Review Board and followed the Declaration of Helsinki. Our study was registered on clinicaltrials.gov (clinicaltrials.gov identifier: NCT01672632).

Aspects of the main study protocol have been previously reported^{23, 24}. Briefly, participants underwent the same clinical procedures at baseline and after 8 weeks of overfeeding. Participants consumed a diet of 44 percent fat, 15 percent protein, and 41 percent carbohydrate, where the total daily intake equated to 140 percent of their normal caloric intake to maintain body weight. Glucose disposal rate (GDR) was determined using a euglycemic-hyperinsulinemic clamp with a low dose insulin infusion of 10mU/min/m², and adjusted for fat free mass (FFM) +17.7 as previously described²⁵. Serum and urine measures were assessed by an enzymatic assay on a Beckman Coulter DXC 600 (Beckman Coulter, Brea, CA). Body composition was assessed by dual x-ray absorptiometry (DXA, QDR 4500A; Hologic, Bedford, MA). Total body water was analyzed by doubly labeled water as previously described²⁶.

Six months following the 8 weeks of overfeeding, 26 participants (21 males, 5 females; 14 Caucasians, 11 African Americans, and 1 other race) took part in a six month follow-up with a DXA performed to assess body composition, fasting blood collection, and blood pressure. Estimated glomerular filtration rate (eGFR) was assessed using the Modification of Diet in Renal Disease (MDRD) formula²⁷, and creatinine clearance rate (Ccr) was assessed by dividing the product of urine flow rate and urinary creatinine by serum creatinine.

Statistical analysis

Data was analyzed using the GraphPad Prism Software, version 6.0 (GraphPad Software, La Jolla, CA). Paired t-tests were used between time points, and the Pearson r correlation coefficient was used to assess the correlation between changes in GDR and Ccr. A p value of 0.05 was considered to be statistically significant. Graphical data is represented as mean $\pm$ SEM.

Results

Overfeeding resulted in increases in weight (6.9 ± 2.0 kg), percent fat, fat mass (FM), and fat free mass (FFM, all $p < 0.001$), and a decrease in glucose disposal rate (GDR, $p < 0.003$). Before the overfeeding intervention, participants consumed an average of 3060 ± 302 kcal/day, and immediately following the overfeeding intervention, participants consumed an average of 4211 ± 501 kcal/day. Both eGFR, using the MDRD formula, and 24-hr creatinine clearance rate (Ccr) increased with overfeeding (both $p = 0.04$). These occurred in parallel with increases in total body water (labeled water; $p < 0.001$) and mean arterial blood pressure ($p = 0.03$). Serum albumin decreased ($p = 0.006$) and serum creatinine trended to decrease ($p = 0.07$). Components of the serum lipid panel all increased significantly (Table 1), with the ratio of total cholesterol-to-HDL increasing ($p = 0.007$) and the ratio of HDL-to-LDL decreasing ($p = 0.03$). After overfeeding, the relative change in Ccr correlated positively with the change in insulin sensitivity (GDR, Pearson $r = 0.39$, $p = 0.02$, Figure 1). Serum glucose did not change with overfeeding ($p = 0.98$), and there were no detectable levels of urinary glucose.

Six months following overfeeding weight (2.8 ± 3.5 kg), percent fat, FM, and FFM were still elevated above baseline levels (all $p < 0.001$; except FFM, $p = 0.05$). The mean serum creatinine was about 5 percent higher than pre-overfeeding conditions, and mean eGFR was about 5.5 percent lower than pre-overfeeding conditions, although neither reached statistical significance ($p = 0.40$ and $p = 0.39$, respectively). Serum creatinine levels were higher, though, from immediately following post-overfeeding levels compared to 6 month follow-up levels ($p = 0.02$). Serum potassium levels were lower from immediately following post-overfeeding conditions when compared to 6 month follow-up levels ($p = 0.005$). HDL decreased below baseline levels ($p = 0.007$). Additionally, the ratio of total cholesterol-to-HDL and serum triglycerides were still elevated above baseline levels ($p = 0.03$ and $p = 0.04$, respectively). Similar to baseline and following overfeeding, there were no detectable levels of urinary glucose six months following overfeeding.

Discussion

Our data, using both the MDRD eGFR formula and Ccr from 24-hr urine collection, showed an increase in GFR within 8 weeks of overfeeding in 35 healthy participants. Additionally, we observed increases in total body water, mean arterial blood pressure, and a decrease in the HDL-to-LDL ratio, a marker of cardiovascular disease risk. Similarly, we saw a decrease in insulin sensitivity as measured by glucose disposal rate (GDR) during a euglycemic-hyperinsulinemic clamp. Based on the definition of renal hyperfiltration, that is, eGFR $125\text{ml/min}/1.73\text{m}^2$,¹⁷ only 4 individuals met this criterion with overfeeding. The fact that

most of these individuals did not reach the clinical definition of renal hyperfiltration may be explained by the fact our volunteers were young, healthy and normoglycemic at baseline. We speculate that excess caloric intake may be involved in the occurrence of renal hyperfiltration as a compensatory mechanism to maintain glucose homeostasis.

While mechanisms for the development of hyperfiltration have not been agreed upon, several studies suggest that it is likely a multi-factorial process. One suggestion has been that hyperfiltration exists as a compensatory mechanism to prevent glomerular injury¹⁸, while another suggests that hyperfiltration results from proximal convoluted tubule hyper-reabsorption of excess glucose¹⁹ or sodium²⁰ within the filtrate. Our data supports a hypothesis that renal hyperfiltration occurs to preserve systemic insulin sensitivity given the positive association between Ccr and change in GDR. With excess calorie load, maintenance of glucose homeostasis within the systemic circulation would become more challenging, affecting hepatic, pancreatic, and renal systems. As we see in our participants, serum glucose levels remain virtually unaffected after 8 weeks of high fat diet overfeeding, yet insulin sensitivity and renal clearance were affected. Furthermore, no glucose was detected in urine at any time point. Since those who increased their Ccr the most were able to maintain better insulin sensitivity with 8 weeks of overfeeding, hyperfiltration could serve as a compensatory mechanism to help maintain glucose homeostasis, thus preserving insulin sensitivity in an “obesogenic” environment.

This compensatory mechanism of hyperfiltration, however, may be unable to keep up with chronic caloric excess, eventually damaging the kidney. During our six month follow up, we saw maintained higher levels of serum triglycerides, reduced HDL cholesterol below baseline, and an increase in the ratio of total cholesterol-to-HDL compared to baseline. Similarly, serum creatinine levels were higher and serum potassium levels were lower from immediately following post-overfeeding conditions. This observation could reflect increased sympathetic activity or increased renin-angiotensin-aldosterone system activity, which would affect renal function. Since excess circulating lipids and elevated blood pressure, which occurred during the 8 weeks of overfeeding, can contribute to renal damage^{21, 22}, having hyperfiltration under a sustained caloric excess could result in renal damage and eventually reduced renal function. However, these speculations require further studies.

To conclude, we have shown that the estimated glomerular filtration rate increases with 8 weeks of overfeeding. The correlation between the increase in creatinine clearance and the changes in insulin sensitivity may suggest that hyperfiltration represents a compensatory mechanism to maintain glucose homeostasis with caloric excess. However, increases in serum lipids and increases in blood pressure, which were seen with overfeeding, may contribute to a decline in kidney function as seen with long duration uncontrolled diabetes.

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Figure 1.

A) Glucose Disposal Rate (GDR) decreases significantly with 8 weeks of overfeeding ($p = 0.003$). B) Creatinine Clearance Rate (Ccr) increases significantly with 8 weeks of overfeeding ($p = 0.04$). C) The change in GDR is positively associated with the percent change from baseline in Ccr ($r = 0.39$, $p = 0.02$). Graphs represent mean $\pm$ SEM, and correlation is assessed by Pearson r correlation coefficient.

Table 1

Athropometric, Serum, and Urinary measures from before to after overfeeding and at six months following overfeeding.

	Baseline Mean ± SD	Post-Overfeeding Mean ± SD	p value	Month 6 Follow-Up Mean ± SD	p value BL-M6	p value PO-M6
Weight (kg)	80.0 ± 10.2	86.9 ± 10.6	< 0.001	82.7 ± 12.5	< 0.001	< 0.001
Percent Fat	21.8 ± 7.1	24.7 ± 7.1	< 0.001	23.4 ± 8.0	< 0.001	0.08
FM (kg)	17.2 ± 5.2	21.4 ± 5.9	< 0.001	19.2 ± 6.3	< 0.001	0.003
FFM (kg)	62.4 ± 10.6	65.7 ± 10.7	< 0.001	63.5 ± 12.3	0.05	< 0.001
eGFR (mg/mL/1.73m ²)	100.8 ± 18.6	104.3 ± 21.3	0.04	94.5 ± 14.0	0.39	0.01
Ccr (mg/mL)	0.08 ± 0.03	0.09 ± 0.03	0.04	--	--	--
Total Body Water, avg (kg)	44.3 ± 7.9	45.9 ± 7.5	< 0.001	--	--	--
Urine Output (mL/hr)	93.2 ± 34.4	87.7 ± 32.0	0.33	--	--	--
Urinary Creatinine (mg/mL)	0.06 ± 0.04	0.07 ± 0.04	0.30	--	--	--
GDR (mg/min/FFM + 17.7)	2.80 ± 1.02	2.41 ± 0.80	0.003	--	--	--
Serum Albumin (g/dL)	4.4 ± 0.2	4.3 ± 0.3	0.006	4.3 ± 0.3	0.01	0.56
Serum Creatinine (mg/dL)	0.95 ± 0.18	0.92 ± 0.18	0.07	1.00 ± 0.18	0.40	0.02
Serum Uric Acid (mg/dL)	5.31 ± 1.06	5.60 ± 1.36	0.09	5.15 ± 1.04	0.97	0.10
Serum Potassium (mmol/L)	4.22 ± 0.27	4.26 ± 0.27	0.49	4.08 ± 0.22	0.06	0.005
Serum Glucose (mg/dL)	91.6 ± 7.4	91.7 ± 9.2	0.98	92.7 ± 7.6	0.36	0.14
Mean Arterial Pressure (mmHg)	84.5 ± 5.2	86.5 ± 4.4	0.03	86.0 ± 7.2	0.19	0.59
Total Cholesterol (mg/dL)	174.8 ± 21.9	195.6 ± 30.0	< 0.001	170.9 ± 30.0	0.36	< 0.001
HDL (mg/dL)	57.2 ± 12.7	60.0 ± 12.9	0.04	52.0 ± 10.4	0.007	< 0.001
LDL (mg/dL)	101.7 ± 20.8	117.9 ± 27.9	< 0.001	101.4 ± 24.7	0.55	< 0.001
Total Cholesterol/HDL	3.22 ± 0.92	3.40 ± 0.93	0.007	3.38 ± 0.79	0.03	0.73
HDL/LDL	0.59 ± 0.21	0.54 ± 0.20	0.03	0.54 ± 0.15	0.12	0.86
Triglycerides (mg/dL)	79.4 ± 53.6	88.5 ± 64.6	0.04	87.5 ± 40.0	0.04	0.53

FM – fat mass; FFM – fat free mass; eGFR – estimated Glomerular Filtration Rate (MDRD formula); Ccr – Creatinine clearance rate; GDR – glucose disposal rate as measured from a euglycemic-hyperinsulinemic clamp; HDL – high density lipoprotein; LDL – low density lipoprotein.