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Effect of Carbohydrate-Restricted Diet on Glucose Tolerance in Streptozotocin-Induced Diabetic Rats

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Abstract

Diabetes is a chronic disease that occurs when insulin production by the pancreas is reduced or when the body cannot effectively use the produced insulin. Type 2 diabetes is a serious problem among middle-aged and elderly individuals. Therefore, a healthy and balanced diet, moderate exercise, and proper weight control are effective in preventing and alleviating type 2 diabetes. In recent years, a carbohydrate-restricted diet（a very low-carbohydrate diet）has been recognized as effective for the prevention and alleviation of diabetes. In this study, we investigated the effects of moderate and severe carbohydrate-restricted diets on glucose tolerance in streptozotocin（STZ）-induced diabetic rats, an insulin-deficient diabetes model. Forty-eight male Wistar rats（3-week-old）were obtained, half of which were administered STZ to induce diabetes. Both groups of rats were fed moderate and severe carbohydrate-restricted diets for four weeks. We confirmed that both moderate and severe carbohydrate-restricted diets increased fasting serum glucose levels and did not improve glucose tolerance in STZ-induced diabetic rats. However, firm conclusions regarding carbohydrate restriction have not yet been reached, and further research is needed to investigate the long-term effects and metabolic mechanisms of carbohydrate restriction.

Key Words: Carbohydrate restriction, diabetes, glucose tolerance, streptozotocin, rat

Introduction

Diabetes is a chronic disease that occurs when insulin production by the pancreas is reduced or when the body cannot effectively use the produced insulin[(1)]. According to the International Diabetes Federation（IDF），463 million people worldwide had diabetes in 2019, with an estimated 382 million people in 2013 and 108 million in 1980[(1-3)]. The number of patients with diabetes is rapidly increasing, and is projected to reach 578 million by 2030 and 700 million by 2045. Type 2 diabetes accounts for approximately 90% of cases[(1)]. This type of disease is common among middle-aged and elderly individuals and is a preventable lifestyle-related disease[(4, 5)]. Therefore, a healthy and balanced diet, moderate exercise, proper weight control, and smoking cessation are effective in preventing and alleviating type 2 diabetes[(6)]. The World Health Organization（WHO）estimated that diabetes caused 1.5 million deaths in 2012, making it the eighth leading cause of death globally[(1)]. However, an additional 2.2 million deaths worldwide have been attributed to increased risks of hyperglycemia, cardiovascular disease, renal failure, and other related complications[(1, 7)], all of which often lead to premature death[(8)].

In recent years, a carbohydrate-restricted diet（very low-carbohydrate diet）has been recognized as an effective diet for the prevention and alleviation of lifestyle-related diseases, such as diabetes[(9)]. This diet restricts carbohydrate consumption to a lesser extent than usual diets. Therefore, carbohydrate-rich foods（including sugar, bread, and pasta）are restricted and replaced with foods high in fat and protein（meat, poultry, fish, shellfish, eggs, cheese, nuts, seeds, etc.）[(10)]. The anti-diabetic effects of a carbohydrate-restricted diet are based on the suppression of postprandial hyperglycemia, resulting in glycation and oxidative stress, which may lead to complications such as cardiovascular diseases[(11, 12)]. This is because carbohydrates are the only nutrients that strongly increase postprandial blood glucose concentration except in diabetes[(12, 13)]. In 2013, the American Diabetes Association（ADA）recommended a carbohydrate-restricted diet

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as the most appropriate option for diabetes treatment[14].

However, there are also negative views regarding carbohydrate-restricted diets. The Japan Diabetes Society (JDS) does not recommend the adoption of a carbohydrate-restricted diet because of the absence of clinical data showing that carbohydrate-restricted diets help alleviate diabetes[5]. The JDS does not allow a carbohydrate intake of less than 50% of the total energy intake[15]. The ability of Japanese people to secrete insulin is lower than that of European and American people. Therefore, even patients with mild obesity may not cope with the increased need for insulin owing to insulin resistance, leading to diabetes[16]. In insulin resistance, fasting plasma glucose levels are often normal, and severe hyperglycemia develops after a glucose load. This study investigated the effects of moderate and severe carbohydrate-restricted diets on glucose tolerance in streptozotocin (STZ)-induced diabetic rats, an insulin-deficient model of diabetes[17].

Materials and Methods

All animal procedures were approved by the Animal Care and Use Committee for Kagawa University (approval number: 14030).

Animals, diets, and experimental design

Forty-eight male Wistar rats (3-week-old) were obtained from Japan SLC (Shizuoka, Japan) and were individually caged at 22 ± 1°C, with light from 08:00 to 20:00. As an acclimatization period for six weeks, they were fed MF, a commercial rodent diet (Oriental Yeast Co., Ltd., Tokyo, Japan), and had access to water *ad libitum* until they were six weeks old (after three weeks of starting the acclimatization period). Then, the rats were meal-fed the MF from 8:00 h to 9:00 h and 20:00 h to 21:00 h for the next three weeks. One week after starting the acclimatization period, rats with equal mean body weight were randomized into two groups, the STZ-injected (diabetic) and non-injected (normal) groups. STZ-induced diabetic rats, which exhibited impaired insulin secretion due to β-cell destruction, were generated by intraperitoneal injection of 5 mg/5 mL/kg STZ (FUJIFILM Wako Chemicals, Osaka, Japan), and normal rats were injected with 5 mL/kg saline. Three weeks after injection, STZ-injected rats were bled from the tail vein using a capillary tube after overnight starvation, plasma glucose levels were measured, and diabetes was confirmed (glucose level > 140 mg/dL)[18]. STZ-injected rats with a glucose level of less than 140 mg/dL were re-injected STZ, and all STZ-injected rats were confirmed to develop diabetes within six weeks of the acclimatization period. Rats in the normal (N) and diabetic (D) groups were divided into three sub-groups (n=8 each) with equal mean body weight and mean fasting plasma glucose levels. The composition of the experimental diets was shown in Table 1. Control (CO), moderate carbohydrate-restricted (MCR), and severe carbohydrate-restricted (SCR) diets contained 55.0, 23.3, and 13.0% carbohydrates of energy, respectively. Soy protein provided by J-Oil Mills, Inc. (Kanagawa, Japan) was used as the protein source for the experimental diets. Vitamin and mineral mixtures were purchased from Oriental Yeast Co., Ltd. (Tokyo, Japan). Three sub-groups each of groups N and D (N-CO, N-MCR, N-SCR, D-CO, D-MCR, and D-SCR) were fed the experimental diets (Table 1) from 8:00 h to 9:00 h and 20:00 h to 21:00h with free access to water for four weeks. Body weights and food intake were recorded daily. On the fi-

Table 1. Composition of experimental diets.

	CO	MCR	SCR
Ingredients (g/kg)			
Soy protein	280.0	365.0	550.0
DL-Methionine	3.0	3.0	3.0
Corn starch	519.9	237.9	59.6
Soybean oil	50.0	50.0	50.0
Beef tallow	50.0	250.0	250.0
Mineral mixture[1]	35.0	35.0	35.0
Vitamin mixture[1]	10.0	10.0	10.0
Cellulose	50.0	47.0	40.3
Chorine chloride	2.0	2.0	2.0
Butylhydroxytoluene	0.1	0.1	0.1
Total	1000.0	1000.0	1000.0
Nutritional composition (g/kg)			
Carbohydrate	509.1	279.8	156.7
Fat	100.1	299.8	299.9
Protein	190.4	247.3	371.2
Fiber	60.1	60.1	60.1
Energy ratio (%)			
Carbohydrate	55.0	23.3	13.0
Fat	24.4	56.1	56.1
Protein	20.6	20.6	30.9
Energy (kcal/g)[2]	3.70	4.81	4.81

[1] Based on the AIN-76 mixture.
[2] Carbohydrate, fat, and protein provide energy at 4, 9, and 4 kcal/g, respectively.
CO, MCR, and SCR are abbreviations for the control, moderate carbohydrate-restricted, and severe carbohydrate-restricted diets.

nal day, all rats were euthanized by decapitation at 9:00 h after overnight starvation and then dissected. Blood was collected to obtain the serum. The heart, liver, pancreas, kidneys, spleen, and abdominal adipose tissues (epididymal, perirenal, and mesenteric) were quickly excised.

Serum glucose, insulin, and pancreatic insulin analyses

Pancreatic insulin was extracted by the method described by Flock et al.[19]. The concentrations of fasting serum glucose and insulin, and pancreatic insulin level were determined using kits (Glucose C Ⅱ-test, LBIS Rat Insulin ELISA Kit [FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan]).

Oral glucose tolerance test

After 3 weeks of feeding, oral glucose tolerance tests (OGTTs) were performed for each group of rats. Rats were weighed after 12 h of fasting. Subsequently, a 2 g/kg body weight freshly prepared 50% glucose solution was administered orally through a gavage needle. Blood samples were obtained from the tail vein using a capillary tube at baseline (0) and 30, 60, 90, and 120 min after glucose administration. Plasma glucose concentration measurements were performed in the same manner as serum glucose measurements, as previously described.

Data analysis

All data were analyzed using two-way analysis of variance (ANOVA) and the Tukey-Kramer test (Bell Curve for Excel, SSRI, Tokyo, Japan). Statistical significance was set at $p < 0.05$.

Results and Discussion

Body weight, energy intake, and abdominal fat weight (Table 2)

Based on the ANOVA results, STZ injection dramatically decreased the initial and final body weights, weight gain, food intake, and food efficiency. Both severe and moderate carbohydrate restriction significantly increased final body weight, weight gain, and food efficiency. Final body weight was sig-

Table 2. Body weights, energy intake, and abdominal fat weights in each group of rats.

	Groups	CO	MCR	SCR	ANOVA		
					CR	STZ	CR x STZ
Body weights (g)							
Initial	N	163 ± 8	162 ± 6	163 ± 7	n.s.	< 0.01	n.s.
	D	110 ± 9**	118 ± 11**	117 ± 7**			
Final	N	178 ± 9^{b}	226 ± 9^{a}	211 ± 10^{a}	< 0.05	< 0.05	n.s.
	D	111 ± 11**	143 ± 19**	138 ± 13**			
Gain	N	17 ± 3	64 ± 6	48 ± 7	< 0.05	< 0.01	n.s.
	D	1 ± 5^{b}**	25 ± 9^{a}**	21 ± 9^{ab}**			
Energy intake (g/day)	N	29 ± 2^{b}	43 ± 3^{a}	39 ± 3^{ab}	< 0.05	n.s.	n.s.
	D	28 ± 2^{b}	37 ± 3^{a}	32 ± 2^{ab}			
Abdominal fat weights (mg/g)							
Epididymal	N	17 ± 2^{b}	25 ± 2^{a}	22 ± 2^{a}	< 0.01	< 0.01	n.s.
	D	4 ± 1^{b}***	14 ± 6^{a}**	12 ± 2^{a}**			
Perirenal	N	11 ± 2^{b}	24 ± 2^{a}	20 ± 2^{a}	< 0.01	< 0.01	n.s.
	D	1 ± 1^{b}**	9 ± 4^{a}**	8 ± 2^{a}**			
Mesenteric	N	14 ± 1^{b}	20 ± 1^{a}	19 ± 2^{a}	< 0.01	< 0.01	n.s.
	D	3 ± 1^{b}**	10 ± 3^{a}**	10 ± 2^{a}**			

Data are the means ± SE for 8 rats.
Superscripts indicate statistical differences within the row ($P < 0.05$). *P<0.05, **P<0.01 vs. N group. n.s., not significant.
CO, MCR, and SCR are abbreviations for the control, moderate carbohydrate-restricted, and severe carbohydrate-restricted groups.
N and D are abbreviations for normal and diabetic rats. CR and STZ are abbreviations for carbohydrate restriction and streptozotocin injection.

nificantly higher in the D-MCR and D-SCR groups than in the D-CO group. No interaction between STZ injection and carbohydrate restriction was detected in terms of body weight or food intake. STZ injection significantly increased the relative weights of abdominal adipose tissues（epididymal, perirenal, and mesenteric）. Both severe and moderate carbohydrate restriction significantly increased the relative weights of the epididymal, perirenal, and mesenteric adipose tissues, which were significantly higher in the N-MCR and N-SCR groups than in the N-CO group, and were significantly higher in the D-MCR and D-SCR groups than in the D-CO group. No interaction between STZ injection and carbohydrate restriction was detected for any of the relative tissue weights.

Serum glucose, insulin, and pancreatic insulin levels（Table 3）

Based on the ANOVA results, STZ injection significantly increased the concentrations of serum glucose and insulin and decreased pancreatic insulin content. Carbohydrate restriction significantly increased the serum glucose concentration, which was higher in the D-MCR and D-SCR groups than in the D-CO group. We detected an interaction between STZ injections and carbohydrate restriction in serum glucose concentration, which was increased in the D groups by carbohydrate restriction.

Plasma glucose concentration after oral glucose administration（Table 4）

Three weeks after feeding, STZ injection significantly increased the increments in plasma glucose levels and the area under the curve（AUC）after glucose administration, whereas carbohydrate restriction did not influence these parameters. At almost all time points, the increments in glucose levels were significantly higher in the D groups than in the N groups, except 30 min after administration. We detected an interaction between STZ injections and carbohydrate restriction in the increase in plasma glucose concentration 120 min after administration, which was suppressed by carbohydrate restriction. The AUC in the STZ-injected rats was the lowest in the D-MCR group, but the difference was not significant.

Some studies have demonstrated the anti-obesity and anti-diabetic effects of carbohydrate-restricted diets[20-22]. Therefore, we expected that the ingestion of a carbohydrate-restricted diet as a therapeutic diet for diabetes could decrease fasting blood glucose levels and improve glucose tolerance in patients with diabetes. Unexpectedly, carbohydrate restriction increased fasting serum glucose levels despite no effects on fasting serum insulin and pancreatic insulin levels（Table 3）. In addition, carbohydrate restriction did not improve glucose tolerance（Table 4）in STZ-induced diabetic rats. These results suggest that carbohydrate restriction exacerbates insulin resistance in insulin-deficient diabetic rats. Several studies have shown that a carbohydrate-restricted diet prevents type 2 diabetes, whereas other studies have shown opposite results[23-25]. Although it is recognized that dietary carbohydrate plays a role in the development of type 2 diabetes, it is unknown how much dietary carbohydrate is too much or sufficient to enhance type 2 diabetes in humans or animals on a carbohydrate-restricted diet.

A carbohydrate-restricted diet is inevitably a high-fat, high-protein diet. A high-protein diet has been shown to induce insulin resistance, possibly through the activation of the mammalian target of rapamycin（mTOR）and S6kinase（S6K）signaling pathways[26,27]. However, in the present study,

Table 3. Concentrations of serum glucose and insulin concentrations, and pancreatic insulin content in each group of rats.

	Groups	CO	MCR	SCR	*P*-value		
					CR	STZ	CR x STZ
Serum glucose（mg/dL）	N	116 ± 6	117 ± 5	118 ± 6	< 0.01	< 0.01	< 0.01
	D	189 ± 21^{b*}	383 ± 35^{a*}	344 ± 51^{a*}			
Serum insulin（ng/mL）	N	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1	n.s.	< 0.01	n.s.
	D	0.1 ± 0.1*	0.1 ± 0.1*	0.1 ± 0.0*			
Pancreatic insulin（μg/mg）	N	0.16 ± 0.05	0.18 ± 0.03	0.15 ± 0.03	n.s.	< 0.01	n.s.
	D	0.01 ± 0.00*	0.01 ± 0.00*	0.02 ± 0.01*			

Data are the means ± SE for 8 rats.
Superscripts indicate statistical differences within the row（$P < 0.05$）. $^{*}P<0.05$, $^{**}P<0.01$ vs. N group. n.s., not significant.
CO, MCR, and SCR are abbreviations for the control, moderate carbohydrate-restricted, and severe carbohydrate-restricted groups.
N and D are abbreviations for normal and diabetic rats. CR and STZ are abbreviations for carbohydrate restriction and streptozotocin injection.

Table 4. Increase in plasma glucose concentrations (mg/dL) after oral glucose administration in each group of rats.

	Groups	CO	MCR	SCR	*P*-value		
					CR	STZ	CR x STZ
Time after administration (min)							
0	N	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	n.s.	n.s.	n.s.
	D	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0			
30	N	36.0 ± 9.6	24.3 ± 8.5	35.4 ± 15.1	n.s.	< 0.01	n.s.
	D	162.6 ± 38.1**	112.4 ± 66.9	105.6 ± 40.7			
60	N	45.7 ± 2.5	42.0 ± 7.3	42.3 ± 9.8	n.s.	< 0.01	n.s.
	D	304.1 ± 30.0**	200.4 ± 72.2*	377.5 ± 138.8*			
90	N	34.0 ± 3.2	36.0 ± 5.6	30.8 ± 7.0	n.s.	< 0.01	n.s.
	D	183.8 ± 40.2**	174.2 ± 58.8*	212.8 ± 34.8**			
120	N	20.2 ± 4.5	30.2 ± 5.1	51.0 ± 7.1	n.s.	< 0.01	< 0.01
	D	202.0 ± 30.4**	178.6 ± 37.6**	102.6 ± 18.3*			
AUC	N	63.0 ± 5.9	60.2 ± 9.1	63.7 ± 13.1	n.s.	< 0.01	n.s.
	D	375.8 ± 40.0**	316.0 ± 62.0**	379.1 ± 62.0**			

Data are the means ± SE for 8 rats.
Superscripts indicate statistical differences within the row ($P < 0.05$). *P<0.05, **P<0.01 vs. N group. n.s., not significant.
CO, MCR, and SCR are abbreviations for the control, moderate carbohydrate-restricted, and severe carbohydrate-restricted groups.
N and D are abbreviations for normal and diabetic rats. CR and STZ are abbreviations for carbohydrate restriction and streptozotocin injection.
AUC, area under the curve.

no differences in fasting glucose and insulin levels and glucose tolerance were observed between the D-MCR and D-SCR groups fed diets with different amounts of protein (20.6 and 30.9% energy ratio, respectively) (Tables 3 and 4). Therefore, the mTOR-S6K signaling pathway was not the study's likely mechanism of insulin resistance in our study.

We confirmed that both moderate and severe carbohydrate-restricted diets increased fasting serum glucose levels and did not improve glucose tolerance in STZ-induced diabetic rats. However, firm conclusions regarding carbohydrate restriction have not yet been reached, and further research is needed to investigate the long-term effects of carbohydrate restriction and metabolic mechanisms.

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糖質制限食がストレプトゾトシン誘発性糖尿病ラットの耐糖能に及ぼす影響

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要　約

糖尿病は，インスリン分泌不全およびインスリン抵抗性により高血糖状態が持続する慢性疾患である．2型糖尿病は中高年者にとって深刻な問題であり，その予防・改善のためには，健康的でバランスの取れた食事，適度な運動，適切な体重管理が必要となる．近年，糖尿病の予防･改善に糖質制限食（超低糖質食）が有効であることが報告されている．本研究では，ストレプトゾトシン（STZ）誘発性糖尿病ラットの耐糖能に及ぼす中程度および厳しい糖質制限食の影響を検討した．48匹の3週齢Wistar系雄ラットの半数にSTZを投与して糖尿病を誘発させ，両群のラットに中程度および厳しい糖質制限食を4週間摂取させた．その結果，STZ誘発性糖尿病ラットにおいて，中程度および厳しい糖質制限食はいずれも空腹時血清グルコース濃度を増加させ，耐糖能を改善しなかった．糖質制限食に関する明確な結論はまだ得られていないため，糖質制限食の長期的な効果と代謝メカニズムを明らかにするためには，さらなる研究が必要である．

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