Impact of low-carbohydrate diet on renal function: a meta-analysis of over 1000 individuals from nine randomised controlled trials

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Abstract

We aimed to clarify the effect of low-carbohydrate diet (LCD) on renal function in overweight and obese individuals without chronic kidney disease (CKD). Literature searches were performed using EMBASE, MEDLINE and Cochrane Library until December 2015. We selected articles that reported human studies from their inception until December 2015 in English using the following searching terms: 'Low carbohydrate diet' AND ('Clinical trial' OR 'Clinical study' OR 'Clinical investigation' OR 'Observational study' OR 'Cohort study'). We compared the effects of LCD on renal function, defined as change in estimated glomerular filtration rate (eGFR), assessed in randomised-controlled trials. We calculated the mean change in eGFR and the mean change in standard deviations by eGFR or creatinine clearance, and compared the mean change in eGFR and standard deviations in LCD with those in the control diet using fixed-effects models. We selected nine randomised controlled trials including 1687 participants (861 were fed LCD and 826 were fed the control diet). The mean change in eGFR in the LCD group was −4·7 to 24·0 ml/min per 1·73 m^2 and that in the control diet group was −4·1 to 10·8 ml/min per 1·73 m^2. The mean change in eGFR in the LCD group was greater than that in the control diet (0·13 ml/min per 1·73 m^2; 95 % CI 0·00, 0·26). In the present meta-analysis, we identified that the increase in eGFR was greater in LCD compared with the control diet in overweight and obese individuals without CKD.

Key words: Low-carbohydrate diets: Renal function: Obesity: Meta-analyses

Obesity, which is a major public health problem worldwide[1], is an important factor for the development and progression of several lifestyle-associated diseases such as hypertension[2], type 2 diabetes[3,4] and CVD[5]. In addition, it has been shown that obesity is associated with the prevalence and progression of chronic kidney disease (CKD)[6–8].

Dietary treatments are effective for weight loss[9]; however, there is currently no consensus on the optimal dietary therapy for weight loss and the prevention of further events. Recently, low-carbohydrate diet (LCD) has been recognised as a weight-loss strategy. Several studies have investigated the effectiveness of LCD for weight loss[10–12]. Furthermore, a high-protein diet corresponding with LCD promotes weight loss, maintains lean body mass and improves lipid and glycaemic metabolism in obese individuals[13,14].

Meanwhile, there is concern about the safety of LCD and corresponding high protein intake on renal function. Previous studies have revealed that high-protein diets are associated with the development and progression of CKD in obese individuals[15]. In addition, it has been reported that individuals who reduced protein intake inhibit renal death, compared with those with higher or unrestricted protein intakes[16]. Furthermore, it has been reported that dietary protein restriction slows the progression of renal dysfunction among individuals with CKD[17], and that a protein limit of 0·8 g/kg for patients with renal dysfunction has been recommended in the KDOQI guidelines[18]. Thus, there is a possibility that LCD has adverse effects on renal function; however, it remains to be elucidated the impact of LCD on renal function in obese individuals. Therefore, we aimed to investigate the effect of LCD on renal function, defined as estimated glomerular filtration rate (eGFR) or creatinine clearance (CCR), among overweight and obese individuals without CKD in this meta-analysis.

Methods

Data sources and searches

Literature search was performed using EMBASE, MEDLINE and Cochrane Library. We selected articles that reported human studies from their inception until December 2015 in English using the following searching terms: 'Low carbohydrate diet' AND

('Clinical trial' OR 'Clinical study' OR 'Clinical investigation' OR 'Observational study' OR 'Cohort study').

Study selection

Inclusion criteria were as follows: (1) the articles should be original, (2) the abstracts of articles should include the term or abbreviations of 'low carbohydrate diet', (3) the study should include overweight, $25 \leq BMI < 29.9\,kg/m^2$ ($23 \leq BMI < 24.9\,kg/m^2$ if Asian), and obese, $BMI \geq 30\,kg/m^2$ ($BMI \geq 25\,kg/m^2$ if Asian) individuals[19] and (4) duration ≥ 6 months. Exclusion criteria included (1) duplicated article in three websites, (2) no original raw data for creatinine, eGFR or CCR, (3) no data on standard deviation for assessed data or (4) no data on the control group. For this meta-analysis, trials were required to use a randomised-controlled design comparing the effects of LCD diet, defined as allowing a maximum intake of 45 % of energy from carbohydrates, with control diet[20].

Data extraction

We extracted the following data from all assessed articles: authors, study title, country, year of publication, study design, study length, sex distribution, age, sample size, dropout rate, intervention for diets and outcomes.

In this meta-analysis, we considered CCR as eGFR[21]. In the study by Krebs et al.[22] and Stern et al.[23], not eGFR but serum creatinine at the end point was described. Thus, we calculated eGFR from the following equation: $eGFR = 175 \times age^{-0.203} \times$ serum $creatinine^{-1.154}$ ($\times 0.742$ if female)[24]. The mean change in eGFR during the courses of the studies was set as the primary outcome of interest in this meta-analysis.

In some studies, we found only the average and standard deviations of eGFR at baseline and at the end point. In these cases, we estimated the mean change in eGFR as follows: eGFR at the end point − eGFR at baseline. In the same way, we calculated SD of change in eGFR as follows: SD of change in eGFR = the square root of (the square (SD of eGFR at the end point) + the square (eGFR at baseline)).

Validity and quality assessment

For the analysis, two reviewers independently checked and selected all references, respectively. We assessed quality of evidence for each study by using the Grading of Evidence, Assessment, Development and Evaluation approach[25]. We validated and performed quality assessment of our systematic review using the Assessment of Multiple Systematic Reviews tool[26].

Quantitative data synthesis

We performed quantitative data synthesis based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[27]. We analysed the impact of LCD on renal function compared with that of the control diet among overweight and obese participants without CKD, defined as $eGFR < 60\,ml/min$ per $1.73\,m^2$ at baseline[28]. As the study by Tirosh et al.[29] included ninety-nine participants with CKD, we excluded them from the analysis.

We performed a meta-analysis to provide quantitative summary estimates of mean change in eGFR of LCD compared with the control diet. Summary averages were calculated using fixed-effects model according to Mantel & Haenszel[30]. Statistical significance was defined at P values <0.05. The I^2 statistic was calculated to assess statistical heterogeneity across studies: 0 % suggests no heterogeneity, 0–25 % very low heterogeneity, 25–50 % low heterogeneity, 50–75 % moderate heterogeneity and a value of 75 % high heterogeneity[31].

A funnel plot was produced for intervention effects to compare each study. Asymmetry may indicate reporting bias, heterogeneity or may occur by chance. All analyses were conducted using R version 3.0.1 (R project for Statistical Computing).

Result

We collected 205 articles from EMBASE, MEDLINE and Cochrane Library. Among them, 194 articles did not report original data. Renal function was assessed in eleven articles[24,29,32–39];
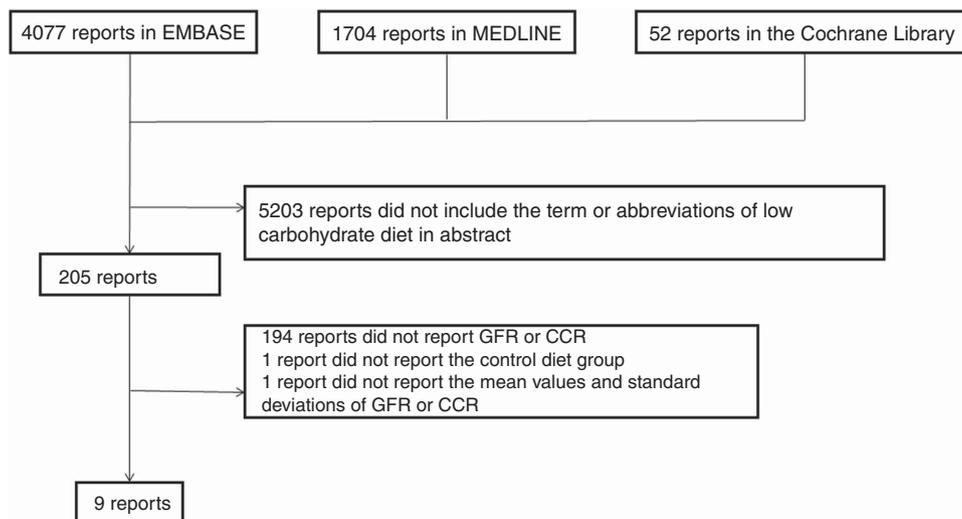

Fig. 1. Flow diagram of study selection. GFR, glomerular filtration rate; CCR, creatinine clearance.

however, one of them was excluded because the control group was not assessed[38], and another was excluded because it did not report data on mean values and standard deviations[39]. Finally, we evaluated nine randomised controlled trials (Fig. 1).

Characteristics of the nine randomised controlled trials are presented in Table 1. These studies included 1687 participants, 861 were in the LCD group and 826 in the control group; 46·2 % of them (779 of 1687) were male. The study duration ranged from 6 to 24 months. Among nine studies, four were conducted on patients with diabetes.

Proportion of carbohydrate intake in the LCD group in these studies was significantly lower than that of the control group. On the other hand, the definition of LCD was not identical among selected studies, with carbohydrate consumption ranging from 4 to 45 % of total energy intake. Total energy and dietary macronutrient composition were not maintained during the follow-up period (Table 2). Even in the LCD group, we found an increasing trend in carbohydrate intakes during the follow-up periods. In addition, the dropout rate was high in most studies[22,12,32–36].

We did not find asymmetry in the funnel plot (Fig. 2); thus, the risk of publication bias in this meta-analysis was thought to be low. On the basis of the quality assessment, the quality of each study was at medium level, although all studies were not of high level.

To compare the effect of LCD on renal function, the participants who dropped out were excluded from the analysis. Therefore, the meta-analysis encompassed a total of 972 participants, with 452 in the LCD group and 520 in the control group. All studies were combined with the fixed-effects model, and the mean change in eGFR in the LCD group was evaluated in comparison with that in the control group. The mean change in eGFR in the LCD group was $-4·7$ to $24·0$ ml/min per $1·73\,m^2$ and that in the control group was $-4·1$ to $10·8$ ml/min per $1·73\,m^2$. The mean change in eGFR in the LCD group was greater than that in the control group ($0·13$ ml/min per $1·73\,m^2$; 95 % CI $0·00$, $0·26$) (Fig. 3).

Discussion

In this present meta-analysis of randomised controlled trials comparing LCD with control diets, we identified that the increase in eGFR in LCD was greater than that in the control group among overweight and obese individuals without CKD.

Obesity is associated with the prevalence and progression of CKD[6–8], and lifestyle interventions including dietary treatment improve body weight in obese individuals[40]. LCD and corresponding high-protein diets have been recognised as the effective treatment to control body weight[10–12]. In addition, it has been reported that LCD improved CVD risk factors at short term[41]. In contrast, it has been reported that LCD is a potential risk for renal dysfunction, because LCD is associated with high protein intake. A recent study showed that LCD does not negatively affect eGFR compared with a low-fat diet among obese individuals[36]. We ensured that LCD did not negatively affect eGFR in overweight and obese individuals without CKD in this meta-analysis.

The possible reasons why LCD is effective for renal function are as follows. Obesity is related to the prevalence and the

Table 1. Study characteristics
(Mean values and standard deviations)

First author (reference)	Country	Duration (months)	Inclusion criteria	Participants (n) LCD	Participants (n) Control	Men (n) LCD	Men (n) Control	Age (years) LCD Mean	Age (years) LCD SD	Age (years) Control Mean	Age (years) Control SD	Index of renal function
Brinkworth[32]	Australia	12	Obesity (BMI; 27–43 kg/m^2), hyperinsulinaemic (IRI > 12 mU/l)	29	29	8	7	51·5	1·6	52·0	2·6	CCR (ml/min)
Stern[23]	USA	12	Obesity (BMI ≥ 35 kg/m^2)	64	68	51	58	53	9	54	9	Serum creatinine (μmol/l)
Rolland[33]	UK	9	Obesity (BMI > 35 kg/m^2)	38	34	3	8	42·7	13·1	39·9	10·4	eGFR (ml/min per 1·73 m^2)
Brinkworth[34]	Australia	24	Obesity (waist; men ≥ 94 cm, women ≥ 80 cm)	57	61		43	51·5 (SD 7·7)				eGFR (ml/min per 1·73 m^2)
Larsen[35]	Australia	12	Obesity (BMI; 27–40 kg/m^2) and type 2 diabetes	53	46	30	18	59·6	2·2	58·8	3·0	eGFR (ml/min per 1·73 m^2)
Friedman[36]	USA	24	Obesity (BMI; 30–40 kg/m^2)	153	154	50	49	44·9	10·2	46·2	9·2	CCR (ml/min)
Krebs[22]	New Zealand	24	Type 2 diabetes and obesity (BMI ≥ 27 kg/m^2)	207	212	95	73	57·7	9·9	58·0	9·2	Serum creatinine (μmol/l)
Tirosh[29]	USA	24	Obesity (BMI ≥ 27 kg/m^2), type 2 diabetes and CVD: With CKD / Without CKD	219 / 29	140 / 70	63 / 28	112 / 70	50·5 (SD 6·3) / 52·5 (SD 6·2)				eGFR (ml/min/1·73 m^2)
Yamada[37]	Japan	6	Type 2 diabetes	12	12	7	5	63·3	13·5	63·2	10·2	eGFR (ml/min/1·73 m^2)

LCD, low-carbohydrate diet; IRI, immunoreactive insulin; CCR, creatinine clearance; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

Table 2. Dietary target and nutrition intake
(Mean values and standard deviations)

First author (reference)	Intervention dietary target		Nutrition intake at end point		Dropout rate (%)	
	LCD	Control	LCD	Control	LCD	Control
Brinkworth[32]	C: 40 %, <140 g/d P: 30 %, <110 g/d F: 30 %, <50 g/d	C: 55 %, <200 g/d P: 15 %, <60 g/d F: 30 %, <50 g/d	E: 7600 (SD 600) kJ C: 46·4 (SD 1·6) % P: 21·5 (SD 0·8) % F: 31·0 (SD 1·2) %	E: 9000 (SD 800) kJ C: 46·3 (SD 1·3) % P: 20·5 (SD 0·7) % F: 32·4 (SD 1·1) %	28	25
Stern[23]	C: reduce <30 g/d P, F: no restriction	E: reduce 2092 kJ/d with <30 % from F	E: 1462 (SD 776) kJ C: 120 (SD 93) g P: 73 (SD 34) g F: 93 (SD 117) g	E: 1822 (SD 1008) kJ C: 230 (SD 150) g P: 74 (SD 50) g F: 69 (SD 48) g	31	37
Rolland[33]	E: 3347–6276 kJ C: <40 g (3347 kJ: C: 20 %, P: 40 %, F: 40 %)	E: 2301 kJ C: 36 % P: 36 % F: 28 %	–	–	48	59
Brinkworth[34]	C: 4 %, 14 g/d P: 35 %, 124 g/d F: 61 %, 99 g/d	C: 46 %, 162 g/d P: 24 %, 85 g/d F: 39 %, 49 g/d	–	–	43	37
Larsen[35]	E: <6400 kJ or 30 % Restriction C: 40 % P: 30 % F: 30 %	E: <6400 kJ or 30 % Restriction C: 55 % P: 15 % F: 30 %	E: 6664 kJ C: 41·8 % P: 26·5 % F: 30·7 %	E: 6628 kJ C: 48·2 % P: 18·9 % F: 32·0 %	19	20
Friedman[36]	Atkins' diet C: 20 g/d × 2 weeks and then increase 5 g/d P, F: no restriction	Men: 6276–7531 kJ Women: 5021–6276 kJ C: 55 % P: 15 % F: 30 %	–	–	64	58
Krebs[22]	C: 40 % P: 30 % F: 30 %	C: 55 % P: 15 % F: 30 %	E: 7170 (SD 1973·6) kJ C: 45·5 (SD 6·9) % P: 20·6 (SD 3·9) % F: 32·8 (SD 6·3) %	E: 7093·2 (SD 1851·2) kJ C: 48·1 (SD 6·6) % P: 20·3 (SD 4·4) % F: 30·4 (SD 6·8) %	31	30
Tirosh[29]	C: 20 g/d × 2 months non-restricted energy content P, F: no restriction	1, Low-fat diet (F: <30 %) 2, Mediterranean diet 6276–7531 kJ/d (1500–1800 kcal/d) (F: <35 %)	–	–		
Yamada[37]	C: 70–130 g/d P, F: no restriction	E: HT (m²) × 22 × 25 × 4.186 05 kJ C: 50–60 % P: 1·0–1·2 g/kg F: <25 %	E: 6837 (SD 2222) kJ C: 29·8 (SD 12·5) % P: 25·3 (SD 7·3) % F: 45·4 (SD 8·9) %	E: 6736 (SD 1619) kJ C: 51·0 (SD 4·6) % P: 16·6 (SD 2·8) % F: 32·3 (SD 5·2) %	0	0

LCD, low-carbohydrate diet; C, carbohydrate; P, protein; F, fat; E, energy; HT, height.

progression of CKD[6–8]; therefore, weight loss by LCD might lead to improvement in renal function. In fact, some studies have revealed that LCD was effective for weight loss[42,43]. In this meta-analysis, body weight decreased significantly from baseline in both LCD and control diet groups; however, there was no significant difference between the LCD and control diet groups with regard to change in body weight (data not shown). On the other hand, there is also a possibility that the increase in eGFR did not reflect improvement of renal function. As creatinine generation is determined by muscle mass and creatinine consumption, LCD and corresponding high-protein diets lead to glomerular hyperfiltration, glomerular hypertrophy and increased glomerular pressure, which might be both a cause and a consequence of renal injury[44]. Glomerular hyperfiltration could be caused by afferent arteriolar vasodilation as seen in patients with diabetes or after a high-protein diet, and/or by efferent arteriolar vasoconstriction owing to activation of the renin–angiotensin–aldosterone system[44]. According to a systematic review of glomerular hyperfiltration assessment, however, the definition of glomerular hyperfiltration threshold ranged from 90·7 to 175 ml/min per

1·73 m² [45]. In this meta-analysis, the mean eGFR values at the end point were 69·4–124·2 ml/min per 1·73 m² in the LCD group and 65·0–112·6 ml/min per 1·73 m² in the control group.

In this study, although the mean change in eGFR in the LCD group was greater than that in the control group, the difference was very low. Therefore, the clinical significance of LCD on renal function might not be great. However, this meta-analysis showed that LCD and the corresponding high-protein diet was not harmful for renal function in overweight and obese individuals without renal dysfunction.

A previous study showed that the adverse effect of high-protein diets on renal function occurred only after long-term follow-up, such as 3 or more years[46]. There is a possibility that the adverse effect of LCD on renal function might not have appeared yet. Thus, we cannot deny the possibility that observational periods might not be enough, and further long-term studies are needed.

The present study has several limitations. First, the definition of LCD was inconsistent and extreme carbohydrate restrictions such as under 40 g/d and 4 % of total energy content[33,34] were included among these studies. Second, the dropout rate was relatively high in most studies[22,23,32–36]. In this meta-analysis, the dropout rate of six studies[22,23,32–34,36] were over 20 %. In addition, poor adherence of study participants is also a limitation. Most of the participants in this study were not able to achieve and maintain target diet macronutrient compositions. In fact, the macronutrient composition tended to be restored to baseline proportions in these study participants, indicating that it is difficult to change the habitual dietary patterns to another dietary pattern. The motivation of participants was also important and this affected retention rates. In fact, several studies revealed that adherence to the diet was greatly diminished after the first few months[47]. Participants who completed the study may have represented a group of motivated participants, and this could have potentially biased the observed effects and might limit the generalisability of the findings. Thus, not randomised controlled trials but observational studies might be suitable for evaluating the effect of diet treatment[10]. Third, the sample size was relatively small and the study duration was
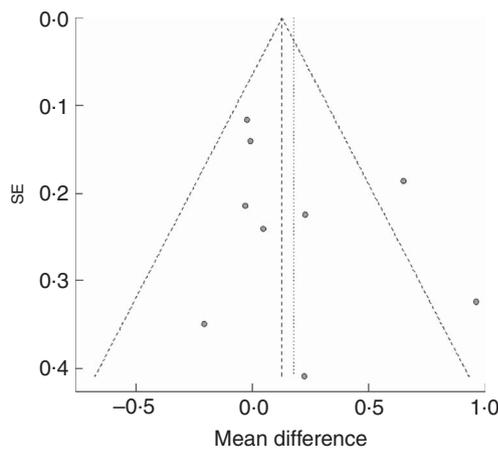

Fig. 2. Funnel plot of nine randomised controlled trials in overweight and obese individuals without chronic kidney disease.
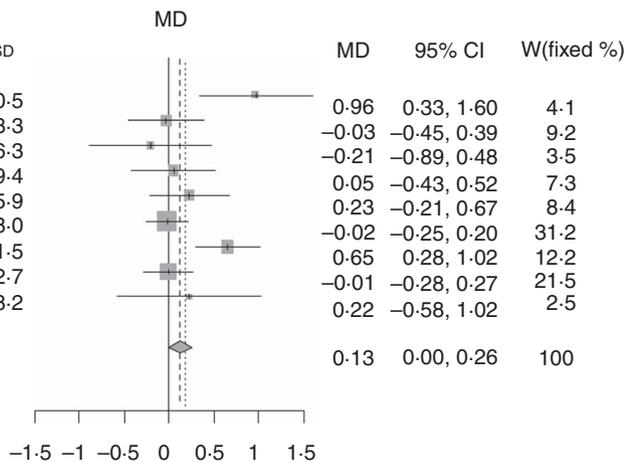

Fig. 3. Forest plot for change in estimated glomerular filtration rate associated with low-carbohydrate diet (LCD) among individuals without chronic kidney disease. The size of the boxes corresponds to each study's weight. MD, mean difference, W, weight.

Study	LCD Total	LCD Mean	LCD SD	Control Total	Control Mean	Control SD	MD	95% CI	W(fixed %)
Brinkworth GD, 2004	21	24·0	16·0	22	10·8	10·5	0·96	0·33, 1·60	4·1
Stern L, 2004	44	−1·4	18·1	43	−0·8	23·3	−0·03	−0·45, 0·39	9·2
Rolland C, 2009	20	−0·9	16·5	14	2·6	16·3	−0·21	−0·89, 0·48	3·5
Brinkworth GD, 2010	33	−0·3	24·4	36	−1·3	19·4	0·05	−0·43, 0·52	7·3
Larsen RN, 2010	43	3·2	4·6	37	2·0	5·9	0·23	−0·21, 0·67	8·4
Krebs JD, 2011	144	−4·7	30·8	150	−4·0	28·0	−0·02	−0·25, 0·20	31·2
Friedman AN, 2012	56	3·7	10·4	66	−3·5	11·5	0·65	0·28, 1·02	12·2
Tirosh A, 2013	79	2·4	22·7	140	2·6	22·7	−0·01	−0·28, 0·27	21·5
Yamada Y, 2014	12	0·4	20·9	12	−4·1	18·2	0·22	−0·58, 1·02	2·5
Fixed effect model	452			520			0·13	0·00, 0·26	100

Heterogeneity: $I^2 = 57·7\%$, $\tau^2 = 0·0569$, $P = 0·0153$

short to provide clear effects of LCD on renal function. Further studies with larger sample sizes and long-term duration are required in order to elucidate the long-term safety and efficacy of this dietary strategy on renal function. Fourth, eGFR was not directly measured, although our findings are consistent with previously reported effects on eGFR[46]. Fifth, there is a possibility that participants who develop renal issues would not continue with the trial and would likely withdraw, and it is possible that such an effect could have been missed in this meta-analysis. Sixth, the changes in proteinuria, microalbuminuria and macroalbuminuria could be more important than that of eGFR. We have also searched for changes in proteinuria, microalbuminuria and macroalbuminuria; six studies[22,35–37,39,48] have reported data on microalbuminuria. However, four studies[22,35,36,39] did not show data on mean values and standard deviations. Therefore, we could not perform a meta-analysis. Further studies are needed to determine the effects of LCD on proteinuria, microalbuminuria and macroalbuminuria. Finally, we did not provide any assessment of physical activity or other lifestyle habits except the diet therapy.

In conclusion, this meta-analysis revealed that the increase in eGFR in the LCD group was greater than that in the control group in overweight and obese individuals without CKD in at least 6 to 24 months.

Acknowledgements

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