Supplementary Materials

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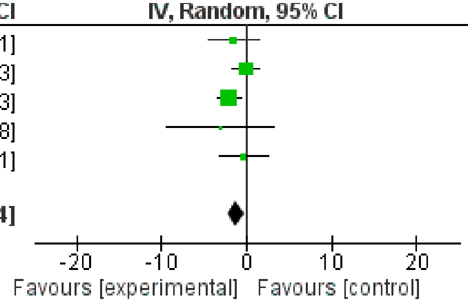
1 Meta-analysis - High protein diets in diabetes patients

1.1 Weight loss (kg)

Figure 1: Results of the meta-analysis - Effect of high protein diet on weight loss in diabetes patients

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F	G	H	I	J	K	L
Brinkworth et al. (2004)	-3.7	4.36	19	-2.2	4.79	19	10.6%	-1.50 [-4.41, 1.41]	+	+	−	−	−	+	+	−	−			
Larsen et al. (2011)	-2.2321	3.779	53	-2.1652	4.2655	46	32.6%	-0.07 [-1.67, 1.53]	+	+	−	−		+	+	+	+			
Luger et al. (2013)	-3.09	2.44	21	-1.01	2.05	22	43.9%	-2.08 [-3.43, -0.73]	+	+	−	−		+	+	+	+			
Pedersen et al. (2013)	-9.7	13.36	21	-6.6	7.1	24	2.3%	-3.10 [-9.48, 3.28]	+	+	−	−	+	+	+	−	−			
Wycherley et al. (2010)	-9	4.8	21	-8.6	4.6	19	10.6%	-0.40 [-3.31, 2.51]	+	+	−	−		+	+	−	+			
Total (95% CI)			**135**			**130**	**100.0%**	**-1.21 [-2.17, -0.24]**												

Heterogeneity: Tau² = 0.08; Chi² = 4.23, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 2.46 (P = 0.01)



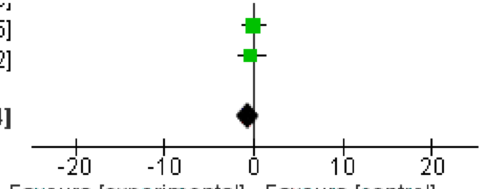
Risk of bias legend
(A) Clearly focused research question
(B) Random sequence generation (selection bias)
(C) Allocation concealment (selection bias)
(D) Blinding of participants and personnel (performance bias)
(E) Blinding of outcome assessment (detection bias)
(F) Groups are similar at the start
(G) Standardised, valid and reliable values
(H) Drop out rate
(I) Intention-to-treat analysis
(J) Incomplete outcome data (attrition bias)
(K) Selective reporting (reporting bias)
(L) Other bias

1.2 Fasting blood glucose (mmol/l)

Study	High protein diet group			Low protein diet group			Weight	Mean Difference
Lager et al. (2010)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pedersen et al. (2013)	-1.49	2.1	21	-1.5	2.13	24	38.8%	0.01 [-1.23, 1.25]
Wycherley et al. (2010)	-2.5	2.7	21	-2.2	2.2	19	32.7%	-0.30 [-1.82, 1.22]
Total (95% CI)			**63**			**65**	**100.0%**	**-0.72 [-1.98, 0.54]**

Heterogeneity: Tau² = 0.67; Chi² = 4.33, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 1.12 (P = 0.26)

Mean Difference



Risk of Bias

K L

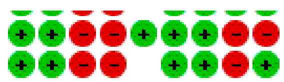


Figure 2: Results of the meta-analysis - Effect of high protein diet on fasting blood glucose in diabetes patients

Risk of bias legend
(**A**) Clearly focused research question
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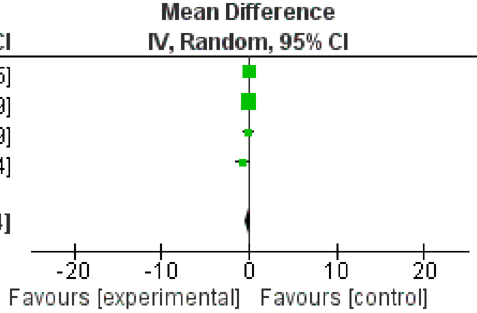
(**K**) Selective reporting (reporting bias)
(**L**) Other bias

1.3 HbA1c (%)

	High protein diet group			Low protein diet group				Mean Difference	Risk of Bias											
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F	G	H	I	J	K	L
Larsen et al. (2011)	-0.234	1.0637	53	-0.2783	0.9944	46	31.8%	0.04 [-0.36, 0.45]	+	+	−	−		+	+	+	+			
Luger et al. (2013)	-0.25	0.56	21	-0.19	0.6	22	42.9%	-0.06 [-0.41, 0.29]	+	+	−	−		+	+	+	+			
Pedersen et al. (2013)	-0.352	1.12	21	-0.25	0.87	24	15.3%	-0.10 [-0.69, 0.49]	+	+	−	−	+	+	+	−	−			
Wycherley et al. (2010)	-1.8	1.6	21	-1.1	0.6	19	10.0%	-0.70 [-1.44, 0.04]	+	+	−	−		+	+	−	+			
Total (95% CI)			**116**			**111**	**100.0%**	**-0.10 [-0.33, 0.14]**												

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.09$, df = 3 (P = 0.38); $I^2 = 3\%$
Test for overall effect: Z = 0.81 (P = 0.42)



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(K) Selective reporting (reporting bias)
(L) Other bias

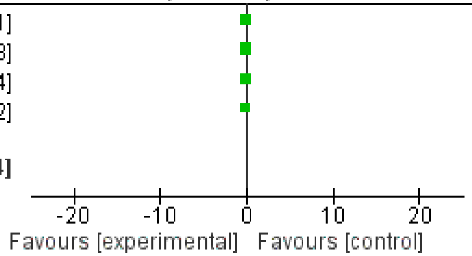
Figure 3: Results of the meta-analysis - Effect of high protein diet on hbA1c in diabetes patients

1.4 High density lipoprotein (mmol/l)

Study or Subgroup	High protein diet group Mean	SD	Total	Low protein diet group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	A	B	C	D	E	F	G	H	I	J	K	L
Larsen et al. (2011)	0.0813	0.2916	53	0.0757	0.2298	46	27.2%	0.01 [-0.10, 0.11]	+	+	−	−		+	+	+	+			
Luger et al. (2013)	0.02	0.18	21	0.04	0.15	21	28.7%	-0.02 [-0.12, 0.08]	+	+	−	−		+	+	+	+			
Pedersen et al. (2013)	0.114	0.127	21	0.083	0.229	24	25.4%	0.03 [-0.08, 0.14]	+	+	−	−	+	+	+	−	−			
Wycherley et al. (2010)	-0.1	0.2	21	0	0.2	19	18.7%	-0.10 [-0.22, 0.02]	+	+	−	−		+	+	−	+			
Total (95% CI)			**116**			**110**	**100.0%**	**-0.02 [-0.07, 0.04]**												

Heterogeneity: Tau² = 0.00; Chi² = 2.68, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)

Mean Difference IV, Random, 95% CI



Risk of Bias

Risk of bias legend
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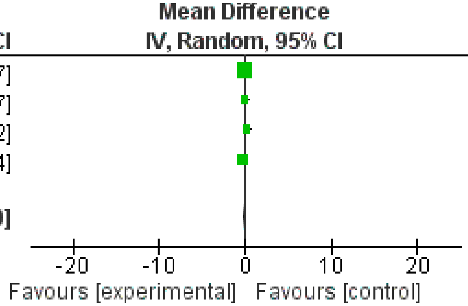
(I) Intention-to-treat analysis
(J) Incomplete outcome data (attrition bias)
(K) Selective reporting (reporting bias)
(L) Other bias

Figure 4: Results of the meta-analysis - Effect of high protein diet on high density lipoprotein in diabetes patients

1.5 Low density lipoprotein (mmol/l)

Study or Subgroup	High protein diet group Mean	SD	Total	Low protein diet group Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	A	B	C	D	E	F	G	H	I	J	K	L
Larsen et al. (2011)	-0.0521	0.58878	53	0.0444	0.7622	46	41.2%	-0.10 [-0.37, 0.17]	+	+	-	-		+	+	+	+			
Luger et al. (2013)	-0.11	0.71	21	-0.05	0.71	21	16.5%	-0.06 [-0.49, 0.37]	+	+	-	-		+	+	+	+			
Pedersen et al. (2013)	0.196	0.8662	21	0.009	0.5587	24	16.2%	0.19 [-0.25, 0.62]	+	+	-	-	+	+	+	-	-			
Wycherley et al. (2010)	-0.2	0.6	21	0	0.5	19	26.1%	-0.20 [-0.54, 0.14]	+	+	-	-		+	+	-	+			
Total (95% CI)			**116**			**110**	**100.0%**	**-0.07 [-0.25, 0.10]**												

Heterogeneity: Tau² = 0.00; Chi² = 1.95, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)



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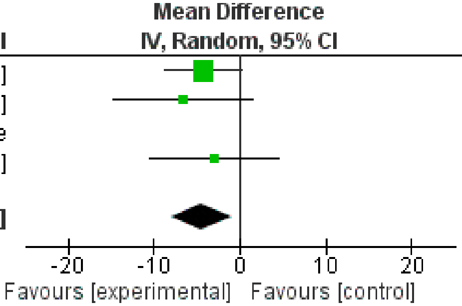
(**K**) Selective reporting (reporting bias)
(**L**) Other bias

Figure 5: Results of the meta-analysis - Effect of high protein diet on low density lipoprotein in diabetes patients

1.6 Systolic blood pressure (mmHg)

	High protein diet group			Low protein diet group				Mean Difference	Risk of Bias											
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F	G	H	I	J	K	L
Larsen et al. (2011)	-5.0259	11.4903	53	-0.7643	11.15458	46	60.4%	-4.26 [-8.73, 0.21]	+	+	−	−		+	+	+	+			
Luger et al. (2013)	-6.19	17.53	21	0.45	8.15	22	17.8%	-6.64 [-14.87, 1.59]	+	+	−	−		+	+	+	+			
Pedersen et al. (2013)	0	0	21	0	0	24		Not estimable	+	+	−	−	+	+	+	−	−			
Wycherley et al. (2010)	-16	13	21	-13	11	19	21.8%	-3.00 [-10.44, 4.44]	+	+	−	−		+	+	−	+			
Total (95% CI)			**116**			**111**	**100.0%**	**-4.41 [-7.88, -0.94]**												

Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.49 (P = 0.01)



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(K) Selective reporting (reporting bias)
(L) Other bias

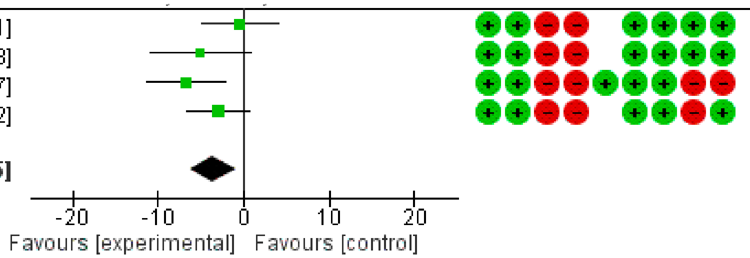
Figure 6: Results of the meta-analysis - Effect of high protein diet on systolic blood pressure in diabetes patients

1.7 Diastolic blood pressure (mmHg)

Figure 7: Results of the meta-analysis - Effect of high protein diet on diastolic blood pressure in diabetes patients

Larsen et al. (2011)	0.2052	11.24745	53	0.6499	11.3026	46	25.8%	-0.44 [-4.90, 4.01]
Luger et al. (2013)	-6.67	9.66	21	-1.59	10.28	22	16.4%	-5.08 [-11.04, 0.88]
Pedersen et al. (2013)	-2.54	6.37	21	4.23	9.25	24	24.7%	-6.77 [-11.37, -2.17]
Wycherley et al. (2010)	-10	6	21	-7	6	19	33.0%	-3.00 [-6.72, 0.72]
Total (95% CI)			**116**			**111**	**100.0%**	**-3.61 [-6.27, -0.95]**

Heterogeneity: Tau² = 1.98; Chi² = 4.09, df = 3 (P = 0.25); I² = 27%
Test for overall effect: Z = 2.66 (P = 0.008)



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(**G**) Standardised, valid and reliable values
(**H**) Drop out rate
(**I**) Intention-to-treat analysis
(**J**) Incomplete outcome data (attrition bias)
(**K**) Selective reporting (reporting bias)
(**L**) Other bias

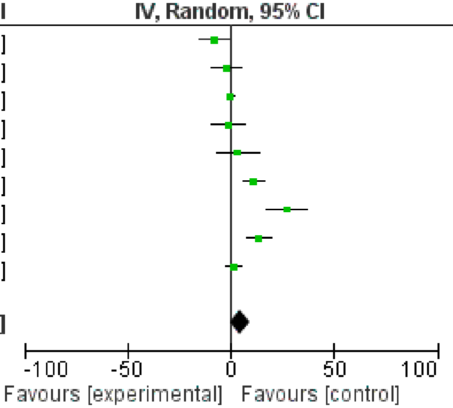
2 Meta-analysis - Low protein diets in diabetic nephropathy

2.1 Glomerular filtration rate (ml/min/1,73m²)

Figure 8: Results of the meta-analysis (Data were adapted and taken from Nezu et al.[1]) - Effect of low protein diet on GFR in diabetic nephropathy

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	A	B	C	D	E	F	G	H	I	J	K	L
Dullaart 1993	-18	12.2	14	-10	6	16	11.0%	-8.00 [-15.03, -0.97]	+	+	−	−	−	−	+	+	+	−		
Dussol 2005	-7	11	22	-5	15	25	10.7%	-2.00 [-9.46, 5.46]	+	+	−	−	−	−	+	+	+			
Hansen 2002	-3.8	3.2	38	-3.9	3.9	38	13.9%	0.10 [-1.50, 1.70]	+	+		−	−	+	+	−	+			
Koya 2009	-21.4	22.8	56	-20.3	20	56	10.4%	-1.10 [-9.04, 6.84]	+	+	−	−	−	+	+	−	+	−		
Pijls 2002	-11.6	29	63	-14.9	32.7	68	8.6%	3.30 [-7.27, 13.87]	+	+	+	+	+	+	+	+	+	−		
Raal 1994	3	6.5	11	-8	6.4	11	12.1%	11.00 [5.61, 16.39]	+	+	−	−	+	+	+	+	−			
Velázquez 2008, macroalbuminuria	17.9	14.1	10	-9.3	7.5	9	9.0%	27.20 [17.18, 37.22]	+	+	−	−	−	+	+	+	−			
Velázquez 2008, microalbuminuria	6.5	9	10	-7.3	5.3	12	11.5%	13.80 [7.47, 20.13]	+	+	−	−	−	+	+	+	−			
Velázquez 2008, normoalbuminuria	-1.3	5.1	9	-2.9	3.5	10	12.9%	1.60 [-2.38, 5.58]	+	+	−	−	−	+	+	+	−			
Total (95% CI)			**233**			**245**	**100.0%**	**4.65 [-0.32, 9.62]**												

Heterogeneity: Tau² = 45.61; Chi² = 62.97, df = 8 (P < 0.00001); I² = 87%
Test for overall effect: Z = 1.83 (P = 0.07)



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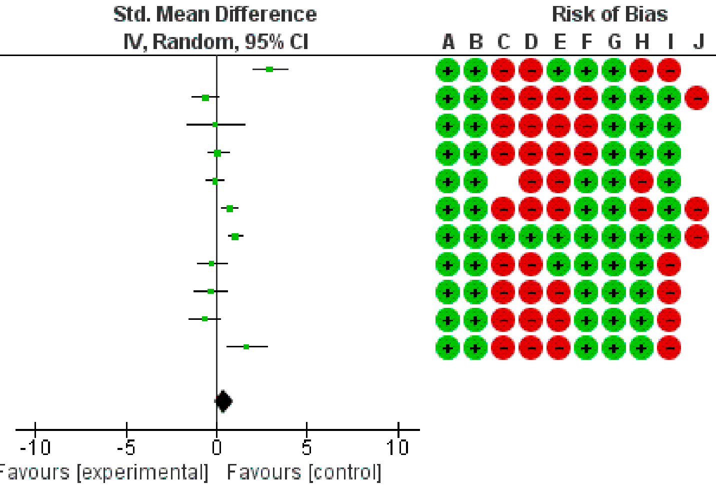
(L) Other bias

2.2 Proteinuria

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brinkworth 2004	0.2	0.1	19	-0.1	0.1	19	8.5%	2.94 [1.99, 3.88]
Dullaart 1993	-6	8.9	14	-2	2.2	16	9.4%	-0.62 [-1.36, 0.12]
Dussol 2005, macroalbuminuria	170	839.6	3	210	615.2	3	5.6%	-0.04 [-1.64, 1.56]
Dussol 2005, microalbuminuria	156	486	19	114	364	22	10.0%	0.10 [-0.52, 0.71]
Hansen 2002	-139	300	38	-107	612.2	34	10.6%	-0.07 [-0.53, 0.40]
Koya 2009	0.3	1.1	47	-0.5	1.1	41	10.7%	0.72 [0.29, 1.15]
Pijls 2002	1.2	23.5	63	-20.5	18.1	68	10.9%	1.03 [0.67, 1.40]
Raal 1994	-1	5.7	11	0.34	4.3	11	9.0%	-0.26 [-1.10, 0.58]
Velázquez 2008, macroalbuminuria	-536.3	868.1	10	-233	987.9	9	8.6%	-0.31 [-1.22, 0.59]
Velázquez 2008, microalbuminuria	1.4	34.6	10	34.12	57.4	12	8.8%	-0.65 [-1.51, 0.22]
Velázquez 2008, normoalbuminuria	3.5	4.8	9	-3.5	3.1	10	7.8%	1.68 [0.59, 2.76]
Total (95% CI)			**243**			**245**	**100.0%**	**0.40 [-0.13, 0.94]**

Heterogeneity: Tau² = 0.64; Chi² = 68.98, df = 10 (P < 0.00001); I² = 86%
Test for overall effect: Z = 1.49 (P = 0.14)



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(L) Other bias

Figure 9: Results of the meta-analysis (Data were adapted and taken from Nezu et al. [1]) - Effect of low protein diet on proteinuria in diabetic nephropathy

3 Tables of evidence

3.1 High protein diet in patients with type 2 diabetes mellitus (RCTs)

Author, year	Quality of evidence	SIGN	Study-type	Participants	Intervention				Results
					Duration	Ratio (carb:pro:fat)			
						prescribed (Interv./Control)	Achieved (Interv./Control)	Energy-R	
Brinkworth, 2004 [2]	1-	Acceptable (+)	RCT	38 T2DM	64 w	40:30:30 vs. 55:15:30	yes	yes	**weight:** -3,7±1 kg (HP) vs. -2,2±1,1 kg (LP); **HDL:** significant increase in both groups
Jesudason, 2013 [3] Pedersen, 2013 [4]	1 -	Acceptable (+)	RCT	76 T2DM	1 y	40:30:30 vs. 50:20:30	36:29:29 vs. 46:19:28	yes	**weight**: I: -9,7 ± 13,29; C: -6,6 ± 6,86 kg **Fasting blood glucose**: I: -1,0 ± 1,375; C: -1,5 ± 2,45
Larsen, 2011 [5]	1 -	Acceptable (+)	RCT	99 T2DM	1 y (3 mo E-R + 9 mo E-B)	40:30:30 vs. 55:15:30	**0**: 44:21:32 vs. 45:20:33 **3 m**: 40:28:30 vs. 49:21:29 **12 m**: 42:26:31 vs. 48:19:32	yes	**weight**: I: -2.23 ± 3.78; C: -2.16 ± 4.26 kg **n.s.** **HbA1c**: I: -0.23 ± 1.06; C: -0.28 ± 0.99 % **HDL**: I: 0.08 ± 0.29; C: 0.07 ± 0.23 mmol/l **LDL**: I: -0.05 ± 0.59; C: 0.04 ± 0.76 mmol/l **SBP**: I: -5.03 ± 11.49; C: -0.76 ± 11.15 mmHg **DBP**: I: 0.205 ± 11.25; C: 0.65 ± 11.30 mmHg
Luger, 2013 [6]	1 -	Acceptable	RCT	44 T2DM	12 w	40:30:30 vs. 55:15:30	**0:** 43:23:32 vs. 43:20:32 **4 w:** 37:26:34 vs. 48:17:30 **12 w:** 37:25:35 vs. 50:17:30	yes	
Wycherley, 2010 [7]	1 -	Acceptable (+)	RCT	83 T2DM	16 w	43:33:22 vs. 53:19:26	**16 w**: 47:32:18 vs. 54:19:23	yes	**weight**: I: -9.0 ± 4.8; C: -8.6 ± 4.6 kg **HbA1c**: I: -1.8 ± 1.6; C: -1.1 ± 0.6 % **Fasting BG**: I: -2.5 ± 2.7; C: -2.2 ± 2.2 mmol/l **HDL**: I: -0.1 ± 0.2; C: 0 ± 0.2 mmol/l **LDL**: I: -0.2 ± 0.6; C: -0.3 ±0.5 mmol/l **SBP**: I: -16 ± 13; C: -13 ± 11 mmHg **DBP**: I: -10 ± 6; C: -7 ± 6 mmHg

3.2 Overview of nutrient intake in high protein diet

Study	Year	N	Ratio	Duration		Point of time	Protein intake

			Carb:**Protein:**Fat		**E-R**[1]		**High protein diet**			**Normal protein diet**		
							g	**%**	**kcal**	**g**	**%**	**kcal**
Brinkworth [2]	2004	38	40:**30**:30 vs. 55:**15**:30	8 W ER; 4 W EB 12 mo Follow-up	Yes	8 weeks	*120g**	30 %	1595	*60g**	15 %	1595
Jesudason [3] **Pedersen [4]**	2013	76	40:**30**:30 vs. 50:**20**:30	1 year	Yes	-	110g	28.4%	1377	97 g	25.1 %	1408
Krebs [8]	2012	419	40:**30**:30 vs. 55:**15**:30	2 year	Yes	6 months 12 months 24 months	95 g 91 g 87 g	22 % 21 % 21 %	1762 1728 1707	81 g 83 g 85 g	20 % 21% 20%	1623 1615 1689
Larsen [5]	2011	99	40:**30**:30 vs. 55:**15**:30	1 year	Yes	3 months 12 months	*108 g** *105 g**	28,2 % 26.5 %	1536 1587	*75 g** *74 g**	20,8 % 18,9 %	1436 1578
Luger [6]	2013	44	40:**30**:30 vs. 55:**15**:30	12 weeks	Yes	0 4 weeks 12 weeks	*75 g** *81 g** *81 g*	22,9 % 26,5 % 25,6 %	1318 1219 1272	*66 g** *57g** *51g**	19,8 % 17,0% 16,6 %	1326 1332 1235
Luscombe [9]	2002	26	42:**28**:30 vs. 55:**16**:29	8 + 4 weeks	Yes	8 weeks + 4 weeks	*112 g** *128 g**	28,2 % 27,7 %	1585 1844	*64 g** *70 g**	16,1 % 15,8 %	1583 1777
Parker [10]	2002	66	42:**28**:28 vs. 55:**16**:27	8 + 4 weeks	Yes	8 weeks + 4 weeks	*112 g** *140 g**	28,1 % 27,7 %	1587 2029	*63 g** *71 g**	16,4 % 16,0 %	1543 1785
Wycherley [7]	2010	28	47:**32**:18 vs. 53:**18**:22	16 weeks	Yes	-	119g	32,3%	1505	68g	18,6%	1494

** = estimated values*

[1] E-R = Energy restriction

3.3 Working document – Results of high protein diets in diabetes patients

Author, Year	Study Design	Population	Intervention and Control (carb:**pro**:fat)	Outcome A *Weight loss (Mean ± SD)*	Outcome B *HbA1c (Mean ± SD)*	Outcome C *Fasting blood glucose (Mean ± SD)*	Outcome D *HDL (Mean ± SD)*	Outcome E *LDL (Mean ± SD)*	Outcome F *SBP (Mean ± SD)*	Outcome G *DBP (Mean ± SD)*
Brinkworth, 2004 [2]	RCT	Type 2 DM I: 19 C: 19	I: 40:**30**:30 C: 55:**15**:30	I: -3.7 ± 4.36 C: -2.2 ± 4.79	-	-	-	-	-	-
Larsen, 2011 [5]	RCT	Type 2 DM I: 53 C:46	I: 40:**30**:30 C: 55:**15**:30	*I: -2.23 ± 3.78** *C: -2.16 ± 4.26**	*I: -0.23 ± 1.06** *C: -0.28 ± 0.99**	-	*I: 0.08 ± 0.29** *C: 0.07 ± 0.23**	*I: -0.05 ± 0.59** *C: 0.04 ± 0.76**	*I: -5.03 ± 11.49** *C: -0.76 ± 11.15**	*I: 0.205 ± 11.25** *C: 0.65 ± 11.30**
Luger, 2013[6]	RCT	Type 2 DM I: 21 C: 22	I: 40:**30**:30 C: 55:**15**:30	*I: -3.09 ± 2.44** *C: -1.01 ± 0.05**	*I: -0.25 ± 0.56** *C: -0.19 ± 0.60**	*I: -2.32 ± 3.47** *C: -0.12 ± 2.17**	*I: 0.02 ± 0.18** *C: 0.04 ± 0.15**	*I: -0.11 ± 0.71** *C: -0.05 ± 0.71**	*I: -6.19 ± 17.53** *C: 0.45 ± 8.15**	*I: -6.67 ± 9.66** *C: -1.59 ± 10.28**
Pedersen, 2013 [4]	RCT	Type 2 DM I: 21 C:24	I: 40:**30**:30 C: 50:**20**:30	*I: -9.7 ± 13.36** *C: -6.6 ± 7.10**	*I: -0.352 ± 1.12** *C: -0.25 ± 0.8**	*I: -1.0 ± 1.375** *C: -1.5 ± 2.45**	*I: 0.49 ± 2.10** *C: 0.08 ± 0.23**	*I: 0.19 ± 0.86** *C: 0.009 ± 0.55**	*I: -4.79 ± 13.08** *C: 1.79 ± 11.19**	*I: 2.54 ± 6.37** *C: 4.23 ± 9.25**
Wycherley, 2010 [7]	RCT	Type 2 DM I: 21 C:19	I: 47:**32**:18 C: 53:**18**:22	I: -9.0 ± 4.8 C: -8.6 ± 4.6	I: -1.8 ± 1.6 C: -1.1 ± 0.6	I: -2.5 ± 2.7 C: -2.2 ± 2.2	I: -0.1 ± 0.2 C: 0 ± 0.2	I: -0.2 ± 0.6 C: -0.3 ±0.5	I: -16 ± 13 C: -13 ± 11	I: -10 ± 6 C: -7 ± 6

* = significant values

*Cursive values = requested from the authors**

3.4 Excluded RCTs

Author, year	Study-type	Participants	Intervention		Exclusion
			Duration	Ratio (Carb:Protein:Fat)	
Bibra, 2013 [11]	Crossover	16 T2DM	2+3 w	25:30:45 vs. 55:20:25	difference between fat intake too high
Boden, 2005 [12]	CT	10 T2DM	2 w	Data in g per day: day 1 – 7: CHO: 309 g; F: 154 g; P: 137 g day 8 – 21: CHO: 21 g; F: 4 g; P: 151 g	no randomization, high risk of bias, difference between protein intake too little
Daly, 2006 [13]	RCT	102 T2DM	12 w	34:26:40 vs. 46:20:33	difference between fat intake too high
Davis, 2011 [14]	RCT	27 T2DM	6 mo	Low Carb vs. Low Fat	no difference in protein intake
Davis, 2009 [15]	RCT	105 T2DM	1 y	24:27:49 vs. 53:22:25	difference between fat intake too high
De Mello, 2011 [16]	RCT	104 P with impaired glucose tolerance	12 w	-	non-diabetics, no information about protein intake
Dyson, 2008 [17]	Review	521 T2DM	-	-	
Dyson, 2007 [18]	RCT	26 (13 diabetic, 13 non-diabetics)	3 mo	17:31:46 vs. 39:20:34	too little diabetics, difference of fat intake too high
Elhayany, 2010 [19]	RCT	259 diabetics	12 mo	LC mediter. diet: 35:20:45 traditional mediter. diet: 50:20:30 ADA nutrition: 50:20:30	comparison mediterranean diet, difference fat intake, no difference between protein intake
Gannon, 2004 [20]	Crossover	8 T2DM	5 w	20:30:50 vs. 55:15:30	fat intake too high
Gutierrez, 1998 [21]	CT	28 T2DM	8 + 12 w	25:45:30 vs. 55:20:25	low quality, difference between fat intake too high
Hussain, 2012 [22]	RCT	363 obese (102 T2DM)	24 w	-	no data about nutrition
Keogh, 2007 [23]	RCT	73 obese hyperinsulinemic	12 mo	30:20:50 vs. 30:40:30	non-diabetics
Kirk, 2008 [24]	Metaanalyse	T2DM	-	-	difference of protein intake?
Khoo, 2011 [25]	RCT	31 T2DM	8w + 44w	0,8 g Protein/kg [LP] vs. 300 g lean meat [HP]	high risk of bias, very high dropout-rate (ca. 50%)
McAuley, 2006 [26]	RCT	93 insulinresistent women	12 mo	HP: 37:22:37; HF: 33:21:41 HC: 45:22:29	non-diabetics
McAuley, 2005 [27]	RCT	93 insulinresistent women	24 w	HP: 35:26:35; HF: 26:24:47 HC: 45:21:28	non-diabetics
McCarthy, 2012 [28]	Review	-	-	-	non-diabetics
Navas-Carretero, 2011 [29]	Longitudinal Studie	17 T2DM	4w+4w	-	no RCT, difference of fat intake
Papakonstantinou, 2010 [30]	Crossover	17 T2DM	4 w	50:30:20 vs. 50:15:35	difference of fat intake too high
Samaha, 2003 [31]	RCT	132 obese (39% diabetic)	6 mo	LF: 51:16:33	too little diabetics, difference of fat intake too high

				LC: 37:22:41	
Seshadri, 2004 [32]	RCT	78 obese (31 T2DM, 36 MetS)	6 mo	LC: CHO =32 ± 20% ; P=25±9%; F=43±17% Conventional Diet: CHO=50±16%; P=16±5%; F=33±14%	difference of fat intake too high, difference of protein intake?
Stern, 2004 [33]	RCT	132 obese (82 T2DM)	1 y	CHO<30g vs. caloric reduction of 500 kcal	fat intake different, not only diabetics
Tay, 2014 [34]	RCT	115	24 w	14:28:58 vs. 53:17:30	difference of fat intake too high
Westman, 2008 [35]	RCT	50 T2DM	24 w	13:28:59 vs. 44:20:36	difference of fat intake too high
Wheeler, 2012 [36]	Systematic Review	T2DM	-	-	
Wolever, 2008 [37]	RCT	162 T2DM	1 y	High GI: 47:22:31 Low GI: 52:21:27 LC: 39:21:40	difference of fat intake too high no difference between protein intake
Yancy, 2010 [38]		146 participants 31% diabetics	1 y	34:32:34 vs. 62:25:13	difference of fat intake too high

3.5 Different types of protein in patients with type 2 diabetes mellitus (RCT)

Author, year	Quality of evidence	SIGN	Study-type	Participants	Intervention		Results			
					Duration	Intervention vs. control	Glycaemic control/HbA1c	Proteinuria/GFR	Serumlipid	Bloodpressure
Azadbakht, 2008 [39]	1-	Acceptable (+)	RCT	41 T2DM with nephropathy	4 y	**Soy protein** (0,8 g/kg/d; 35% animal,35% TVP, 30% vegetable) vs. **Control** (0,8 g/kg/d; 70% animal, 30% vegetable)	FPG SP: 141+-55 >121+-42 CG: 137+-54>147+-57 T*G P=0.02	**SP:** **84+-19 > 88+-33** **CG:** **78+-23 > 81 +-35** **T*G n.s.**	**TC: SP:** **225+-48 > 201+-35** **CG:** **218+-38 > 228 +- 48** **T*G p=0.01** **TG, LDL, HDL n.s.**	n.s.
Pecis, 1994 [40]	1-	Acceptable (+)	RCT, crossover	15 T1DM	13 w (3x3 w interv. and 2 w washout)	**Usual diet** (meat: 79,4% beef, 20,6% chicken) vs. **Low protein diet** (0,5g/kg/d vegetable and milk protein, 7% P/60% CHO/33% F) vs. **Test diet** (same like usual, red meat replaced by 85% chicken and 15% fish)	No change	**GFR:** significant ↓ after LPD and test diet **UAE:** no change	**Chol:** significant ↑ in usual diet **HDL:** no change **TG:** no change	No change
Wheeler, 2002 [41]	1-	Acceptable (+)	RCT, crossover	23 T2DM	16 w (2x6 w interv. and 4 w washout)	**Animal protein** (60% animal, 40% plant) vs. **Plant protein** (tofu, TVP, soy, legumes)	**AP:** 7,9%→7,4% (P<0,01) **PP:** 8,1%→7,5% (P<0,01) **No diet effect**	**GFR and AER**: no change	**Chol:** 4,75→4,34 mmol/l (P<0,01) in both groups **TG:** no change **HDL:** no change	**Diastolic pressure:** **AP:**82→78 mmHg (P<0,02) **PP:**83→80 mmHg (P<0,02) **Systolic pressure:** no change

Gross, 2002 [42]	1-	Acceptable (+)	RCT, crossover	33 T2DM	20 w (3x4 w interv. and 4 w washout)	**Usual diet** (*achieved 1,43±0,3 g/kg/d*) vs. **Low protein** (0,5-0,8 g/kg/d, only milk and vegetable protein, *achieved 0,66±0,2 g/kg/d*) vs. **Chicken diet** (1,2-1,5 g/kg/d, red meat replaced by chicken*, achieved 1,35±0,3 g/kg/d*)	No change	**GFR in normoalbuminuric:** Lower after chicken (101,3±22,9 ml/min/1,73m²) and low protein (93,8±20,5ml/min/1,73m²) than after usual (113,4±31,4ml/min/1,73m²), P<0,05 **GFR in microalbuminuric:** Lower after low protein (93,5±8,5ml/min/1,73m²) than after chicken (102,8±22,5ml/min/1,73m²) and usual (107,1±20,1ml/min/1,73m²), P<0,05 **UAER in normoalbuminuric:** No change **UAER in microalbuminuric:** After chicken (median 34,3µg/min) significantly lower than after usual (median 63,8µg/min) and low protein (median 52,3µg/min), P<0,05	**Normoalbuminuric:** No change in chol, HDL, LDL, apolipo B, TG **Microalbuminuric:** Apolipo B significantly lower after chicken(113,5±36mg/dl) and low protein (103,5±40,1mg/dl) than after usual (134,3±30,7mg/dl), P<0,05	No change
Pipe, 2009 [43]	1-	Acceptable (+)	RCT, crossover, doubleblind, placebo-controlled	34 T2DM	2x57 d with 28 d washout	**Soy protein isolate** (40 g protein and 88 mg isoflavones) vs. **Milk protein isolate** (40 g protein, no isoflavones)	Not measured	Not measured	**LDL:** **MPI:** 2,98±0,14→2,9±0,12mmol/l **SPI:** 2,95±0,12→2,78±0,13mmol/l P=0,04 **LDL:HDL:** **MPI:** 2,66±0,12→2,66±0,11 **SPI:** 2,53±0,1→2,5±0,1	Not measured

									P=0,02 **<u>Apolipo B:apolipo A-I:</u>** **MPI:** 0,67±0,03→0,67±0,03 **SPI:** 0,67±0,03→0,64±0,03 P=0,05	

3.6 Low protein intake in diabetic nephropathy (RCT)

Author, year	Quality of evidence	SIGN	Study-type	Participants	Intervention					Results		
					Duration	Protein intake (g/kg Bodyweight) “Low protein”		“Normal protein”				
						prescribed	achieved	prescribed	achieved	Nephro pathy	GFR	HbA1c
Dullaart, 1993 [44]	1 -	Accep table (+)	RCT	31 IDDM	2 y	0,6	0,79	free	1,09	Microalb.	GFR-changes: LP: 131 ± 34 → 120 ± 20 → 113 ± 24 NP: 122 ± 26 → 119 ± 19 → 112 ± 21	changes : LP: 7,84 ± 0,93 → 8,02 ± 0,85 NP: 7,82 ± 1,01 → 8,01 ± 1,20
Dussol, 2005 [45]	1-	Accep table (+)	RCT	63 T1DM + T2DM	24 mo	0,8	0,87	1,2	1,03	Microalb + Macroalb.	GFR- changes : LP: 82 ± 21 → 80 ± 23 → 74 ± 25 decline: -7 ± 11 NP: 89 ± 27 → 84 ± 33 → 82 ± 24 decline:-5 ± 15	changes: LP:8,4 ± 1,8 → 8,2 ± 1,3 → 7,9 ± 2,1 NP:8,0 ± 1,1 → 8,2 ± 1,4 →8,1 ± 2,2
Hansen, 2002 [46]	1 -	Accep table (+)	RCT	82 T1DM	4 y	0,6	0,89	free	1,02	Macroalb.	GFR-decline: LP: 7,6 (4,9 – 10,2) → -3,8 (2,8 – 4,8) NP:6,6 (5,2 – 8,1) → -3,9 (2,7 – 5,2)	changes : LP: 9,8 % (9,4 – 10,1) → 9,5 (9,1 – 9,9) NP: 9,6% (9,2 – 9,9) → 9,6 (9,3 – 10,0)
Koya, 2009 [47]	1 -	Accep table (+)	RCT	112 T2DM	60 mo	0,8	1,0	1,2	1,0	Macroalb.	eGFR (annual changes): LP: - 6,1 ± 6,5 NP: -5,8 ± 5,7	Baseline: LP: 7,8 ± 1,5 NP: 7,5 ± 1,7
Meloni, 2002 [48]	1 -	Accep table (+)	RCT	69 (32 T1 and 37 T2DM)	1 y	0,6	0,68 ± 0,21	free	1,39 ± 0,28	Diabet. Nephrop.	GFR- changes : LP: 43 ± 4,7 →38 ± 9,6 NP: 45 ± 5,1 →39 ± 7,2	changes: LP: 7,2 ± 0,5 →6,0 ± 1,1 NP: 6,7 ± 0,5 →6,2 ± 0,8
Pedersen, 2013 [4]			RCT	45 T2DM	1 y	-	-	-	-	Microalb. + Macroalb.	iGFR- changes : HP: 108 ± 7,3 → 101 ± 6,1 NP: 91,9 ± 5,5 → 93,9 ± 5,4	changes: HP: 7,5 ± 0,2 → 7,2 ± 0,2 NP: 7,2 ± 0,1 → 6,9 ± 0,2
Pijls, 2002 [49]	1 -	Accep table (+)	RCT	131 T2DM	28 ± 7 mo	0,8	1,1	free	1,14	Normoalb. + Microalb.	GFR decline 6 Mo- LP: -2,9 ± 17 ; NP: -1,3 ± 15	Baseline: LP: 7,7 ± 1,4 NP: 7,7 ± 1,5

											12 Mo-LP: -4,8 ± 12; NP: -6,4 ± 14	
Raal, 1994 [50]	1 -	Accep table (+)	RCT	22 IDDM	6 mo	0,8	0,87	1,6	2,0	Macroalb.	GFR- changes : LPD: 50 ± 19 → 53 ±23 UPD: 66 ± 28 → 58 ± 26	changes: LPD: 12,0 ± 3,4 → 11,7 ± 4,6 UPD: 13,9 ± 2,4 → 12,4 ± 5,5
Velazquez, 2008 [51]	1 -	Accep table (+)	RCT	T2DM	4 mo	0,6 – 0,8	0,82	1,0 – 1,2	1,2	Normoalb. + Microalb + Macroalb.	GFR- changes : LPD normo: 87,5 ± 15,2 →86,2 ± 18,2 LPD microalb: 69,7 ± 36,9 → 76,2 ± 35,6 LPD macroalb: 56,3 ± 29,0 → 74,2 ± 40,4 NPD normo: 81,5 ± 21,7 → 78,6 ± 19,7 NPD microalb: 89,2 ± 32,1 → 81,9 ± 34,6 NPD macroalb: 74,4 ± 31,4 → 65,1 ± 25,5	changes: LPD normo: 7,5 ± 1,5 → 6,8 ± 0,8 LPD microalb: 8,2 ± 1,6 → 7,2 ± 1,8 LPD macroalb: 8,4 ± 2,1 → 7,6 ± 1,0 NPD normo: 8,8 ± 2,2 → 7,9 ± 1,3 NPD microalb: 8,8 ± 1,9 → 7,1 ± 0,8 NPD macroalb: 8,1 ± 1,8 → 6,9 ± 1,6
Walker, 1989 [52]	-	Reject (-)	CT	19 IDDM	NP: 29 mo LP: 33 mo	-	0,67	-	1,13	Macroalb. Alb-excretion: > 300µg	GFR-decline: LP: 0,14 ml/min per month NP: 0,61 ml/min per month (signif.)	?
Zeller, 1991 [53]	-	Reject (-)	RCT	35 T1DM with Nephropathy	Ø 3 y	0,6	0,72	> 1,0	1,08	Macroalb.		7,9 %

3.7 Low protein intake in diabetic nephropathy (existing meta-analysis)

<table>
<tr><th>Author, Year</th><th>Evidence</th><th>SIGN</th><th>Study-type</th><th>Aim</th><th>Search strategy</th><th>Inclusion criteria</th><th>Participants</th><th>Results</th></tr>
<tr><td>Kasiske, 1998 [54]</td><td>0</td><td>Unacceptable - Reject</td><td>MA</td><td>Effect of low-protein diet on kidney function in diabetic nephropathy</td><td>Not described</td><td></td><td>23 studies (6 studies with diabetes patients and 17 persons without diabetes</td><td>Dietary protein restriction retards the rate of renal function decline.</td></tr>
<tr><td>Maeda, 2007 [55]</td><td>0</td><td>No SR</td><td>R</td><td>Diet therapy in diabetic nephropathy</td><td colspan="3">No Systematic Review</td><td>Protein restriction should be prescribed for patients with diabetic nephropathy, as far as calorie intake is sufficient and the prescribed protein intake does not cause malnutrition.</td></tr>
<tr><td>Nezu, 2013 [1]</td><td>1 ++</td><td>High quality (++)</td><td>SR + MA</td><td>Effect of low-protein diet on kidney function in diabetic nephropathy</td><td>PubMed, EMBASE, Cochrane library, ClinicalTrials.gov, International Standard RCT, UMIN-CTR</td><td>Fulltext available
- RCT
- measured: GFR, CCr, proteinurie, albuminuria, HbA1c, serum albumin</td><td>779 Persons with Diabetes mellitus Type 1 and type 2</td><td>A diet intervention by a low protein diet hast modest but significant effects on the course of kidney prognosis in patients with diabetic nephropathy, especially when the intervention is sustainable regarding patients compliance.

The quality of the evidence for GFR was low.</td></tr>
<tr><td>Otoda, 2014 [56]</td><td>0</td><td>No SR</td><td>R</td><td>Protein restriction in diabetic nephropathy</td><td>MEDLINE, PubMed, EMBASE, ClinicalTrials.gov, Cochrane Controlled Clinical Trials</td><td colspan="2">No Systematic Review</td><td>The significant benefits of LPD on progressive renal diseases in rodent and human studies did not reveal that there is much impact of the renoprotective strategies against kidney disease including diabetes.</td></tr>
</table>

Pan, 2008 [57]	1 +	Acceptable (+)	MA	Protein restriction in diabetic nephropathy	MEDLINE, EMBASE, ClinicalTrials.gov, Cochrane Controlled Clinical Trials	- > 6 month - RCT - measured: GFR, CCr)	8 included studies (Type 1 und Type 2 Diabetes with diabetic nephropathy)	A low protein diet was not associated with a significant improvement of renal function in patients with either type 1 and 2 diabetic nephropathy
Pedrini, 1996 [58]	0	Unacceptable - Reject	MA	The effect of dietary protein restriction on the progression of renal disease	MEDLINE, references in review articles	- Fulltext available - RCT	5 studies with persons without diabetes (1413 participants) 5 studies with insulin dependent diabetes (108 participants)	Dietary protein restriction effectively slows the progression of both diabetic and nondiabetic renal disease
Robertson, 2009 [59]	1 ++	High quality (++)	SR	Protein restriction for diabetic renal disease	The Cochrane library MEDLINE EMBASE ISI Proceedings Science citation index expanded	- > 4 month - Type 1 und type 2 diabetes - Comparison Low-Protein vs. Normal (Usual-) Protein	160 persons with Diabetes mellitus Type 1 und type 2	Overall, a restricted protein intake does appear to slow the progression of diabetic nephropathy albeit in a non-significant way**.** Studies did not give sufficient details to quantify this.

3.8 Working document – Results of low protein diet in diabetic nephropathy

Author, Year	Study Type	Population	Actual Protein intake (g/kg/BW)	Outcome A *GFR changes ml/min/1,73 m²* *(Mean ± SD)*	Outcome B *HbA1c %* *(Mean ± SD)*
Dullaart, 1993 [44]	RCT	31 IDDM	I: 0,79 C: 1,09	Changes in GFR: LP: 131 ± 34 → 120 ± 20 → 113 ± 24 NP: 122 ± 26 → 119 ± 19 → 112 ± 21	LP: 7,84 ± 0,93 → 8,02 ± 0,85 NP: 7,82 ± 1,01 → 8,01 ± 1,20
Dussol, 2005 [45]	RCT	63 T1+T2DM	I: 0,87 C: 1,03	Changes in GFR: LP: 82 ± 21 → 80 ± 23 → 74 ± 25 decline: -7 ± 11 NP: 89 ± 27 → 84 ± 33 → 82 ± 24 decline:-5 ± 15	LP:8,4 ± 1,8 → 8,2 ± 1,3 → 7,9 ± 2,1 NP:8,0 ± 1,1 → 8,2 ± 1,4 →8,1 ± 2,2
Hansen, 2002 [46]	RCT	82 T1DM	I: 0,89 C: 1,02	Decline of GFR: LP: 7,6 (4,9 – 10,2) → - 3,8 (2,8 – 4,8) NP:6,6 (5,2 – 8,1) → -3,9 (2,7 – 5,2)	LP: 9,8 % (9,4 – 10,1) → 9,5 (9,1 – 9,9) NP: 9,6% (9,2 – 9,9) → 9,6 (9,3 – 10,0)
Koya, 2009 [47]	RCT	112 T2DM	I: 1,0 C: 1,0	eGFR (annual changes): LP: - 6,1 ± 6,5 NP: -5,8 ± 5,7	-
Meloni, 2002 [48]	RCT	69 T1+T2DM	I: 0,68 C: 1,39	Changes in GFR: LP: 43 ± 4,7 →38 ± 9,6 NP: 45 ± 5,1 →39 ± 7,2	LP: 7,2 ± 0,5 →6,0 ± 1,1 NP: 6,7 ± 0,5 →6,2 ± 0,8
Pedersen, 2013 [4]	RCT	45 T2DM	-	Changes in iGFR: HP: 108 ± 7,3 → 101 ± 6,1 NP: 91,9 ± 5,5 → 93,9 ± 5,4	LP: 7,2 ± 0,5 →6,0 ± 1,1 NP: 6,7 ± 0,5 →6,2 ± 0,8
Pijls, 2002 [49]	RCT	131 T2DM	I: 1,1 C: 1,14	Decline of GFR 6 mo- LP: -2,9 ± 17 ; NP: -1,3 ± 15 12 mo-LP: -4,8 ± 12; NP: -6,4 ± 14	-
Raal, 1994 [50]	RCT	22 IDDM	I: 0,87 C: 2,0	Changes in GFR: LPD: 50 ± 19 → 53 ±23 UPD: 66 ± 28 → 58 ± 26	LPD: 12,0 ± 3,4 → 11,7 ± 4,6 UPD: 13,9 ± 2,4 → 12,4 ± 5,5
Velazquez, 2008 [51]	RCT	60 T2DM	I: 0,82 C: 1,2	Changes in GFR: LPD normo: 87,5 ± 15,2 →86,2 ± 18,2 LPD microalb: 69,7 ± 36,9 → 76,2 ± 35,6 LPD macroalb: 56,3 ± 29,0 → 74,2 ± 40,4 NPD normo: 81,5 ± 21,7 → 78,6 ± 19,7 NPD microalb: 89,2 ± 32,1 → 81,9 ± 34,6 NPD macroalb: 74,4 ± 31,4 → 65,1 ± 25,5	LPD normo: 7,5 ± 1,5 → 6,8 ± 0,8 LPD microalb: 8,2 ± 1,6 → 7,2 ± 1,8 LPD macroalb: 8,4 ± 2,1 → 7,6 ± 1,0 NPD normo: 8,8 ± 2,2 → 7,9 ± 1,3 NPD microalb: 8,8 ± 1,9 → 7,1 ± 0,8 NPD macroalb: 8,1 ± 1,8 → 6,9 ± 1,6

4 GRADE

4.1 Summary of findings table - high protein diets in diabetes patients

high protein diet compared to normal protein diet for diabetes mellitus

Patient or population: patients with diabetes mellitus
Settings: outpatient
Intervention: high protein diet
Comparison: normal protein diet

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Normal protein diet**	Corresponding risk **High protein diet**				
Weight loss (kg) Scale Follow-up: 4 to 15 months	The mean weight loss (kg) ranged across control groups from **-1.01 to 8.6 kg**	The mean weight loss (kg) in the intervention groups was **1.21 lower** (2.17 to 0.24 lower)		265 (5 studies)	⊕⊕⊝⊝ **low**[1,2,3,4,5,6]	
Fasting blood glucose (mmol/l) Standard methods Follow-up: 3 to 12 months	The mean fasting blood glucose (mmol/l) ranged across control groups from **-0.12 to -1.5 mmol/l**	The mean fasting blood glucose (mmol/l) in the intervention groups was **0.72 lower** (1.98 lower to 0.54 higher)		128 (3 studies)	⊕⊝⊝⊝ **very low**[1,2,5,7,8,9,10]	
HbA1c (%) High performance liquid chromatography (HPLC) Follow-up: 3 to 12 months	The mean hba1c (%) ranged across control groups from **-0.19 to -1.1 %**	The mean hba1c (%) in the intervention groups was **0.1 lower** (0.33 lower to 0.14 higher)		227 (4 studies)	⊕⊕⊝⊝ **low**[1,2,5,6,7,8]	
High density lipoprotein (HDL) (mmol/l) Standard methods Follow-up: 3 to 12 months	The mean high density lipoprotein (hdl) (mmol/l) ranged across control groups from **0 to 0.083 mmol/l**	The mean high density lipoprotein (hdl) (mmol/l) in the intervention groups was **0.02 lower** (0.07 lower to 0.04 higher)		226 (4 studies)	⊕⊕⊝⊝ **low**[1,2,5,6,7,8]	
Low density lipoprotein (LDL) (mmol/l) Standard methods Follow-up: 3 to 12 months	The mean low density lipoprotein (ldl) (mmol/l) ranged across control groups from **-0.05 to 0.0444 mmol/l**	The mean low density lipoprotein (ldl) (mmol/l) in the intervention groups was **0.07 lower** (0.25 lower to 0.1 higher)		226 (4 studies)	⊕⊕⊝⊝ **low**[1,2,5,6,7,8]	
Systolic blood pressure (mmHg) Automated sphygmanometer Follow-up: 3 to 12 months	The mean systolic blood pressure (mmhg) ranged across control groups from **-13 to 0.45 mmHg**	The mean systolic blood pressure (mmhg) in the intervention groups was **4.41 lower** (7.88 to 0.94 lower)		227 (4 studies)	⊕⊕⊝⊝ **low**[1,2,5,6,7,8]	

Diastolic blood pressure Automated sphygmanometer Follow-up: 3 to 12 months	The mean diastolic blood pressure ranged across control groups from **-7 to 4.23 mmHg**	The mean diastolic blood pressure in the intervention groups was **3.61 lower** (6.27 to 0.95 lower)		227 (4 studies)	⊕⊕⊖⊖ **low**[1,2,5,6,7,8]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] The subjects were not blinded to treatment allocation
[2] With one exception there were no blinding of outcome assessment
[3] Two studies did not analyse all subjects in the groups which they were randomly allocated (intention-to-treat)
[4] Three studies had a high dropout rate. (> 20%)
[5] Publication bias was not assessed as there were inadequate numbers of included trials to properly assess a funnel plot or more advanced regression-based assessments
[6] Two studies were partly funded by the meat industry
[7] Two studies had a high dropout rate (> 20%)
[8] One study did not analyses all subjects in the groups which they were randomly allocated (intention-to-treat)
[9] $I^2 = 54\%$ (Cochrane Handbook 5.0: substantial heterogeneity)
[10] One study were partly funded by the meat industry

4.2 GRADE profile – high protein diets in diabetes patients

Question: Should high protein diet vs normal protein diet be used for diabetes mellitus?

Bibliography: High protein diets for Type 2 diabetes

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Normal protein diet	**With High protein diet**		**Risk with Normal protein diet**	**Risk difference with High protein diet** (95% CI)
Weight loss (kg) (IMPORTANT OUTCOME; measured with: Scale; Better indicated by lower values)											
265 (5 studies) 4 to 15 months	very serious[1,2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[5,6]	⊕⊕⊖⊖ **LOW**[1,2,3,4,5,6] due to risk of bias	130	135	-	The mean weight loss (kg) ranged across control groups from **-1.01 to 8.6 kg**	The mean weight loss (kg) in the intervention groups was **1.21 lower** (2.17 to 0.24 lower)
Fasting blood glucose (mmol/l) (IMPORTANT OUTCOME; measured with: Standard methods; Better indicated by lower values)											
128 (3 studies) 3 to 12 months	very serious[1,2,7,8]	serious[9]	no serious indirectness	no serious imprecision	undetected[5,10]	⊕⊖⊖⊖ **VERY LOW**[1,2,5,7,8,9,10] due to risk of bias, inconsistency	65	63	-	The mean fasting blood glucose (mmol/l) ranged across control groups from **-0.12 to -1.5 mmol/l**	The mean fasting blood glucose (mmol/l) in the intervention groups was **0.72 lower** (1.98 lower to 0.54 higher)
HbA1c (%) (IMPORTANT OUTCOME; measured with: High performance liquid chromatography (HPLC); Better indicated by lower values)											
227 (4 studies)	very serious[1,2,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[5,6]	⊕⊕⊖⊖ **LOW**[1,2,5,6,7,8] due to risk of bias	111	116	-	The mean hba1c (%) ranged across control	The mean hba1c (%) in the intervention groups was

3 to 12 months										groups from **-0.19 to -1.1 %**	**0.1 lower** (0.33 lower to 0.14 higher)
High density lipoprotein (HDL) (mmol/l) (IMPORTANT OUTCOME; measured with: Standard methods; Better indicated by lower values)											
226 (4 studies) 3 to 12 months	very serious[1,2,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[5,6]	⊕⊕⊝⊝ **LOW**[1,2,5,6,7,8] due to risk of bias	110	116	-	The mean high density lipoprotein (hdl) (mmol/l) ranged across control groups from **0 to 0.083 mmol/l**	The mean high density lipoprotein (hdl) (mmol/l) in the intervention groups was **0.02 lower** (0.07 lower to 0.04 higher)
Low density lipoprotein (LDL) (mmol/l) (IMPORTANT OUTCOME; measured with: Standard methods; Better indicated by lower values)											
226 (4 studies) 3 to 12 months	very serious[1,2,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[5,6]	⊕⊕⊝⊝ **LOW**[1,2,5,6,7,8] due to risk of bias	110	116	-	The mean low density lipoprotein (ldl) (mmol/l) ranged across control groups from **-0.05 to 0.0444 mmol/l**	The mean low density lipoprotein (ldl) (mmol/l) in the intervention groups was **0.07 lower** (0.25 lower to 0.1 higher)
Systolic blood pressure (mmHg) (IMPORTANT OUTCOME; measured with: Automated sphygmanometer; Better indicated by lower values)											
227 (4 studies) 3 to 12 months	very serious[1,2,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[5,6]	⊕⊕⊝⊝ **LOW**[1,2,5,6,7,8] due to risk of bias	111	116	-	The mean systolic blood pressure (mmhg) ranged across control groups from **-13 to 0.45 mmHg**	The mean systolic blood pressure (mmhg) in the intervention groups was **4.41 lower** (7.88 to 0.94 lower)
Diastolic blood pressure (IMPORTANT OUTCOME; measured with: Automated sphygmanometer; Better indicated by lower values)											
227 (4 studies) 3 to 12 months	very serious[1,2,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected[5,6]	⊕⊕⊝⊝ **LOW**[1,2,5,6,7,8] due to risk of bias	111	116	-	The mean diastolic blood pressure ranged across control groups from **-7 to 4.23 mmHg**	The mean diastolic blood pressure in the intervention groups was **3.61 lower** (6.27 to 0.95 lower)

4.3 Summary of findings table – low protein diets in diabetic nephropathy

Low Protein Diet compared to Normal Protein Diet for Albuminuria in patients with type 2 diabetes

Patient or population: patients with Albuminuria in patients with type 2 diabetes
Settings:
Intervention: Low Protein Diet
Comparison: Normal Protein Diet

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Normal Protein Diet**	Corresponding risk **Low Protein Diet**				
GFR Follow-up: 4 to 60 months	The mean gfr ranged across control groups from **-2.9 to -20.3 ml/min/1.73m²**	The mean gfr in the intervention groups was **4.65 higher** (0.32 lower to 9.62 higher)		478 (9 studies)	⊕⊕⊝⊝ **low**[1,2,3,4,5]	
proteinuria Follow-up: 4 to 60 months	The mean proteinuria ranged across control groups from **210 to -233**	The mean proteinuria in the intervention groups was **0.4 standard deviations higher** (0.13 lower to 0.94 higher)		488 (11 studies)	⊕⊕⊝⊝ **low**[1,5,6,7,8]	SMD 0.4 (-0.13 to 0.94)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Most of the patients were not blinded to treatment allocation
[2] Four studies did not analyse all subjects in the groups which they were randomly allocated (intention-to-treat)
[3] Two studies had a high dropout rate (> 20 %)
[4] I^2 = 87% (Cochrane Handbook 5.0: considerable heterogeneity)
[5] Publication bias was not assessed as there were inadequate numbers of included trials to properly assess a funnel plot or more advanced regression-based assessments
[6] Five studies did not analyses all subjects in the group which they were randomly allocated (intention-to-treat)
[7] Three studies had a high dropout rate (> 20 %)
[8] I^2 =86% (Cochrane Handbook 5.0: considerable heterogeneity)

4.4 GRADE profile – low protein diets in diabetic nephropathy

Question: Low Protein Diet vs Normal Protein Diet for Albuminuria in patients with type 2 diabetes
Bibliography: Low Protein Diet for Albuminuria in patients with type 2 diabetes.

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Normal Protein Diet	**With Low Protein Diet**		**Risk with Normal Protein Diet**	**Risk difference with Low Protein Diet** (95% CI)
GFR (Better indicated by lower values)											
478 (9 studies) 4 to 60 months	serious[1,2,3]	serious[4]	no serious indirectness	no serious imprecision	undetected[5]	⊕⊕⊝⊝ **LOW**[1,2,3,4,5] due to risk of bias, inconsistency	245	233	-	The mean gfr ranged across control groups from **-2.9 to -20.3 ml/min/1.73m²**	The mean gfr in the intervention groups was **4.65 higher** (0.32 lower to 9.62 higher)
proteinuria (Better indicated by lower values)											
488 (11 studies) 4 to 60 months	serious[1,6,7]	serious[8]	no serious indirectness	no serious imprecision	undetected[5]	⊕⊕⊝⊝ **LOW**[1,5,6,7,8] due to risk of bias, inconsistency	245	243	-	The mean proteinuria ranged across control groups from **210 to -233**	The mean proteinuria in the intervention groups was **0.4 standard deviations higher** (0.13 lower to 0.94 higher)

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