REVIEW

AN Advances in Nutrition An International Review Journal

Prevention of Type 2 Diabetes through Lifestyle Modification: Is There a Role for Higher-Protein Diets?[1,2]

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ABSTRACT

Type 2 diabetes (T2D) incidence is increasing worldwide, driven by a rapidly changing environment and lifestyle and increasing rates of overweight and obesity. Prevention of diabetes is key and is most likely achieved through prevention of weight gain and/or successful long-term weight loss maintenance. Weight loss is readily achievable but there is considerable challenge in maintaining that weight loss over the long term. Lower-fat carbohydrate-based diets are widely used for T2D prevention. This is supported primarily by 3 successful long-term interventions, the US Diabetes Prevention Program, the Finnish Diabetes Prevention Study, and the Chinese Da Qing Study, but evidence is building in support of novel higher-protein (>20% of energy) diets for successful weight loss maintenance and prevention of T2D. Higher-protein diets have the advantage of having relatively low energy density, aiding longer-term appetite suppression, and preserving lean body mass, all central to successful weight loss and prevention of weight regain. Here, we review the carbohydrate-based intervention trials and present mechanistic evidence in support of increased dietary protein for weight loss maintenance and a possible novel role in prevention of dysglycemia and T2D. *Adv Nutr* 2015;6:665–73.

Keywords: lifestyle modification, dietary protein, carbohydrate, fat, prediabetes, T2D, obesity

Introduction

The incidence of type 2 diabetes (T2D)[3] is increasing worldwide, arising from weight gain and obesity, and the cost to society is rising with the increased prevalence, paralleled by a decreased quality of life and increased morbidity and health care costs (1). There were 110 million individuals reported globally with T2D in 1994 and 382 million in 2013 (2), and in the United States alone, prevalence doubled from 5.1% in 1988–1994 to 10.9% in 2013 (3, 4). The highest global prevalence of 40% is on the small South Pacific Island of Tokelau (4), and other Pacific nations such as New Zealand are following a similar trend (4, 5). Demographics are rapidly changing (4, 6) with ~80% from low- and middle-income countries (1, 4), led in large part by China, where a prevalence of <1% in 1980 has grown to 9.6%, and where sheer size of numbers means ~100 million individuals are living with T2D (4, 7). Those diagnosed are also getting younger, a consequence of rising obesity in the adolescent population (8). Economic costs are astronomical. In 2010, the estimated T2D-related global health expense was $376 billion (12% of the total) with a US estimated cost of $245 billion [$13,700/(person · y)] in 2012 (8), >2-fold higher than for those without T2D (9). Prevention is essential and must be a central focus for health policy and government action, where programs based on lifestyle modification [diet and physical activity (PA)] provide a cost-effective opportunity to target overweight, high-risk individuals (10, 11).

Current Status of Knowledge

Obesity and T2D risk

A primary cause of T2D is weight gain and obesity, with the WHO reporting 2.3 billion overweight and >700 million obese adults in 2013, driving the T2D epidemic (4). The

[1] Supported by the Neige Todhunters Award, Dietitians New Zealand (AYL), University of Auckland Faculty Research Development Fund Fellowship (MPS), and New Zealand Heath Research Council (SDP).

[2] Author disclosures: SDP holds the Fonterra Chair in Human Nutrition. AY Liu, MP Silvestre, and SD Poppitt, no conflicts of interest.

[3] Abbreviations used: BCAA, branch chain amino acids; BW, body weight; DPP, diabetes prevention program; DPS, diabetes prevention study; EPIC, European Prospective Investigation into Cancer and Nutrition; GI, glycemic index; HP, higher protein; IGT, impaired glucose tolerance; LM, lean mass; PA, physical activity; PREVIEW, PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World; SLIM, Study on Lifestyle Intervention and impaired glucose tolerance Maastricht; T2D, type 2 diabetes.

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characteristic phenotype includes older age, overweight/obesity, central adiposity, hyperinsulinemia, dyslipidemia, and hypertension (12–14). Excess adiposity drives worsening insulin resistance and/or β cell dysfunction, which is central to the underlying cause of T2D. The US Diabetes Prevention Program (DPP) showed weight loss to be the dominant predictor for decrease in incidence, with T2D risk decreasing by 16%/kg body weight (BW) lost in a 3 y intervention (15, 16). Obesity is the number 1 risk factor in the American Diabetes Association standards of medical care, upon which T2D status in asymptomatic patients is based (14). Of the 3 primary risk factors of family history, age, and obesity, obesity is the only modifiable cause (13), and is hence a major target of T2D prevention.

Prevention of diabetes

Prediabetes, the presence of impaired fasting glucose or impaired glucose tolerance (IGT) and commonly identified through chronically raised glycated hemoglobin, represents a significantly increased risk of T2D (14). The impaired glucose homeostasis and insulin resistance of prediabetes is directly linked to obesity and physical inactivity, and is a key target of T2D prevention (7, 17). Meta-analysis of lifestyle and pharmacologic intervention concluded that lifestyle intervention may decrease the risk in individuals with IGT by 50% (18), with greater efficacy in those with a higher BMI (10, 16, 19–25). There has been a succession of carbohydrate-based prevention trials that have investigated long-term lifestyle modification for weight loss in prediabetics targeted at substituting dietary fat for carbohydrate to normalize glycemia. **Table 1** summarizes long-term (>2 y follow-up) trials in which modification of the fat-to-carbohydrate macronutrient ratio has been the primary target, the success of which has been encouraging, with a significant reduction in T2D risk across populations.

Diet and PA lifestyle modification studies

Early studies—Bedford, Whitehall, and Malmö. Whereas many trials have investigated the effect of diet on intermediary risk, far fewer have conducted long-term studies to determine the effect on incident T2D, with those studies focused primarily on fat and carbohydrate modification. The early Bedford survey (26, 27) and Whitehall (28) studies reported that whereas BW loss aided T2D prevention, intensive training in dietary carbohydrate restriction (<120 g/d) had no differential effect. Soon after, what may be the first combined lifestyle intervention for T2D prevention was conducted in Malmö, Sweden, in 415 middle-aged men with IGT or T2D (20, 29), who were given healthy eating advice, regular PA advice, and encouragement to lose weight. Successful weight loss resulted in a 63% RR of incident T2D (20), and, at 12-y follow-up, mortality rates were similar to healthy controls (29).

Randomized studies—Da Qing (China), Mercy (Australia), Japanese diabetes prevention study, United Kingdom, and New Zealand. The 6 y Chinese Da Qing diabetes prevention study (DPS) was the first large randomized lifestyle modification trial, in 577 adults with IGT allocated to diet and/or PA (7, 21), with individualized advice of a lower fat/higher carbohydrate diet, PA counseling, and weight loss goals. Diet, PA, and a combination lifestyle approach were all successful, with a risk reduction of 33–47% after 6 y (10) and 43% and 45% at 20 y and 23 y follow-up, respectively (21, 30). Four other lifestyle prevention trials rapidly followed. A 6 y study was conducted in 200 Australian women with IGT and a previous history of gestational diabetes (31) in which intensive healthy diet advice achieved a trend toward risk reduction (36%; $P > 0.05$). The Japanese DPS in 458 males with IGT was conducted over 4 y (32), with individualized advice to consume lower saturated and total fat and higher carbohydrate, in which the risk of incident T2D significantly decreased by 68%. In the United Kingdom, men with IGT were randomly allocated to intensive lower fat, higher complex carbohydrate/fiber and PA or no diet or PA advice over 6 mo (33). Risk was not assessed, and at the 2 y follow-up there was no significant improvement in fasting glycemia. A similar small but uncontrolled intervention in New Zealand, also with the goals of lowering saturated and total fat and increasing carbohydrate and dietary fiber, resulted in improved BW, postprandial glycemia, and fasting lipids at 2 y (34).

Finnish DPS, US DPP, and Indian DPP. The Finnish DPS was an important 3 y intervention in 522 middle-aged, overweight adults with IGT, with follow-up at 7 and 13 y (22, 35–37). The goal was 5% BW loss, followed by long-term weight loss maintenance and diet intervention was also lower fat and higher carbohydrate and fiber, plus PA. Significant risk reductions of 58%, 43%, and 32% were reported at 3, 7, and 13 y follow-up, respectively (35, 36, 38). To identify those at high risk of developing T2D, the well-known Finnish Diabetes Risk Score was developed in this trial (38, 39). These findings were replicated in the US DPP, a much larger 3 y trial in 3234 overweight adults with IGT who were randomly assigned to lifestyle modification (diet plus PA) or metformin (40). Recommendations were >7% BW loss through lower fat (~30% energy), lower calorie intake plus increased PA (40). T2D incidence was successfully reduced by 58% with lifestyle modification but by only 31% with metformin (40, 41). The 10 y follow-up DPP outcome study (DPPOS) then confirmed the long-term efficacy of lifestyle modification, with cumulative incidence of T2D reduced by 34% compared with 18% for metformin (42) and a delay in onset of T2D of 4 y. Recent reporting of a 15 y follow-up showed the risk reduction maintained at 27% (43). The Indian DPP repeated the US DPP, comparing lifestyle modification and metformin with a combined metformin plus lifestyle modification group in 531 middle-aged overweight adults with IGT (44) who decreased total fat, refined carbohydrate, and sugar intake, and increased dietary fiber intake. Although there was no BW loss, there was a significant risk reduction of 28.5%, 26.4%, and 28.2% in lifestyle modification, metformin, and lifestyle modification plus metformin intervention groups, respectively (44).

TABLE 1 Lifestyle intervention studies for diabetes prevention[1]

Trial, (reference), duration, and year	Population	Intervention	Effect on BW/BMI	Effect on T2D risk	Follow-up T2D risk
Bedford study United Kingdom (26, 27) 10 y (5+5)[2] 1962–1972	*n* = 241 49% F middle-aged O/W IGT	Carbohydrate restriction vs. general advice on table sugar vs. tolbutamide	No difference between groups at 5 y ($P > 0.05$), ns	No risk reduction for carbohydrate restriction at 5 y ($P > 0.05$), ns	10 y: no risk reduction for carbohydrate restriction ($P > 0.05$), ns
Whitehall study United Kingdom (28) 10 y (5+5)[2] 1967–1980	*n* = 204 M 48–65 y H, O/W IGT	Carbohydrate restriction vs. general advice on table sugar vs. phenformin	No difference between groups at 5 y ($P > 0.05$), ns	No risk reduction for carbohydrate restriction at 5 y ($P > 0.05$), ns	10 y: no risk reduction for carbohydrate restriction ($P > 0.05$), ns
Malmö study Sweden (20, 29) 6 y 1974–1992	*n* = 415 M 47–49 y H, O/W T2D, IGT NG	D+PA: nonrandomized 55 en% carbohydrate (high fiber), 10–15 en% protein, <30 en% fat vs. standard advice	2.0–3.3 kg BW loss for D+PA vs. 0.2–2.0 kg gain for standard advice ($P < 0.0001$)	63% risk reduction for D+PA at 6 y ($P < 0.003$)	12 y: lower mortality for D+PA ($P = 0.009$)
Da Qing study China (10, 21, 30) 6 y 1986–1992	*n* = 577 47% F >25 y H + O/W IGT	D only: 55–65 en% carbohydrate, 10–15 en% protein, 25–30 en% fat vs. PA only: increase leisure activity vs. D+PA vs. general information	0.9 kg BW gain for D only vs. 0.7 kg gain for PA only vs.1.8 kg loss for D+PA vs. 0.3 kg gain for general information	33% risk reduction for D only ($P < 0.03$), 47% for PA only ($P < 0.0005$), 38% for D+PA ($P < 0.005$)	20 y: 43% lower T2D incidence for combined lifestyle 23 y: 45% lower T2D incidence for combined lifestyle
Mercy Hospital Australia (31) 6 y 1989–1997	*n* = 200 F >36 y Previous GD H, O/W IGT	Intensive advice: healthy D+PA, regular follow-up vs, routine advice: healthy D+PA, no follow-up	0.8 kg/m^2 BMI gain for intensive D+PA vs. 0.6 kg/m^2 gain for routine advice	36.6% risk reduction, but ns ($P = 0.12$)	N/A
Japanese DPS (32) 4 y 1990–1996	*n* = 458 M 30–69 y H, O/W IGT	Intensive D+PA: 52–61 en% carbohydrate, 18–20 en% protein, 21–28 en% fat (low SFAs) vs. standard D+PA	2.18 kg BW loss for intensive D+PA vs. 0.39 kg loss for standard ($P < 0.001$)	67.4% risk reduction ($P < 0.001$)	N/A
Oxford United Kingdom (33) 6 mo Before 1990	*n* = 31 29% F 18–60 y H, O/W IGT	D+PA: 55 en% carbohydrate (high fiber), 15 en % protein, <30 en% fat, limit SFA vs. no D or PA advice	No BMI change from baseline for D+PA or difference between groups (both, $P > 0.05$), ns	Risk not reported; no FPG change from baseline for D+PA or difference between groups (both, $P > 0.05$), ns	2 y: FPG increase from baseline in D+PA ($P < 0.05$) but no difference between groups ($P > 0.05$), ns
New Zealand (34) 2 y 1988–1992	*n* = 52 52% F 18–79 y H, O/W T2D, IGT	D+PA: 50–55 en% carbohydrate (high fiber), 15–20 en% protein, <30 en% fat, limit SFA and sugars. No control group	0.6 kg BW loss for D+PA ($P < 0.001$); No between-group comparison	Risk not reported; 0.3 mmol/L reduction in OGTT 2 h glucose for D+PA ($P = 0.007$); no between-group comparison	N/A
Finnish DPS (22, 35–39) 3.2 y 1993–1998	*n* = 522 67% F 40–64 y O/W IGT	D+PA: high fiber, 30 en% fat, <10 en% SFA vs. general advice	3.5 kg BW loss for D+PA vs. 0.9 kg loss for general advice ($P < 0.0001$)	58% risk reduction for D+PA ($P < 0.001$)	7 y: 43% risk reduction ($P < 0.0001$) 13 y: 32% risk reduction ($P < 0.023$)
US DPP (40–43) 3 y 1996–2001	*n* = 3234 27 centers 68% F 25–85 y H, O/W IGT	D+PA: <25 en% fat, low EI, individualized vs. MF + standard advice vs. placebo + standard advice	5.6 kg BW loss for D+PA vs. 2.1 kg loss for MF vs. 0.1kg loss for placebo; between groups ($P < 0.001$)	58% risk reduction for D+PA; 31% risk reduction for MF; between groups, ($P < 0.001$)	10 y: 34% risk reduction for D+PA; 18% risk reduction for MF 15 y: 27% risk reduction for D+PA
Indian DPP (44) 3 y 2001–2005	*n* = 531 21% F 35–55 y H, O/W IGT	D+PA: low fat, low EI, low refined carbohydrate/ increased fiber vs. MF vs. D+PA+MF vs. usual care	~0.8 kg BW gain for D +PA ($P < 0.035$) vs. ~1 kg gain for usual care ($P < 0.01$); between groups ($P > 0.05$), ns	28.5% risk reduction in D+PA ($P = 0.018$); 26.4% in MF ($P = 0.029$); 28.2% in D+PA+MF ($P = 0.022$)	N/A

(Continued)

TABLE 1 (*Continued*)

Trial, (reference), duration, and year	Population	Intervention	Effect on BW/BMI	Effect on T2D risk	Follow-up T2D risk
SLIM Netherlands (19, 45,46) 3 y 1999–2005	*n* = 147 49% F >40 y O/W IGT	D+PA: >50 en% carbohydrate (high fiber), 30–35 en% fat, <10 en% SFAs vs. healthy eating	1.08 kg BW loss for D+PA vs. 0.16 kg BW gain ($P = 0.01$) for heathy eating	58% risk reduction for D+PA ($P = 0.025$)	N/A
EDIPS-Ncl (23, 24) 3 y 2000–2007	*n* = 102 59% F >40 y O/W IGT	D+PA: >50 en% carbohydrate (high fiber), <30% fat, <10% SFAs vs. health promotion advice	2.3 kg BW loss for D+PA vs. 0.01 kg BW gain for advice (year 1: $P < 0.007$)	55% risk reduction for D+PA, but ns ($P > 0.05$)	N/A
US (47) Japanese ethnicity 2 y 2002–2005	*n* = 74 55% F 42–66 y H, O/W IGT	D+PA: AHA Step 2, 55 en% carbohydrate, <30 en% fat, <7 en% SFAs, endurance PA vs. AHA Step 1, 50 en% carbohydrate, <30 en% fat, 10 en% SFAs, stretching PA	1.8 kg BW loss for Step 2 vs. 0.7 kg BW gain for Step 1 ($P < 0.0043$)	Risk not reported; improvement in IGT for Step 2 vs. Step 1 ($P < 0.010$)	N/A
Japanese DPP (25) 3 y 1999–2006	*n* = 304 50% F 30–60 y H, O/W IGT	D+PA: <25 en% fat, limit alcohol vs. healthy lifestyle advice	1.8 kg BW loss for D+PA vs. 1.4 kg loss for healthy lifestyle ($P = 0.069$), ns	51% risk reduction in D+PA, but ns ($P = 0.097$)	N/A
Zensharen (48) Japan 3 y 2004–2009	*n* = 641 28.5% F 30–60 y H, O/W IGT	D+PA: 55–60 en% carbohydrate (high fiber), 20–25 en% fat, frequent intervention vs. less frequent	2.5 kg BW loss for D+PA frequent intervention vs. 1.1 kg loss for less frequent ($P < 0.001$)	HR 0.56 (95% CI 0.36, 0.87) for D+PA frequent intervention	N/A
China (49) N/A	*n* = 60 43% F 34–65 y O/W, IGT	D+PA vs. D advice only	N/A	HR 0.30 (95% CI 0.10, 0.93) in D+PA	N/A
China (50) 5 y	*n* = 178 45% F 34–65 y IGT	D+PA: education + monitoring vs. education vs. acarbose vs. flumamine	N/A	HR 0.75 (95% CI 0.35, 1.60) in D+PA	N/A

[1] BW, body weight; D, diet; DPP, diabetes prevention program; DPS, diabetes prevention study; D+PA, diet plus physical activity; EDIPS-Ncl, European Diabetes Prevention Study–Newcastle; EI, energy intake; en%, percentage of energy; F, female; FPG, fasting plasma glucose; GD, gestational diabetes; H, healthy (BMI <25 kg/m^2); IGT, impaired glucose tolerance; M, male; MF, metformin; N/A, not available; NG, normoglycemia; ns, not statistically significant; OGTT, oral glucose tolerance test; O/W, overweight (BMI ≥25 kg/m^2); PA, physical activity; SLIM, study on lifestyle intervention and impaired glucose tolerance Maastricht; T2D, type 2 diabetes.
[2] Interim analysis at 5 y.

Other studies—SLIM, EDIPS-Ncl, Japanese-American study, Japanese DPP, Zensharen study, and Chinese studies. The European DPS replicated the DPS protocol both in the Netherlands [Study on Lifestyle-intervention and Impaired Glucose Tolerance Maastricht (SLIM)] and in the United Kingdom [European Diabetes Prevention Study–Newcastle (EDIPS-NcL)] (19, 23). SLIM was a 3 y intervention in 147 overweight middle-aged, individuals with IGT (19, 45, 46) that focused on lowering total and saturated fat and increasing PA, with a BW loss goal of 5–7%. This intervention resulted in a substantial 58% risk reduction (19). EDIPS-Ncl included 102 overweight adults with IGT in an identical 3 y intervention (23, 24); it reported a substantial 55% risk reduction. Since these studies, to our knowledge, 5 other prevention trials have been conducted with similar dietary aims of replacing fat in the diet with polysaccharide carbohydrate and dietary fiber. In middle-aged Japanese Americans with IGT, the AHA Step 2 diet significantly improved IGT variables, but risk data were not collected (47). The Japanese DPP included 304 adults with IGT in an intervention involving intensive diet plus PA advice and weight loss (25); it reported a 51% risk reduction. Zensharen was a larger study of 641 Japanese adults involving frequent individualized diet plus PA advice; it reported a 3-y HR of 0.56 (48). Finally, 2 Chinese studies, published in Mandarin but with English abstracts, have shown lifestyle intervention to decrease HRs to 0.30 and 0.75, respectively (49, 50).

It is clear that lifestyle modification can have a marked effect on the prevention of T2D in high-risk groups across genders and ethnicity. Commonly observed is the positive correlation between BW loss, maintenance of weight loss, and risk reduction. The largest of these trials, the US DPP, found a 16% risk reduction for every 1 kg BW loss (15), and other studies reported a 40–60% risk reduction for 5–7% BW loss in overweight populations with IGT. Notably in all of these studies, dietary strategy focused on replacing total and saturated fat with a higher-fiber, low-sugar carbohydrate diet (51). Replacement with dietary protein for weight loss, long-term weight loss maintenance, and prevention of T2D has not been investigated.

Higher-protein diets for weight loss and diabetes prevention

Clearly, lifestyle changes are important for T2D prevention, and should represent first-line public health recommendation. Diet intervention, as outlined in the studies presented in Table 1, has focused almost entirely on lipid and carbohydrate content and composition. Based on this evidence, international bodies such as the European Association for the Study of Diabetes recommend a lower-fat and moderate (45–60% of energy)–carbohydrate diet for the prevention of T2D based on increased vegetables, legumes, fruit, and whole grain cereals to provide foods rich in dietary fiber with a low glycemic index (GI). Recommended protein intake is 10–20% of energy (0.8–1.2 g/kg). To date, the evidence base has been insufficient to support specific recommendations for a higher-protein (HP) diet (>20% of energy) for T2D prevention. There is, however, a growing body of research that shows that HP diets may provide a useful aid for short-term weight loss, with evidence building in support of low-fat (25–30% of energy), moderate-carbohydrate (40–50% of energy), HP (20–25% of energy) diets for longer-term maintenance of weight loss and, hence, for T2D prevention (52–59). Higher dietary protein appears likely to promote weight management (52–56, 60), with estimates of weight loss as high as ~1 kg/wk when consumed ad libitum (57, 58). A recent meta-analysis (59) of 32 trials assessing HP diets selected on the basis of >12 mo follow-up concluded that benefits observed in the short term persist to a smaller degree in the long term, with greater benefits associated with better compliance to the diet. A second meta-analysis of 9 studies lasting ≤6 mo also confirmed a beneficial effect of HP diets on weight loss in T2D cohorts (61). Although not all data support these findings (62), clearly the global macronutrient composition of the diet may be important. Protein can be substituted into the diet in place of either fat, carbohydrate, or both. Low-carbohydrate diets, which have been shown to promote short-term weight loss are commonly diets in which protein has been increased, if not HP diets per se (63). It has been hypothesized that the efficacy of low-carbohydrate diets may be driven by substitution with dietary protein, given that this macronutrient switch has been common in many of these trials (64–66). Unraveling this issue, however, is complex. A recent review reported that "body-weight loss and weight-maintenance depends on the high-protein, but not on the 'low carb' component of the diet" (67), but this has not been a universal conclusion. It has also been proposed that low-carbohydrate diets promote BW loss, even when protein content remains little (68) or entirely unchanged (69). Irrespective of the causative nutrient, and even if not driving these positive changes in BW, decreasing the carbohydrate content of the diet has long been shown to have a positive effect on aspects of metabolic health, including serum lipids and lipoproteins, VLDL-TGs, and HDL cholesterol, with some evidence of improved blood pressure (63).

To have an impact on T2D prevention, HP diets must prevent the gradual weight creep and long-term weight regain that is associated with most weight-loss regimens. The pan-European DioGenes (Diet, Obesity and Genes) Study investigated HP diets in association with GI in a 6 mo intervention of maintenance after enforced weight loss (55). Approximately 1000 overweight participants completed an 8 wk low-calorie diet (800 kcal/d) to induce >8% BW loss. Participants were randomly assigned to diets in which dietary fat was replaced in part by protein or carbohydrate. Lower-protein (13% of energy)/low- or high-GI diets were compared with HP (25% of energy)/low- or high-GI diets. The HP diet group had the lowest dropout rate and least weight regain, further enhanced by lower GI. The DioGenes Study has sparked renewed interest in HP diets for longer-term weight maintenance and, in turn, amelioration of T2D risk. The global 3 y lifestyle intervention PREVention of diabetes through lifestyle Intervention in Europe and around the World (PREVIEW) (70) is now underway to investigate HP/lower GI diets for longer-term control of glycemia and prevention of T2D. A total of 2500 high-risk obese and dysglycemic adults and children will be included in this study, with findings expected in 2018.

Mechanisms promoting weight loss, weight loss maintenance, and glycemic control

A number of well-established mechanisms acting on energy intake, expenditure, and utilization may contribute to the success of HP diets for weight loss and the prevention of weight rebound (71). Arguably satiety is the most important mechanism. Dietary protein has long been shown to have favorable effects on hunger and satiety (72–79), although not all studies also find modification of eating behavior (80–83). Different protein types may have differential satiety effects (84–91), although again, mechanisms underpinning this have yet to be identified. Whether individual amino acids or dietary peptides alter satiety is also poorly understood, with a great deal of focus on tryptophan because of its relation with the appetite-modulating neurotransmitter 5-hydroxytryptophan (serotonin) (92). The gastrointestinal peptides cholecystokinin, glucagon-like peptide 1 (GLP-1), and peptide YY, among others, may also play a role (93–95), although whether they directly regulate postprandial hunger and/or eating behavior is again unclear (81, 89). Our review of the literature and that of others (96) shows that the role of these peptides is poorly understood, with response to diet considerably lower than that achieved through exogenous delivery (97) and, although suppressing hunger at supra-physiologic dosages (98), they are questionable as a causative factor after a meal (96). Protein may also differentially stimulate diet-induced thermogenesis. Despite an Atwater metabolic energy content of 17 kJ/g, protein has been proposed to have a lower net value of 13 kJ/g, making it lower than carbohydrate, fat, or alcohol (53). A further advantage is the anabolic effect of dietary protein on lean mass (LM), such that branch chain amino acids enhance muscle protein synthesis and may protect against loss of LM during

weight loss (99). Maintenance of LM, as a metabolically active tissue, may in turn contribute to long-term weight maintenance. HP diets may also improve glycemia (55, 97, 100, 101), with data showing effects on metabolic regulation independent of BW (102). Whey protein, for example, is an insulin secretagogue with reports of up to 20% amelioration of postprandial hyperglycemia (103) and a positive effect on the incretin system, altering the gastrointestinal peptides gastric inhibitory polypeptide, GLP-1, and dipeptidyl peptidase 4 (DPP-4) (103).

In addition, mechanisms proposed include protein-induced promotion of gluconeogenesis (104), with increased intestinal glucose detected via sensing cells within the portal vein wall (83) and/or promotion of ketosis and secretion of β-hydroxybutyrate (BHB), both hypothesized to promote satiety and suppress food intake. Whereas decreased portal glucose concentration has been shown to activate vagal afferent activity in animal models, triggering increased food intake (105), and dietary protein conversely promotes increased glucose concentrations via gluconeogenesis, there is little clinical evidence that appetite is directly suppressed through this mechanism (104). However, increased concentrations of BHB and increased dietary fat oxidation, both clear markers of a ketogenic state, do appear to contribute to the appetite suppressive effect of HP diets (104). Recent data on the role that large-bowel microbiota may play with respect to noncarbohydrate nutrients is also of interest, with some evidence indicating that dietary proteins, as well as proteins derived endogenously from epithelial cells within the gut, are hydrolyzed into peptides and amino acids by bacteria-derived proteases and peptidases (106), thereby contributing to protein digestion and absorption, and in turn potentially altering energy utilization.

Content and composition of HP diets for diabetes prevention

When recommending HP diets for weight loss and glycemic control, both the total content and composition must be considered, with advice to increase the percentage of dietary protein rather than just total protein (and associated energy) and the composition of the protein source considered. Protein groups such as dairy (102), marine (107), and soy (108) may have considerable advantages over animal-origin proteins. For example, the ~90,000-participant European Prospective Investigation into Cancer and Nutrition (EPIC) cohort showed a positive association between the consumption of animal-origin protein, e.g., red meat, processed meat, and chicken, but not fish and dairy, and greater weight gain over 6.5 y (109, 110). This positive association was repeated in the >373,000-participant EPIC-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity (PANACEA) study, in which an increase in the consumption of red/processed meat and poultry of 250 g/d was predicted to increase BW by 2 kg over 5 y (111). Also of concern is the association between animal-origin protein and development of T2D. Pan et al. (112) reported a strong correlation between red (particularly processed) meat consumption and T2D, with a 50% increased risk. Data from 3 Harvard cohorts, the Health Professionals Follow-Up Study, the Nurses' Health Study, and the Nurses' Health Study 2, have shown that an additional 0.5 servings/d (~42 g/d) of processed red meat over 4 y also is associated with up to a 50% increased risk of T2D (112–114). Processed red meat is high in saturated fats, nitrate, sodium, and heme iron, and is hypothesized to affect glucose metabolism, insulin resistance, endothelial function, glycoxidation, and oxidative stress (113). Potential confounding prevents attribution of cause and effect, and a micronutrient-poor diet (low whole grain, fruit, and vegetable consumption), overweight/obesity, and an increase likelihood of smoking and physical inactivity may each contribute (113). Data from the NHANES III 18 y follow-up reported that consumption of >20% of energy from protein of animal origin was associated with increased all-cause mortality and cancer in middle age (115). US guidelines, however, found no clear evidence that HP diets increase cancer risk or cardiovascular disease, among other conditions. Based on the RDA of 0.8 g/kg, the acceptable macronutrient distribution range for protein is set as 10–35% of energy for adults, with recommended protein sources being low-fat dairy, lean meat, fish, poultry, legumes, nuts, and whole grain with vegetables, and limited amounts of processed red meat (116).

Conclusions

Development of T2D even in high-risk groups is not inevitable. Diet and PA lifestyle modification has long been shown to delay the progression from prediabetes to diabetes, but the lifestyle strategy chosen may be of considerable importance. T2D prevention studies such as Da Qing (21), the Finnish DPS (22), and the US DPP (16), among others, have shown a lower-fat, higher–complex-carbohydrate diet to be effective in decreasing the risk of progression to disease. We hypothesize that a lower-fat, moderately HP diet may further improve dietary adherence and promote maintenance of weight loss in the longer term, thereby further preventing disease progression. Certainly, HP diets look to be efficacious in shorter-term studies, with positive effects on satiety, food intake, thermogenesis, and lean and fat mass, all of which may contribute to enhanced glycemic control and improved diabetic risk. There is a need for longer-term interventions investigating the role that HP diets can play in T2D prevention, particularly in overweight groups at heightened risk. One such trial is the international PREVIEW diabetes prevention trial (70). This and other trials are needed to determine whether improvements can be made in current best practice recommendations, specifically whether low-fat, HP diets may provide an efficacious alternative to current higher–complex-carbohydrate diets in the prevention of T2D.

Acknowledgments

All authors read and approved the final manuscript.

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