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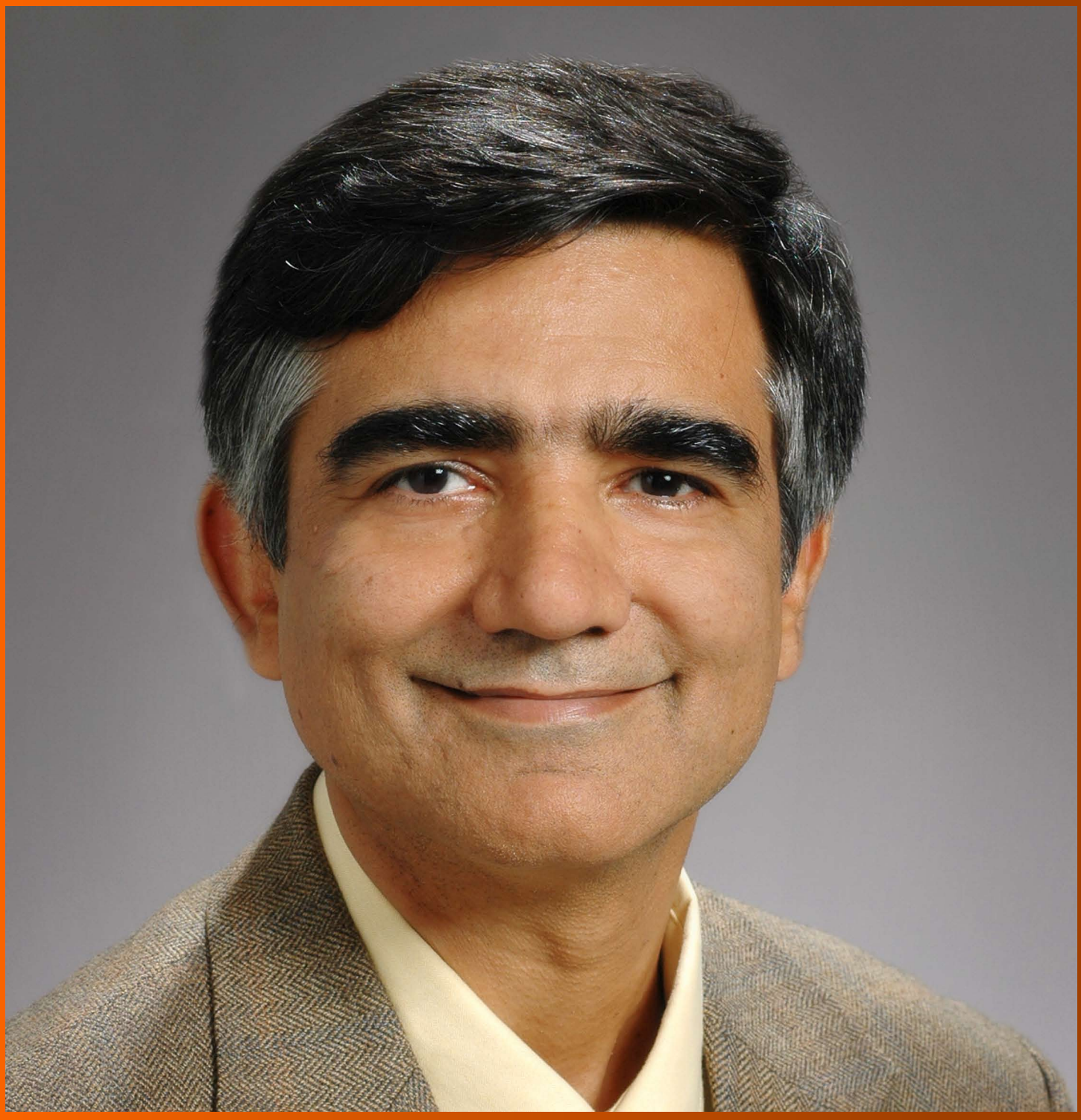

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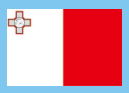

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REVIEW

Assessing the evidence for weight loss strategies in people with and without type 2 diabetes

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Abstract

This review will examine topical issues in weight loss and weight maintenance in people with and without diabetes. A high protein, low glycemic index diet would appear to be best for 12-mo weight maintenance in people without type 2 diabetes. This dietary pattern is currently being explored in a large prevention of diabetes intervention. Intermittent energy restriction is useful but no better than daily energy restriction but there needs to be larger and longer term trials performed. There appears to be no evidence that intermittent fasting or intermittent severe energy restriction has a metabolic benefit beyond the weight loss produced and does not spare lean mass compared with daily energy restriction. Meal replacements are useful and can produce weight loss similar to or better than food restriction alone. Very low calorie diets can produce weight loss of 11-16 kg at 12 mo with persistent weight loss of 1-2 kg at 4-6 years with a very wide variation in long term results. Long term medication or meal replacement support can produce more sustained weight loss. In type 2 diabetes very low carbohydrate diets are strongly recommended by some groups but the long term evidence is very limited and no published trial is longer than 12 mo. Although obesity is strongly genetically based the microbiome may play a small role but human evidence is currently very limited.

Key words: Protein; Glycemic index; Very low calorie diet; Very low carbohydrate diet; Low fat diets; Intermittent energy restriction; Alternate day fasting

Core tip: Very low energy or very low calorie diet (VLCD) may reverse early type 2 diabetes and very low carbohydrate diets may offer a short term advantage in reducing medication use and/or lower HbA1c more than a more conventional diet. Intermittent energy restriction may be helpful in some people but more data is required. Long term weight maintenance after VLCD may be helped by a higher protein lower glycemic index diet but drugs and partial meal replacements are also helpful.

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OBSERVATION COHORTS

Observational cohorts from the Nurses' Health Study Ⅰ and Ⅱ and the Health Professionals Follow up study with a total of 120000 participants have been very useful at examining dietary predictors of weight gain[1,2]. In these cohorts there was a weight gain of 1.45 kg over 4 years. A one cup increase in: (1) sugar sweetened beverages increased weight gain by 0.36 kg; and (2) fruit juice by 0.22 kg while a 1 cup increase in coffee decreased weight by 0.14 kg as did tea by 0.03 kg. Substituting water for sugar sweetened beverages decreased weight gain by 0.49 kg. Greater than average increase in weight was associated with potatoes and French Fries, sugar-sweetened beverages, red meat, alcohol, TV watching, short or long hours of sleep (< 6 or > 8 h/night) and quitting smoking. Lower than average weight gain was associated with a high consumption of vegetables, whole grains, fruit, nuts, yogurt and physical activity.

ISSUES FOR WEIGHT LOSS AND WEIGHT MAINTENANCE

Long term caloric reduction and weight loss induces a reduction in resting metabolic rate that is usually greater than expected by the lean tissue loss[3], and increased energy efficiency of digestion and absorption and movement[4] all of which make weight maintenance a difficult proposition. Hunger is increased and appetite and satiety hormones still deranged 12 mo after initial weight loss despite weight stability or even some weight regain[5]. Whether the higher thermic effect[6] and higher satiety value of protein[7] helps maintain weight loss is not totally clear. Higher fiber intake and lower energy density plus increased polyunsaturated fat intake have been associated with better weight maintenance[8]. Long term weight maintenance after large weight losses in the National Weight Control Register is associated with frequent self-monitoring of body weight and food intake, consistency of food intake, always eating breakfast, low variety of food, low fat, low fast food intakes and high levels of regular physical activity (10-11 mJ/wk) although none of these behaviors may be causally related to weight maintenance Once these successful maintainers have maintained a weight loss for 2-5 years, the chances of longer-term success greatly increase[9,10].

LOW FAT DIETS

Low fat ad libitum diets have been recommended for many decades on the basis of several observations: (1) energy from fat is less satiating than energy from carbohydrate, and a high fat/carbohydrate ratio (and thus higher energy density) in the diet can promote passive overconsumption, a positive energy balance and weight gain in susceptible individuals as most individuals eat a fixed volume of food[11-13]; (2) fat is more readily absorbed from the intestine than carbohydrate and faecal energy loss is much lower with a high dietary fat/carbohydrate ratio; (3) carbohydrate is more thermogenic than fat[14] and energy expenditure is lower during positive energy balance produced by a diet with a high fat/carbohydrate ratio than during positive energy balance produced by a diet with a low fat/carbohydrate ratio[15]; and (4) a high fat diet may damage the intestinal barrier and cause intestinal dysbiosis[16,17].

Low fat diets were reviewed many years ago by Astrup *et al*[18]. Summaries for all the diets are found in Table 1. He found that low-fat diets cause weight loss proportional to pretreatment body weight and weight loss is correlated positively to the reduction in dietary fat content. A reduction of 10% fat energy produces an average 5-kg weight loss in obese persons. After major weight loss, an ad libitum low-fat diet program appeared to be superior to caloric counting in maintaining the weight loss 2 years later. A recent meta-analysis from Tobias *et al*[19] found low diets were not different to high fat weight loss diets but worth 5 kg compared with no intervention. A Cochrane meta-analysis from Hooper confirmed the weight loss effects of a low fat diet compared with usual diet with an effect size of 1.5 kg[20].

HIGH PROTEIN DIETS

High protein weight loss diets reduce the intake of carbohydrate and fat but maintain protein intake to take advantage of their greater satiety (10%-15% less food intake after a protein preload[21]) and thermic effects. Atkins and South Beach diets maintain protein intake but in addition dramatically reduce carbohydrate and replace it with fat. Omitting a major food group inevitably leads to weight loss but long term adherence is difficult.

Clifton *et al*[22] performed a meta-analysis of planned high protein diets *vs* normal protein weight loss diets with at least 10% protein difference planned or expected (*e.g.*, Atkins diets) and followed up for 12 mo or more. The actual reported difference in protein intake at the end of the study was usually 2%-5% of energy. Thirty-two studies with 3492 individuals were analyzed with data on fat and lean mass, glucose and insulin data was available from 18 to 22 studies and lipids from 28 studies. This meta-analysis included the large but very negative Sacks study[23]. A difference in favor of the high protein of about 0.4 kg for weight and fat mass was found. A difference of 5% or greater in percentage protein between diets at 12 mo was associated with a 3-fold greater effect size compared with < 5% (P = 0.038) in fat mass (0.9 *vs* 0.3 kg). Fasting triglyceride and insulin were also lower with high protein diets.

Table 1 Weight loss diets in people without diabetes

Type of diet	Type of summary document	Effect size	Long term data	Recommendation	Risk markers
Low fat diet	Systematic review[18]	10% reduction in fat lowers weight by 5 kg			
Low fat diet	Meta-analysis[19]	Not different to high fat weight loss diets			
Low fat diet	Cochrane[20] meta-analysis 32 RCT, 54000 participants At least 6-mo duration	Worth 5 kg compared with control Mean reduction 1.5 kg for low fat without intention to lose weight	No reduction with time	High quality evidence-effect seen in almost all studies	
Conclusion				A useful strategy well worth pursuing	
High protein diet	Meta-analysis of 12 m or greater weight loss studies 3492 individuals[22]	SMD 0.14 for weight $P = 0.008$) and 0.22 for fat mass, $P < 0.001$ for 2%-5% energy differences in protein. > 5% energy protein difference 0.9 kg weight loss	Data out to 5 yr still shows a small residual effect		Lower triglyceride (SMD 0.17, $P = 0.003$) and lower insulin (SMD 0.22, $P = 0.042$)
High protein diet	Meta-analysis of controlled short term studies[24]	0.79 kg weight 95%CI: -1.50, -0.08 kg), 0.8 kg greater fat mass loss (-0.87 kg; 95%CI: -1.26, 0.48), 0.43 kg (95%CI: 0.09, 0.78) reduction in lean loss			Lower triglyceride (-0.23 mmol/L; 95%CI: -0.33, -0.12 mmol/L). Reductions in falls in REE (595.5 kJ/d; 95%CI: 67.0, 1124.1 kJ/d)
Conclusion				Small effects. Difficult to maintain a higher protein intake long term as other sources of calories creep in	
Very low carbohydrate diets	Energy controlled < 45% CHO *vs* < 30% fat 23 trials 2788 participants[31]	Weight outcomes same			Slightly lower LDL, TG, increased HDL
Very low carbohydrate diets	Meta-analysis of 6 mo studies, 11 studies[25]	Atkins diet better by WMD -2.17 kg; 95%CI: -3.36, -0.99	Not long term	No long term benefit, possible adverse CVD effects	Triglyceride was lowered WMD -0.26 mmol/L; 95%CI: -0.37, -0.15 by the low carbohydrate diet; LDL elevated by WMD 0.16 mmol/L; 95%CI: 0.003, 0.33). HDL elevated WMD 0.14 mmol/L; 95%CI: 0.09, 0.19
Very low carbohydrate diets	Meta-analysis of 12 mo or > studies, $n = 5$[25]	Weight outcomes same		No long term benefit	
Conclusion				No long term benefit	
Very low calorie diet	Review of 12 studies[35] of VLCD *vs* behavioural program and diet change	VLCD was worth an additional 3.9 kg at 12 m and 1.4 kg at 24 m and 1.3 kg at 38-60 m. Dropouts were the same at 19%-20% which was lower than expected	Long term benefit seen	Worth trying with weight loss maintenance programs	
Very low calorie diet	Single hospital based clinic $n = 1109$[36]	19% still attending at 3 yr and the mean weight loss of this group was 6.4 kg. Weight loss was 7.7% *vs* 2.3% for drugs (topiramate plus phentermine or sibutramine) compared with no drugs			
Conclusion				Well worth trying if large weight loss required	
Weight maintenance after VLCD	8 European centres[38] 11% weight loss with VLCD after 8 wk Randomised to high or normal protein 25% *vs* 13% and high or low GI 15U different	Fewer participants in the high-protein and the low glycemic-index groups than in the low-protein–high-glycemic-index group dropped out of the study (26.4% and 25.6% *vs* 37.4%; $P = 0.02$ and $P = 0.01$)	The difference in weight regain after 1 yr[39] between protein groups was 2.0 (0.4, 3.6) kg ($P = 0.017$) (completers analysis, $n = 139$) or 2.8 (1.4, 4.1) kg ($P < 0.001$) (intention-to-treat analysis, $n = 256$)	In the shop centres (where food was provided) protein had a more powerful effect (2.7 kg compared with low protein, $P < 0.001$) while low GI had less effect (0.48 kg, NS)	

				Protein may have modest long term weight maintenance effects	
Weight maintenance after VLCD	189 participants on VLCD for 3 mo then high or normal protein for 12 mo[40]	No difference between diets Weight regain over 9 mo was modest at 2 kg with a final weight loss of 14.5 kg overall. Overall dropout rate was 53% and compliance measures to the high protein diet were limited		Because compliance measures were limited conclusions on benefit (or absence of benefit) are limited	
Conclusions				Protein may be of some benefit, GI isn't long term. More trials required	
Intermittent energy restriction	2 d partial fast and 5 normal days or alternate day fasting	Weight loss similar to CER over 3-6 mo[40-42,44,45]	No long term data		No additional metabolic benefit[47,48]
Conclusion				Insufficient data, no long term data. More work required	
Glycemic index	23 young adults[50] low GI ad lib *vs* Low fat diet with energy reduction of 250-500 kcal	Weight loss 7.8% *vs* 6.1% (NS)			Triglyceride was lowered by 37.2% and 19.1% (P = 0.005) at 6 mo with no difference at 12 mo. PAI-1 was lowered by 39% with the low GI diet *vs* a 33% rise (despite the weight loss)
Glycemic index	73 young adults low gIycemic load diet *vs* low fat diet[51]	No difference at 6, 12, 18 mo Insulin above the median (57.5 μIU/mL; n = 28) at 30 min of OGTT -5.8 *vs* -1.2 kg on low GL diet *vs* low fat diet (P = 0.004) and body fat percentage (-2.6% *vs* -0.9%; P = 0.03). No difference in insulin sensitive group			CVD risk markers the same
Conclusion				Insufficient data for any conclusions	
Mediterranean diet	Mediterranean *vs* low fat *vs* low carbohydrate diet in 322 people in a workplace setting[51]	Weight loss in the 272 completers was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group; a moderate reduction only (P < 0.001 for the interaction between diet group and time)	During 6 follow-up period, participants had regained 2.7 kg of weight lost in the low-fat group, 1.4 kg in the Mediterranean group, and 4.1 kg in the low-carbohydrate group (P = 0.004 for all comparisons) For the entire 6-yr period, the total weight loss was 0.6 kg in the low-fat group, 3.1 kg in the Mediterranean group, and 1.7 kg in the low-carbohydrate group (P = 0.01 for all comparisons) with the Mediterranean group and the low-carbohydrate group not different from each other (P = 0.22)[52]		
Conclusion				Mediterranean diet best long term and has the longest follow up along with VLCD	

Low sugar diet	Meta-analysis of 30 trials and 38 cohorts[53]	Adults decrease in body weight (0.80 kg, 95%CI: 0.39 to 1.21; $P < 0.001$) Cohort studies sugar caused increase weight increase of 0.75 kg, 95%CI: 0.30 to 1.19; $P = 0.001$) Interventions in children SSB *vs* control beverage 1 kg (95%CI for the difference, -1.54 to -0.48)[54]	12 mo difference in weight of 1.9 kg SSB *vs* water disappeared 12 mo after trial stopped[55]	
Conclusion				Strong evidence for the benefit of sugar reduction in beverages
Multicomponent	33 RCTS of at least 1 yr's duration[56]	Weight loss *vs* exercise 3.2 kg, 95%CI: -4.8 kg to -1.6 kg) Type of diet not important	Low-fat diets, some with meal replacements, with physical activity and behavior change training gave most effective long-term weight change in men (-5.2 kg after 4 yr)	
Multicomponent	Commercial weight loss programs[57]	Pooled results from five study arms in commercial weight management programs showed significant weight loss at 12 mo (-2.22 kg, 95%CI: -2.90 to -1.54) Two commercial weight loss arms (mean difference -6.83 kg, 95%CI: -8.39 to -5.26) GP interventions mean difference -0.45 kg, 95%CI: -1.34 to 0.43)		
Conclusion				Commercial plans of some value
Calcium	Meta-analysis of calcium RCTs	RCTs of about 600 overweight and obese individuals from 7 trials dietary calcium supplementation of about 1000 mg was associated with weight loss and fat loss of approximately 1 kg over 6 mo and had a greater effect in pre - than in postmenopausal women[59]	Calcium (1000 mg) and vitamin D after 3 yr of follow-up women with daily calcium intakes of < 1200 mg at baseline on supplements were 11% less likely to experience weight gain[61]	
Conclusion				Marginal effect only
Dairy	Meta-analysis of 27 trials of dairy added to energy restriction[62] Meta-analysis of added calcium or dairy without weight restriction-no effects seen[60]	A greater reduction in body weight [-1.16 kg (95%CI: -1.66 to -0.66), $P < 0.001$, $I^2 = 11\%$, QR = high, $n = 644$) and body fat mass [-1.49 kg (95%CI: -2.06 to -0.92), $P < 0.001$, $I^2 = 21\%$, $n = 521$, QR = high) smaller loss of lean mass of 0.36 kg (0.01, 0.71 kg), $P = 0.04$, $I^2 = 64\%$, $n = 651$, QR = moderate)	No long term data	
Conclusion				Dairy may be useful component of a weight loss diet but does nothing by itself in the absence of weight loss

CER: Continuous energy restriction; CHO: Carbohydrate; GI: Glycemic index; PAI-1: Plasminogen activator inhibitor-1; QR: Quality rating; RCT: Randomised control trial; SMD: Standardized mean difference; VLCD: Very low calorie diet; WMD: Weight mean difference.

Other lipids and glucose were not different. A meta-analysis of short term calorie controlled interventions was performed by Wycherley *et al*[24]. Despite the similar energy prescription weight loss was greater on the high protein, low fat diet with a difference in weight of -0.79 kg and fat mass of 0.8 kg with lower triglycerides. There

was also mitigation of reductions in fat-free mass of 0.43 kg and resting energy expenditure.

There have been several meta-analysis of low carbohydrate diets[25-31]. One compared low carbohydrate diets (< 45%) *vs* low fat (< 30%) diets in an energy controlled, constant protein design. In 23 trials containing 2788 participants weight outcomes were the same with slightly lower low-density lipoprotein (LDL), increased high-density lipoprotein and lower TG[31]. In a meta-analysis of 5 studies[25] of 12 mo or more duration there was no difference in weight although 11 studies of 6 mo or more duration[25] showed a 2 kg difference in favor of the Atkins diet. Although triglyceride was lowered as expected by 0.35 mmol/L by the low carbohydrate diet LDL cholesterol was still elevated by 0.2 mmol/L by the high saturated fat diet which could increase the risk of cardiovascular disease (CVD) suggesting the Atkins diet may not be the best diet for those at risk of CVD[25,32-34]. Flow mediated dilatation which is a reasonable proxy for CVD risk is impaired after an Atkins diet despite weight loss and blood pressure and glucose reduction[35]. South Beach style diets which use unsaturated fats instead may be better for those at risk of CVD[34].

MEAL REPLACEMENTS AND VERY LOW CALORIE DIETS

Another variant of a high protein diet is the meal replacement which provides mostly protein with a small amount of carbohydrate or fat but also provides a very structured, controlled intake especially in its very low calorie diet (VLCD) form. The latter is not frequently used because of rapid weight regain after its cessation but if drugs are used better weight maintenance can be achieved.

A recent review examined 12 studies with 974 participants comparing VLCD to behavioural programs that would be conducted in a medical clinic. Compared with behavioural programs (mostly diet alone) VLCD was worth an additional 3.9 kg at 12 m and 1.4 kg at 24 m and 1.3 kg at 38-60 m. Dropouts were the same at 19%-20% which was lower than expected[36]. A follow up of an obesity clinic hospital population of 1109 hospital patients given VLCD showed that 19% were still attending at 3 years and the mean weight loss of this group was 6.4 kg. Weight loss was 7.7% *vs* 2.3% for drugs (topiramate plus phentermine or sibutramine) compared with no drugs[37].

WEIGHT MAINTENANCE AFTER VLCD

Larsen *et al*[38] completed a large pan European trial in 8 centres which randomised participants to a normal or high protein diet or a low glycemic index or moderate glycemic index. After 773 completed the VLCD phase they were randomised to the maintenance diets for 6 mo. Although the high protein diet was planned to be 25% of energy compared with 13% in the normal diet the difference between the two was only 5%. The GI was planned to be 15 U different but only a 5 U difference was achieved. In an intention-to-treat analysis, the weight regain was 0.93 kg less in the high-protein group than in the low-protein group (P = 0.003) and 0.95 kg less in low-GI diet than in the high GI diet (P = 0.003). Only the low protein, low GI group gained a significant amount of weight over the 6 mo (1.67 kg; P < 0.01). The follow up was extended to 1 year in 2 of the centres. The difference in weight regain after 1 year between protein groups was 2.0 kg (P = 0.017). No consistent effect of GI on weight regain was found[39].

Contrary results were found by Delbridge *et al*[40] who placed 180 participants on a VLCD for 3 mo and then randomised them to a high protein weight maintenance diet or a normal protein diet. Weight regain over 9 mo was modest at 2 kg with a final weight loss of 14.5 kg overall. Overall dropout rate was 53% and compliance measures to the high protein diet were limited so it is difficult to draw any firm conclusions form this study.

ALTERNATIVE APPROACHES TO FULL VLCD

Intermittent energy restriction consists of either 2 d of 600-880 kcal/d with 5 d of a normal diet or alternate day fasting. The weight loss results are very similar to a 25%-30% calorie reduction every day over 3-6 mo[41,42]. Similar results have been seen with alternate day fasting[43] and week on/week off diets[44] and there is some evidence of usefulness in people with type 2 diabetes[45,46]. Alternate day fasting may be just as efficacious as full VLCD[47]. The suggestion there may be metabolic benefit of intermittent energy restriction is currently unproven[48,49].

GLYCEMIC INDEX

There are very limited studies for weight loss in people without diabetes. Ebbeling *et al*[50] studied 23 young obese adults over 12 mo comparing an ad libitum low GI diet to a low fat diet with an energy reduction of 250-500 kcal/d. Body weight was lowered by a similar amount at 12 mo. Plasminogen activator inhibitor-1 was lowered by 39% with the low GI diet *vs* a 33% rise (despite the weight loss). In a second study of 73 young obese adults a low glycemic load diet was not different from a low fat diet at 6, 12 and 18 mo[51]. For those with a high insulin concentration at 30 min after a 75 g OGTT (*i.e.,* insulin resistant) the low-glycemic load diet produced a greater decrease in weight (-5.8 kg *vs* -1.2 kg; P = 0.004) than the low-fat diet at 18 mo. No differences were seen in the insulin sensitive group. CVD risk markers were not influenced by insulin response status.

MEDITERRANEAN DIET

Shai *et al*[52] compared a Mediterranean to an Atkins and a low fat weight loss diet in 322 subjects with a mean body mass index (BMI) 31 of whom 86% male in

a controlled workplace setting in the Negev desert (The DIRECT study). At 2 years 84.6% were still enrolled in the study. Weight loss in the 272 completers was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group (a moderate reduction) (only $P < 0.001$ for the interaction between diet group and time). Predictors of successful weight loss at 6 m were increasing the intake of vegetables and decreasing the intake of sweets and cakes.

At 6 years after study initiation, 67% of the participants had continued with their originally assigned diet, 11% had switched to another diet, and 22% were not dieting ($P = 0.36$ for all comparisons). For the entire 6-year period, the total weight loss was 0.6 kg in the low-fat group, 3.1 kg in the Mediterranean group, and 1.7 kg in the low-carbohydrate group ($P = 0.01$ for all comparisons) with the Mediterranean group and the low-carbohydrate group not different from each other ($P = 0.22$)[53].

LOW SUGAR DIETS

Te Morenga *et al*[54] performed a meta-analysis of low sugar diets. In trials of adults with ad libitum diets reduced intake of dietary sugars was associated with a decrease in body weight of 0.80 kg, $P < 0.001$. Isoenergetic exchange of dietary sugars with other carbohydrates showed no change in body weight. In cohort studies increased sugar intake was associated with a weight increase of 0.75 kg, $P = 0.001$). In children a controlled randomised beverage trials of sugar sweetened beverages *vs* artificially sweetened over 18m demonstrated a weight increase of 6.35 kg in the sugar-free group as compared with 7.37 kg in the sugar group[55]. In 223 overweight/obese adolescents home delivery of water and diet beverages in children who were regular consumers of sugar sweetened beverages for 1 year induced changes in weight (-1.9 kg, $P = 0.04$) compared with the control group at 1 year but this disappeared at 2 years[56].

MULTICOMPONENT AND COMMUNITY-BASED INTERVENTIONS

Robertson *et al*[57] examined weight loss studies in men of at least 1 year's duration and 33 RCTs were located which met the inclusion criteria. Reducing diets tended to produce more favorable weight loss than physical activity alone (mean weight difference after 1 year from a reducing diet compared with an exercise program of 3.2 kg). The type of reducing diet did not affect long-term weight loss. A reducing diet plus physical activity and behavior change gave the most effective results. Low-fat reducing diets, some with meal replacements, combined with physical activity and behavior change training gave the most effective long-term weight change in men of 5.2 kg after 4 years.

Hartmann-Boyce *et al*[58] examined multicomponent interventions delivered in a routine clinical practice environment with assessment at 12 mo. Pooled results from five study arms in commercial weight management programs showed significant weight loss at 12 mo of 2.22 kg. Results from two arms of a study testing a commercial program providing meal replacements also showed a significant weight loss of 6.8 kg. In contrast, pooled results from five interventions delivered by primary care teams showed no evidence of an effect on weight. Clearly commercial weight loss programs can be of value.

DAIRY AND HIGH CALCIUM DIETS FOR WEIGHT LOSS

Calcium

Calcium binds fat in the gut so that an additional dietary calcium intake of 1000 mg increases faecal fat excretion by approximately 5 g/d[59] which has the potential to add to weight loss. In a meta-analysis of RCTs of about 600 overweight and obese individuals from 7 trials dietary calcium supplementation of about 1000 mg was associated with weight loss and fat loss of approximately 1 kg over 6 mo and had a greater effect in pre- than in postmenopausal women[60]. Booth *et al*[61] however found no effect in their meta-analysis. Most interventions used low fat milk as fat intake was not different between intervention and control in these studies. Women who received calcium (1000 mg) and vitamin D had a slightly lower weight gain than did those receiving placebo, and after 3 years of follow-up women with daily calcium intakes of < 1200 mg at baseline who were randomly assigned to supplements were 11% less likely to experience weight gain[62].

Dairy

There have been several meta-analyses of the effect of addition of dairy foods to an energy restricted diet. The most recent one examined 27 trials of > 4 wk's duration[63]. Participants consumed between 2 and 4 standard servings/day of dairy food and 20-84 g/d of whey protein compared to low dairy control diets, over a median of 16 wk. A greater reduction in body weight of 1.16 kg, $n = 644$ and body fat mass 1.49 kg, $n = 521$, 90% of whom were women. These effects were absent in studies that imposed resistance training. Dairy intake resulted in smaller loss of lean mass of 0.36 kg. No between study dose-response effects were seen. A previous meta-analysis[61] found no effect of the addition of calcium or dairy on weight, thirty-one with dairy foods ($n = 2091$), and twenty with Ca supplements ($n = 2711$).

DIETS FOR WEIGHT LOSS IN TYPE 2 DIABETES

In this section we will examine the effects of diets not just on weight but on HbA1c as an HbA1c > 7% would

be one of the prime reasons overweight and obese people with diabetes would be recommended to lose weight. Weight stable dietary changes to lower HbA1c will not be examined (Table 2).

LOWER GLYCEMIC INDEX/LOWER GLYCEMIC LOAD DIETS

Although these diets would be recommended predominantly to lower HbA1c they are also used for weight loss. The Canadian Trial of Carbohydrates in Diabetes[64] enrolled 162 people treated by diet alone who were randomly assigned to high-carbohydrate/high-glycemic-index (HGI) diets; high-carbohydrate/low-glycemic-index (LGI) diets or lower-carbohydrate/high-monounsaturated-fat (LC) diets for 1 year. No differences were seen in weight or HbA1c over 1 year but achieved GI differences were small. A second Canadian low glycemic index diet study[65] in 210 participants with type 2 diabetes on hypoglycemic medication showed no differences in weight over 6 mo compared with a high cereal fibre diet although HbA1c was lowered by 0.32%[65].

Franz *et al*[66] examined randomized clinical trials implementing weight-loss interventions in overweight or obese adults with type 2 diabetes with a minimum 12-mo study duration, a 70% completion rate, and an HbA1c value reported at 12 mo. Eight trials compared different diets while 3 compared diets to usual care. Only two study groups reported a weight loss of $\geqslant$ 5%: A Mediterranean-style diet implemented in newly diagnosed adults with type 2 diabetes and an intensive lifestyle intervention implemented in the Look AHEAD (Action for Health in Diabetes) trial. Both included regular physical activity and frequent contact with health professionals and reported significant beneficial effects on HbA1c, lipids, and blood pressure. All other trials either achieved a weight loss of < 5% and no benefit on HbA1c or CVD risk factors or found no differences between macronutrient interventions in weight or HbA1c.

LOOK AHEAD STUDY

The Look Ahead Study[67] enrolled 5145, aged 45-74 years, with BMI > 25 (> 27 if taking insulin) into a weight loss (with meal replacements if required) and exercise intervention. The Intensive lifestyle intervention produced an 8.6% weight loss at 1 year *vs* 0.7% in control group. Mean HbA1c dropped from 7.3% to 6.6%. At 4 years weight was still 5.3% lower compared with control and HbA1c-0.27% lower[68].

Although the study was ceased after 8 years because of lack of CVD differences compared with the control group[69] there were many benefits seen in the intervention in mood, quality of life and physical function[70]. It clearly showed that a weight loss of 10% or more could be achieved and maintained at 8 years in 27% of the intensive lifestyle group with 50% achieving more than 5% weight loss[71]. One of the reasons the trial failed to achieve its primary end point was because the support and education control group achieved a weight loss of 10% or more in 17% of the group with 5% or more weight loss achieved by 36%. The intervention led to reductions in hospitalizations (11%, $P = 0.004$), hospital days (15%, $P = 0.01$), and number of medications (6%, $P = 0.001$) compared with control participants who were invited to three sessions of diabetes support and education a year. No benefit was unfortunately seen in the 15% of the population with pre-existing CVD. There were fewer deaths in the intervention group (6.8% *vs* 7.8%) but this was not significant ($P = 0.15$)[72].

In secondary analyses of the full cohort[73] (both intervention and control groups), over a median 10.2 years of follow-up, individuals who lost at least 10% of their bodyweight in the first year of the study had a 21% lower risk of the primary outcome [death from CVD, MI, stroke or admission for angina (adjusted hazard ratio $P = 0.034$)] compared with individuals with stable weight or weight gain. In analyses treating the control group as the reference group, participants in the intensive lifestyle intervention group who lost at least 10% of their bodyweight had a 20% lower risk of the primary outcome $P = 0.039$.

ATKINS AND SOUTH BEACH DIETS

There is a small group of advocates for low carbohydrate Atkins style diets for clinical treatment in type 2 diabetes[74-76]. A 6-mo study from one group compared Atkins (LCKD) *vs* calorie-reduced low GI diet (LGID) in volunteers with a BMI 38, of whom 80% were women. There was a high dropout rate with 58.3% (49) participants completing. Body weight fell by 11.1 kg *vs* 6.9 kg ($P = 0.008$) and HbA1c was reduced by -1.5% *vs* -0.5% ($P = 0.03$). LDL was higher in the Atkins group by 4% which although small is of some theoretical concern[77]. There was no long term follow up which is important as Atkins adherence drops off dramatically after 6 mo. In a 48w study comparing an Atkins diet to a low fat diet plus orlistat in which 32% of the volunteers had type 2 diabetes ($n = 46$) weight loss was excellent in both groups at 8.65% to 9.5% with no differences between groups[78].

In an energy controlled low carbohydrate South Beach diet compared to a usual carbohydrate weight loss diet weight loss was the same as planned (9.8 and 10.1 kg) the overall HbA1c fall was the same but there was a greater effect in the low carbohydrate group at 6 mo if HbA1c was greater than 7.8% (2.6% *vs* 1.9%). Drug reductions were also greater in the South Beach group. At 12 mo the HbA1c difference had disappeared[34,79].

VLCD

Somewhat surprisingly the number of publications of

Table 2 Weight loss diets in people with type 2 diabetes

Type of diet	Type of summary document	Effect size	Long term data	Recommendation	Risk markers
Low glycemic index/low glycemic load	Canadian Trial of Carbohydrate in Diabetes[63] 12 mo study in 162 volunteers The HGI, LGI and LC diets contained 47% ± 1%, 52% ± 1% and 40% ± 1% energy carbohydrate; 30% ± 1%, 27% ± 1% and 40% ± 1% fat with GI 64 ± 0.4, 55 ± 0.4 and 59 ± 0.4	No difference between diets	None		
Low glycemic index	Canadian low glycemic index diet study[64] in 210 participants with type 2 diabetes on hypoglycemic medication	No effect on weight	None		HbA1c lower buy 0.32% on low glycemic index diet compared with high fibre diet
				No value in type 2 diabetes	
All randomised diets in type 2 diabetes of 12 mo or more duration	Eleven trials[65] were identified with 6754 participants were reviewed. Eight trials compared different diets while 3 compared diets to usual care. Only two study groups reported a weight loss of ⩾ 5%: A Mediterranean-style diet implemented in newly diagnosed adults with type 2 diabetes and an intensive lifestyle intervention implemented in the Look AHEAD (Action for Health in Diabetes) trial				
Conclusion				Mediterranean diet best	
Look ahead study	The Look Ahead Study[66] enrolled 5145, aged 45-74 yr, with BMI > 25 (> 27 if taking insulin) into a weight loss (with meal replacements if required) and exercise intervention	The Intensive lifestyle intervention produced an 8.6% weight loss at 1 yr *vs* 0.7% in control group	At 4 yr weight was still 5.3% lower compared with control. Weight loss of 10% or more at 8 yr in 27% of the intensive lifestyle group with 50% achieving more than 5% weight loss[70] support and education control group achieved a weight loss of 10% or more in 17% of the group with 5% or more weight loss achieved by 36%		Mean HbA1c dropped from 7.3% to 6.6% At 4 yr HbA1c-0.27% lower *Post hoc* analysis in the whole population (4834) over 10 yr[72] showed that those who lost at least 10% of their body weight in the first year had a 21% lower (HR 0.79, 95%CI: 0.64-0.98, *P* = 0.034) risk of primary outcome (death from CVD, MI, stroke, admission for angina), and a 24% reduced risk of the secondary outcome (primary plus CABG, carotid endarterectomy, stent, heart failure, PVD or total mortality) (adjusted HR 0.76, 95%CI: 0.63-0.91; *P* = 0.003)

Conclusion				Only non-surgical weight loss study with reduction in hard end points	
Atkins diet	A 6-mo study from one group of Atkins *vs* calorie-reduced low GI diet in volunteers with a BMI 38, of whom 80% were women[76]	Body weight fell by 11.1 kg *vs* 6.9 kg, P = 0.008 58.3% (49) participants completing			HbA1c was reduced by -1.5% *vs* -0.5% (P = 0.03) LDL was higher in the Atkins group by 4%
Atkins diet	48w study[77] comparing an Atkins diet to a low fat diet plus orlistat in which 32% of the volunteers had type 2 diabetes (n = 46)	Weight loss 8.65% to 9.5% with no differences between groups			
South Beach diet	80 volunteers completed a 12 mo very low carbohydrate diet *vs* an energy matched high carbohydrate diet[34,78]	9.8 and 10.1 kg at 12 mo			Hba1c changes different at 6 mo but not at 12.1% reduction
Conclusions				Low carbohydrate diets good in short term with intensive support	
VLCD	Meta-analysis of 5 studies of VLCD in volunteers with diabetes or no diabetes[80]	Weekly weight loss was similar in the two groups at 0.5 to 0.6 kg/wk. Weight losses of > 15%-20% were observed in these studies			
VLCD	Retrospective analysis of 355 patients with diabetes matched with nondiabetics	After 12 wk, there was significant weight loss within each group when compared with baseline (T2DM: 115.0 ± 24.4 kg *vs* 96.7 ± 21.4 kg, P < 0.0001; non-T2DM: 117.2 ± 25.8 kg *vs* 97.3 ± 22.2 kg, P < 0.0001)	No long term data available		
	Total cohort comprised 204 males: 506 females, age 54.0 ± 9.1; BMI 41.6 ± 8.1; weight 116.1 ± 25.1 kg[81]	At 12 wk, weight change (-18.3 ± 7.3 kg *vs* -19.9 ± 7.0 kg, P = 0.012) were significantly less in the T2DM group when compared with the non-T2DM group			
VLCD	40 individuals with type 2 diabetes and no control group	Weight loss of 10 kg at 1 yr after an 8 wk VLCD. Five year data from a comparison of self-selected VLCD (15) to modest caloric restriction (n = 15) showed better weight loss in the conventional diet 8.9 kg *vs* 4.8 kg[83] Early use of VLCD can cause remission of type 2 diabetes[84]	Long term data shows benefit	VLCD useful	
Conclusion				Although expensive VLCD has long term benefits	
Diet plus exercise	2 controlled studies adding aerobic or resistance exercise to significant weight loss over 12 to 16 wk[86,87]	No additional benefit of adding exercise on weight	No long term data		No additional benefit on HbA1c or any other markers
Conclusions				No added benefit	

CER: Continuous energy restriction; CHO: Carbohydrate; GI: Glycemic index; VLCD: Very low calorie diet.

the use of meal replacements and VLCD in diabetes is limited[80]. In a meta-analysis of 5 studies of VLCD in both people with and without diabetes there was no difference in achieved weight loss between these two groups. Weekly weight loss was similar in the two groups at 0.5 to 0.6 kg/wk. Weight losses of > 15%-20% were observed in these studies[81]. In a retrospective analysis[82] 355 participants with T2DM were matched for age, BMI and gender to participants without T2DM. The program included a daily intake of 550 kcal in addition to group support and behavior therapy provided by trained facilitators within a community-based setting. At 12 wk, weight change (-18.3 ± 7.3 kg *vs* -19.9 ± 7.0 kg, P = 0.012) was significantly less in the T2DM group when compared with the non-T2DM group. In a study of 40 individuals with type 2 diabetes and no control group Dhindsa *et al*[83] found a weight loss of 10 kg at 1 year after an 8 wk VLCD. Five year data from a comparison of self-selected VLCD (15) to modest caloric restriction (n = 15) showed better weight loss in the conventional diet 8.9 kg *vs* 4.8 kg[84]. Early use of VLCD can cause remission of type 2 diabetes[85].

Johansson *et al*[86] reviewed weight maintenance strategies and found that medication, meal replacements and high protein diets were helpful over a 5-18 mo period while exercise and supplements were not.

DIET PLUS EXERCISE

The final question we will examine in this review is whether exercise has additive benefits to weight loss. Wycherley *et al*[87,88] performed 2 studies adding aerobic or resistance exercise to significant weight loss over 12 to 16 wk and found no additional benefit of adding exercise on HbA1c or any other markers.

THE FINAL WORD FOR THIS REVIEW IS THE MICROBIOME

Rodent studies from Gordon *et al* taking germ-free mice and giving them a "fat" microbial population made them fat, while a lean microbial population keeps them lean[89,90]. Fat mice and lean mice[91] (and humans[92]) have different bacterial populations and the population changes as weight changes (Phyla: Firmicutes up and Bacteroidetes down with increased weight). An increase in calorie intake (from 2400 to 3400 kcal/d) in obese and lean human individuals promotes rapid changes in the gut microbiota (20% increase in *Firmicutes* and a corresponding decrease in *Bacteroidetes*) and this was associated with an increased energy harvest of approximately 150 kcal, the overfeeding in lean individuals being accompanied by a greater fractional decrease in stool energy loss[93].

Increasing dietary fat alters the microbiome, increases gut leakiness ans lipopolysaccharide absorption and enhances insulin resistance[94,95] while feeding oligofructans increase Bifido, reduce insulin resistance and inflammation[96]. Feeding flaxseed mucilage for 6w improved insulin resistance, altered 33 microbial species, lowered 8 including faecalibacterium. The species change could not be related to the change in insulin resistance[97]. Pedersen *et al*[98] fed a galacto-oligosaccharide mix (5.5 g/d) for 12 wk or placebo and demonstrated no changes in insulin sensitivity, glucose tolerance, gut leakiness, inflammatory markers or the microbiome. Changes in the bacterial family Veillonellaceae correlated inversely with changes in glucose response and IL-6 levels (r = -0.90, P = 0.042 for both) following prebiotic intake. Metformin may mediate some of its therapeutic effects through short-chain fatty acid production, while its intestinal adverse effects may be due to relative increase in abundance of Escherichia species. Controlling for metformin treatment, the gut microbiome shifts in T2D with a depletion of butyrate-producing taxa[99].

Weight loss induced by Roux on Y gastric bypass led to reduction of Firmicutes and Bacteroidetes and an increase of Proteobacteria and these species were related to BMI and CRP[100]. Faecalibacterium prausnitzii was directly correlated to fasting blood glucose. In an earlier study Faecalibacterium prausnitzii species was lower in subjects with diabetes and associated negatively with inflammatory markers at baseline and throughout the follow-up after surgery independently of changes in food intake[101].

CONCLUSION

Weight loss occurs with many different diets and there are no clear conclusions on the optimal diet apart from the diet which the individual can stick to long term, whatever the composition. Whether phenotyping (*e.g.*, degree of insulin resistance) or genotyping will help diet choice is not clear.

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ORIGINAL ARTICLE

Randomized Controlled Trial

Neutral protamine hagedorn/regular insulin in the treatment of inpatient hyperglycemia: Comparison of 3 basal-bolus regimens

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Author contributions: Quintanilla-Flores DL and García-De la Cruz G were involved in conception and design of the study, acquisition of data, analysis and interpretarion of data; Tamez-Pérez HE outlined and coordinated the writing of the paper and added significant contributions to the text; González-González JG provided input in writing the paper and made significant contributions to the text.

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Abstract

AIM

To compare the safety and efficacy or 3 basal-bolus regimens of neutral protamine hagedorn (NPH)/regular insulin in the management of inpatient hyperglycemia.

METHODS

We randomized 105 patients with blood glucose levels

between 140 and 400 mg/dL to a basal-bolus regimen of NPH insulin given once (n = 30), twice (n = 40) or three times (n = 35) daily, in addition to pre-meal regular insulin. Major outcomes included were differences in glycemic control, frequency of hypoglycemia and total insulin dose.

RESULTS

NPH insulin given in a once-daily regimen was associated with better glycemic control (58.3%) compared to twice daily (42.4%) and three times daily (48.9) regimens (P = 0.031). The frequency of hypoglycemia was similar between the three groups (2.0%, 0.7% and 1.2%, P = 0.21). The mean insulin dose at discharge was 0.48 ± 0.14 U/kg in the once-daily group compared to 0.69 ± 0.28 in the twice-daily, and 0.65 ± 0.20 in the three times daily regimens (P < 0.001).

CONCLUSION

NPH insulin administered in a once-daily regimen resulted in improvement in glycemic control with similar rates of hypoglycemia compared to a twice-daily and a three times-daily regimen. Further studies are needed to evaluate whether this regimen could be implemented in all hospitalized patients with hyperglycemia.

Key words: Neutral protamine hagedorn insulin; Hospital hyperglycemia; Basal-bolus regimen; Type 2 diabetes mellitus; Inpatient care units

Core tip: In this parallel randomized clinical trial, we compared various insulin regimes. Administration of one-daily neutral protamine hagedorn (NPH) regimen improved glycemic control with similar rates compared to a twice-daily and a three times daily regimen. Furthermore, the use of NPH insulin in a once-daily regimen is associated with lower requirements as well as lower variability in the insulin dose during follow up.

Quintanilla-Flores DL, González-González JG, García-De la Cruz G, Tamez-Pérez HE. Neutral protamine hagedorn/regular insulin in the treatment of inpatient hyperglycemia: Comparison of 3 basal-bolus regimens. *World J Diabetes* 2017; 8(10): 455-463 Available from: URL: http://www.wjgnet.com/1948-9358/full/v8/i10/455.htm DOI: http://dx.doi.org/10.4239/wjd.v8.i10.455

INTRODUCTION

Hyperglycemia is a common finding in hospitalized patients with a prevalence of approximately 25%[1]. It can be secondary to undiagnosed diabetes, stress hyperglycemia pharmacological agents, glucocorticoids or poorly controlled diabetes. For every 2 patients hospitalized with a diagnosis of type 2 diabetes mellitus (DM2), there is one with previously undetected hyperglycemia[2]. In addition, about 90% of hospitalized patients with diabetes have hyperglycemia (> 200 mg/dL) and in 20% of these patients hyperglycemia persists for 3 or more days[3].

Poor glycemic control has been established as a risk factor for poor clinical outcome and mortality[2,4]. Glucose levels between 140-180 mg/dL are associated with a reduction in mortality, systemic infections, risk of multi-organ failure, bacetermia, critical illness polyneuropathy, inflammation and hospital stay[4-6]. Subcutaneous insulin, given as a daily basal-bolus, is the only agent that has proven efficacy and safety for glycemic control in general medical and surgical patients with hyperglycemia.

Despite its benefits, treatment of hyperglycemia still remains delayed. The fear of causing hypoglycemia[3] and the clinical inertia of no treatment remain the main barriers for initiating insulin. Physicians commonly use a sliding-scale regimen until stabilization of glucose levels[7]; however, a study by Umpierrez *et al*[8] found that a basal-bolus insulin algorithm was more effective than a sliding-scale regimen for glucose control.

The use of a basal-bolus regimen with both insulin analogs and a neutral protamine hagedorn (NPH)/regular insulin mix has been studied. Similar rates of glucose control and hypoglycemic events were found with both regimens making them suitable for the treatment of inpatient hyperglycemia[4,9,10]. Current guidelines do not specify whether the NPH dose of insulin should be administered in a once daily, twice daily or three times daily regimen during hospitalization. The twice daily regimen has been traditionally used in previous clinical trials as the standard regimen of reference, suggesting it to be the most physiologic form of administration. Accordingly, we conducted a prospective, randomized non-blinded study to compare the efficacy and safety of three basal-bolus regimens of NPH/regular insulin for the control of hyperglycemia in patients admitted to an internal medicine ward.

MATERIALS AND METHODS

Subjects

Subjects were men and women aged > 16 years, admitted to medical services with a persistent blood glucose level > 140 mg/dL and with an expected stay $\geqslant$ 48 h. Exclusion criteria included individuals with type 1 diabetes mellitus, parenteral nutrition, blood glucose levels $\geqslant$ 400 mg/dL at screening, diabetic ketoacidosis or nonketotic hyperosmolar syndrome, clinically relevant hepatic disease, glomerular filtration rate $\leqslant$ 30 mL/min, pregnancy, terminal disease, and/or inability to provide informed consent. Patients were eliminated when there was poor adherence to the administration of insulin or glucose measurements (defined as $\leqslant$ 70% of total insulin doses or glucose measurements), discharge or death within the first 48 h of enrollment or when glucocorticoids were given during follow up.

Study design

We developed a single center, open-label, randomized, parallel comparative study in the Internal Medicine Department, at the "Dr. José Eleuterio González" University Hospital from September 2013 to September 2015. It was conducted in accordance with the Declaration of Helsinki revised in 2008 and approved by the local ethical committees. All subjects provided informed consent. Participants were randomized using an online randomization generator available at http://www.randomization.com. A database including the sequential order of randomization was generated in an Excel file. Both the enrollment and follow-up of the included subjects was performed by the members of the research team in cooperation with the attending physicians. The protocol was registered in clinicalrials.gov (Trial registry number: NCT02758522).

Study protocol and treatment

All patients were managed by physicians of an internal medicine residency program. The primary care teams decided on the treatment for all other medical problems for which the patients were admitted. Oral antidiabetic drugs were suspended during hospitalization. HbA1c was measured during the first day of hospital stay. Post-discharge follow up was not included as part of this study.

Patients were randomized to receive NPH insulin either once-daily, twice-daily or three times-daily. The twice-daily regimen was also included as the reference regimen, since it has been traditionally used in previous trials when NPH/Regular insulin is administered in hospitalized patients. The starting dose was calculated according to body mass index (BMI): 0.3 U/kg for BMI < 18 kg/m^2, 0.4 U/kg for BMI 18-24.9 kg/m^2, 0.5 U/kg for BMI 25-29.9 kg/m^2 and 0.6 U/kg for BMI $\geqslant$ 30 kg/m^2. The resulting dose was fractioned to be given 60% as basal insulin (NPH) and 40% as prandial (regular) insulin. NPH insulin once-daily was administered subcutaneously before breakfast; in the twice-daily regimen it was given before breakfast and before dinner; and in the three times daily regimen it was administered before each meal. Regular insulin was given in three equally divided doses before each meal. A sliding-scale regimen of supplemental regular insulin was given in addition to the scheduled pre-meal insulin when blood glucose levels were $\geqslant$ 140 mg/dL. When the patient was not able to eat, the dose of regular insulin was held until meals were resumed. Furthermore, when glucose values between 70 mg/dL and 100 mg/dL were detected before meals, the corresponding dose of insulin was suspended in order to prevent hypoglycemia.

Hypoglycemia was defined as a glucose level < 70 mg/dL. Severe hypoglycemia was defined as a glucose level < 40 mg/dL or the need of assistance. All blood glucose values less than 70 mg/dL were treated with 20 g oral carbohydrate (fruit or juice) or 25 g of intravenous glucose depending on the neurologic state. The dose of total daily insulin was reduced by 20% when an episode of hypoglycemia was reported.

Blood glucose was determined four times a day: Before each meal and at bedtime using a glucose meter. The insulin dose was adjusted daily according to glucose values: If blood glucose was not in the target range of fasting glucose $\leqslant$ 140 mg/dL and random glucose was $\leqslant$ 180 mg/dL (nonfasting glucose measured at any time during the day), the total insulin dose was increased by 20%, fractioned in 60% NPH and 40% rapid insulin.

Outcome measures

The primary outcome was to determine the differences in glycemic control between the treatment groups. Glycemic control was defined as the proportion of patients that achieved fasting glucose between 70-140 mg/dL and random glucose levels of < 180 mg/dL during the whole hospital stay. Mean overall, fasting and random, glucoses were also used to assess differences in glycemic control between the three regimens. They were established as the average of daily repeated measurements taken each day during hospitalization. Secondary outcomes included differences in the percentage of glucose levels in the hypoglycemic range (overall and severe hypoglycemia), and the total insulin dose required during follow up and at discharge to achieve glycemic control and differences in mortality and hospital stay.

Statistical analysis

Based on previous data about glycemic control in hospitalized patients, we calculated that 93 subjects (31 per group) had the power to provide an 80% chance of detecting, with an α error rate of 5%, a difference greater than 30% in glycemic control between the 3 regimens. Data were analyzed using SPSS version 19.0 software package. For the continuous variables, differences were examined by ANOVA or Kruskal Wallis as needed. The χ^2 test was used for categorical data. $P < 0.05$ was considered significant.

RESULTS

A total of 105 patients were finally included for analysis, 85 of them with known type 2 diabetes mellitus. Figure 1 shows the enrollment of the patients. No between-treatment differences were apparent at baseline, except that patients in the once-daily regimen had a shorter duration of diabetes (P = 0.01) and were less prone to insulin use before hospitalization (P = 0.01) (Table 1). Metformin and glibenclamide were the only oral anti-diabetic drugs used by the patients prior hospitalization. These drugs were drugs were suspended during hospitalization. Over 19% subjects had an unrecognized history of diabetes mellitus, and more than half had received prior therapy with insulin before hospitalization. The most common diagnoses on admission were coronary artery disease, infections and neoplastic disorders. Pneumonia was the most common

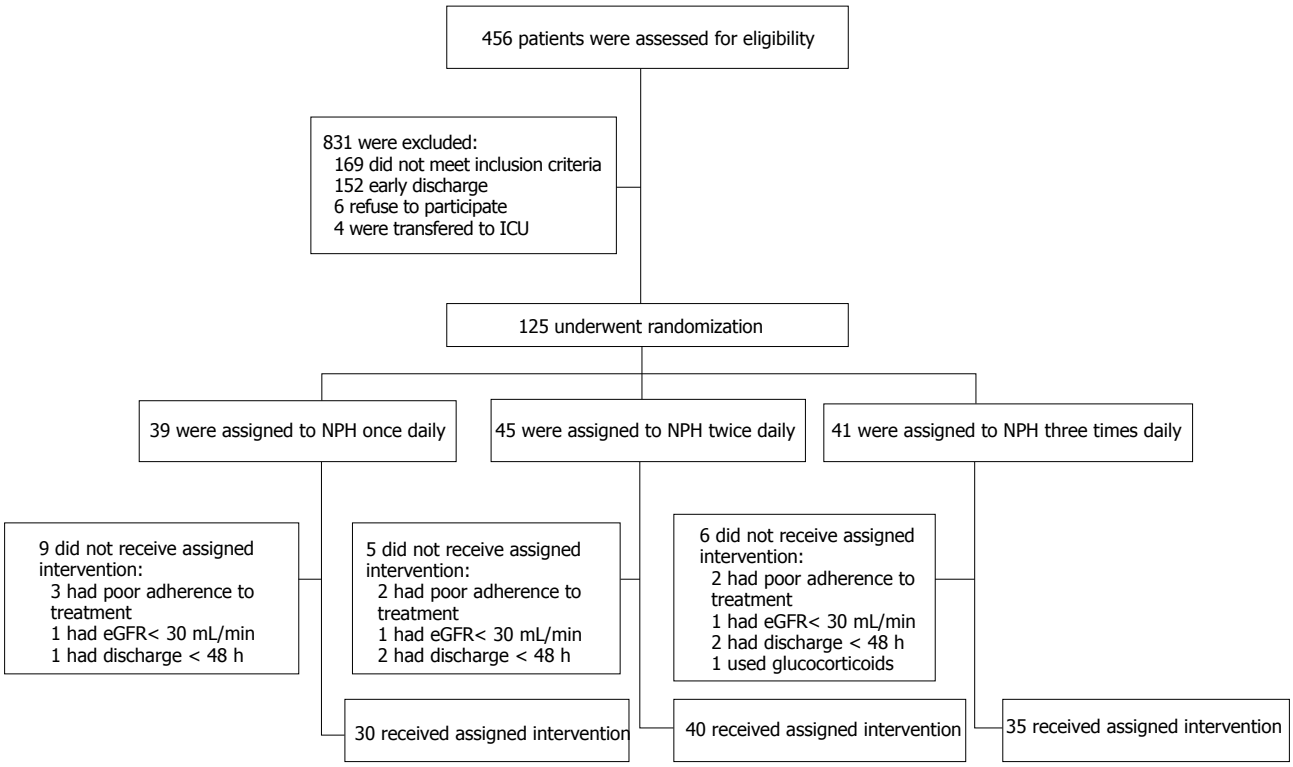

Figure 1 Enrollment and randomization of patients.

Table 1 Baseline clinical characteristics

	NPH × 1	NPH × 2	NPH × 3	*P*
n	30	40	35	
Age (yr, X ± DS)	60 ± 15	58 ± 15	54 ± 14	0.39
Gender (% female)	12 (40)	20 (50)	22 (63)	0.18
Unknown history of T2DM, *n* (%)	12 (40.0)	4 (10.0)	4 (11.4)	0.01
Duration of T2DM (yr), med (min-max)	5 (0-30)	15 (0-30)	10 (0-25)	0.01
Prior T2DM therapy, *n* (%)				0.02
None	17 (56.7)	7 (17.5)	9 (25.7)	
Oral antidiabetics	9 (30.0)	20 (50.0)	15 (42.9)	
Insulin	4 (13.3)	21 (52.5)	15 (42.9)	
Insulin + oral antidiabetics	-	8 (20.0)	4 (11.4)	
Charlson score, med (min-max)	3 (1-9)	3 (1-5)	3 (1-7)	0.14
Hospitalization diagnosis, *n* (%)				
Coronary artery disease	7 (23.3)	13 (32.5)	11 (31.4)	0.69
Infectious disease	5 (16.7)	13 (32.5)	9 (25.7)	0.35
Neoplasm	7 (23.3)	3 (7.5)	2 (5.7)	0.051
Dysrhythmias	4 (13.3)	1 (2.5)	2 (5.7)	0.23
Gastrointestinal hemorrhage	4 (13.3)	1 (2.5)	3 (8.6)	0.24
Pancreatitis	2 (6.7)	1 (2.5)	1 (2.9)	0.68
Stroke	-	2 (5.0)	1 (2.9)	0.78
Other	1 (3.3)	6 (15.0)	6 (15.0)	0.88
Hypertension, *n* (%)	8 (26.7)	12 (31.6)	15 (42.9)	0.33
Body mass index (kg/m^2), X ± DS	26.4 ± 5.2	27.5 ± 5.6	27.5 ± 5.3	0.65
HbA1c (%), X ± DS	9.5 ± 2.4	10.2 ± 2.4	10.4 ± 2.8	0.45
HbA1c (mmol/mol)	80 ± 26	88 ± 26	90 ± 30	
Admission blood glucose (mg/dL), X ± DS	272 ± 84	308 ± 62	306 ± 70	0.08
Glomerular filtration rate[1] (mL/min), X ± DS	77.3 ± 32.9	86.9 ± 30.1	92.4 ± 23.4	0.13
Treatment follow-up (d), med (min-max)	6 (2-14)	6 (2-14)	7 (2-14)	0.41
Hospital stay (d), med (min-max)	8 (4-31)	8 (2-28)	10 (4-36)	0.39

[1]Calculated with Chronic Kidney Disease Epidemiology Collaboration. T2DM: Type 2 diabetes mellitus; HbA1c: Glycosylated hemoglobin.

cause of infection, followed by urinary tract infections and diarrhea. None of the subjects with sepsis were included.

The median duration of treatment was 6 (2-14) d, and the median hospital stay was 8 (2-36) d. No deaths were

Table 2 Glycemic control and insulin dose[1]

	NPH × 1, *n* = 30	NPH × 2, *n* = 40	NPH × 3, *n* = 35	*P*
Mean glucose (mg/dL)	160.3 ± 36.4	190.4 ± 48.0	178.7 ± 44.2	0.02
Fasting glucose (mg/dL)	149.2 ± 36.5	175.9 ± 54.6	169.5 ± 43.2	0.054
Random glucose (mg/dL)	164.4 ± 38.2	198.9 ± 53.2	181.0 ± 47.8	0.013
Glycemic control (%)	58.3 ± 25.3	42.4 ± 24.3	48.9 ± 24.1	0.031
Fasting glucose (%)	47.0 ± 35.0	34.0 ± 30.8	42.5 ± 32.3	0.253
Random glucose (%)	62.8 ± 25.9	45.5 ± 25.2	52.8 ± 26.6	0.024
50% daily glucoses within target range (%)	53.0 ± 29.4	43.8 ± 29.5	48.1 ± 30.6	0.455
Time to achieve 50% of daily glucoses within target range (h)	48.9 ± 27.8	61.2 ± 33.9	59.6 ± 47.0	0.438
75% daily glucoses within target range (%)	27.4 ± 26.5	14.3 ± 21.1	21.8 ± 25.5	0.069
Time to achieve 75% of daily glucoses within target range (h)	76.8 ± 48.4	84.8 ± 57.3	99.8 ± 85.1	0.904
Insulin dose (UI/kg)				
Basal	0.44 ± 0.13	0.51 ± 0.18	0.52 ± 0.15	0.1
At discharge	0.48 ± 0.14	0.69 ± 0.28	0.65 ± 0.20	< 0.001
Δ Insulin dose	0.04 ± 0.10	0.19 ± 0.22	0.13 ± 0.18	0.004

[1]Data are expressed as X ± SD.

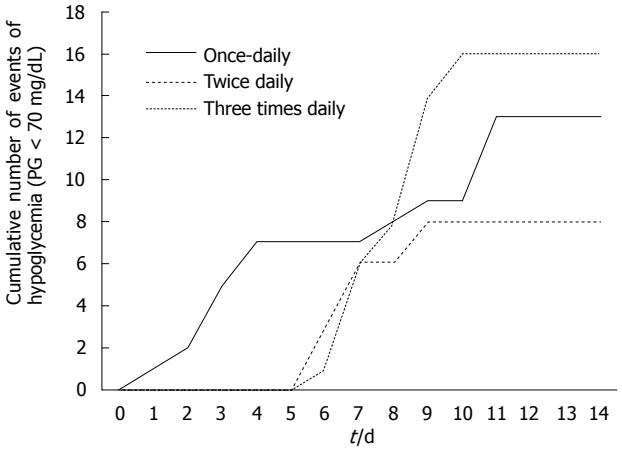

Figure 2 Cumulative number of hypoglycemia events. Pearson χ^2 (P = 0.004).

reported among the study subjects. Diabetes related chronic complications were not evaluated in this study.

Glycemic response and insulin dose

Mean baseline glucose levels were similar between the three groups. Mean glucose levels during follow up were 160, 190 and 179 mg/dL for the once-daily, twice-daily and three times-daily regimens, respectively (P = 0.02). The percentage of patients within the target range of glycemic control were 58% in patients treated with the once-daily regimen, 42% in the twice-daily regimen and 49% in the three times-daily regimen (P = 0.03). In the *post-hoc* analysis patients treated with the once-daily regimen had greater improvement in glycemic control than those treated with the twice-daily regimen (P = 0.03), maintaining significant differences only in random glucose samples (P = 0.02). There was no significant difference between the subjects in the once-daily regimen and the three times-daily regimen. Nearly half of the patients achieved had least 50% of the glucose measures of the day within the target ranges (P = 0.39), and about one quarter achieved 75% within the target ranges (P = 0.09) (Table 2).

The once-daily regimen provided glycemic control when the duration of diabetes was < 10 years, the patient received treatment with insulin before hospitalization, the HbA1c was > 9% (75 mmol/mol), there was an absence of infection and the BMI was ⩾ 25 kg/m^2 (Table 3).

Mean total insulin daily doses were significantly higher in both the three times-daily and the twice-daily regimens compared with that in the once-daily regimen (P < 0.001). Furthermore the once-daily regimen was associated with less variability in insulin dose during the entire study, as shown in the Δ of insulin dose (P = 0.004) (Table 2).

Rate of hypoglycemia

Figure 2 shows the cumulative incidence of hypoglycemic events. Fewer events occurred with the twice-daily regimen, followed by the once-daily regimen, and the three times-daily regimen (P = 0.004). Expressed as rate of hypoglycemia (proportion of events/total glucoses), the differences did not reach statistical significance. A total of 492 glucose readings were performed in the once-daily regimen; of these 13 (2.0%) were < 70 mg/dL. Of the 754 glucose readings in the twice-daily regimen 8 (0.7%) were < 70 mg/dL. Finally, of the 745 glucose readings of the three times-daily regimen 16 (1.2%) were < 70 mg/dL (P = 0.21). Only one episode of severe hypoglycemia was documented in the twice-daily regimen.

A higher proportion of patients in the three times-daily regimen experienced hypoglycemia before dinner (P = 0.04). The insulin dose of presentation of an event of hypoglycemia was significantly lower in the once-daily regimen (0.38 ± 0.13 U/kg) compared to the twice-daily (0.67 ± 0.17 U/kg) and the three times-daily [0.94 ± 0.48 (U/kg)] regimens (P < 0.001) (Table 4). When adjusting the rate of hypoglycemia according to different variables, the once-daily regimen proved to be associated with higher rates when HbA1c < 9% (75 mmol/mol) (rate 4.3%) compared to the twice daily

Table 3 Glycemic control among subgroups

	NPH × 1, *n* = 30, (%)	NPH × 2, *n* = 40, (%)	NPH × 3, *n* = 35, (%)	*P*
DM ⩽ 10 yr				
Overall	62.1 ± 24.8	47.3 ± 25.6	50.4 ± 23.4	0.17
Fasting glucose	53.7 ± 31.9	35.2 ± 30.5	42.1 ± 32.0	0.03
Random glucose	65.9 ± 24.9	51.1 ± 27.2	55.8 ± 28.2	0.25
Pre-hospital insulin				
Overall	77.5 ± 12.4	37.6 ± 23.9	37.7 ± 26.1	0.012
Fasting glucose	39.5 ± 35.5	29.7 ± 27.5	24.1 ± 25.1	0.59
Random glucose	91.8 ± 7.5	41.0 ± 26.1	46.0 ± 31.2	0.01
Baseline glucose > 300 mg/dL				
Overall	52.9 ± 24.5	37.7 ± 26.9	40.8 ± 20.0	0.36
Fasting glucose	38.1 ± 35.6	33.6 ± 34.8	36.0 ± 26.7	0.94
Random glucose	57.4 ± 22.4	38.7 ± 26.1	42.7 ± 22.5	0.21
HbA1c > 9% (75 mmol/mol)				
Overall	55.2 ± 24.0	33.7 ± 22.6	45.8 ± 28.1	0.06
Fasting glucose	43.0 ± 33.9	25.5 ± 27.3	40.4 ± 31.0	0.18
Random glucose	60.0 ± 22.3	36.6 ± 23.1	48.2 ± 28.3	0.04
Absence of infectious disease				
Overall	61.0 ± 24.1	39.8 ± 25.1	50.9 ± 25.6	0.01
Fasting glucose	50.8 ± 34.0	34.2 ± 32.8	44.1 ± 35.8	0.22
Random glucose	65.4 ± 25.4	41.8 ± 25.3	54.3 ± 26.5	0.01
Glomerular filtration rate < 60 mL/min				
Overall	62.8 ± 25.3	42.0 ± 29.7	45.2 ± 16.7	0.20
Fasting glucose	40.0 ± 34.7	35.1 ± 32.8	31.2 ± 20.3	0.87
Random glucose	71.9 ± 27.3	44.4 ± 30.4	55.4 ± 29.5	0.14
Body mass index, dex ± 29.52				
Overall	63.4 ± 22.8	44.1 ± 25.2	48.0 ± 23.3	0.03
Fasting glucose	47.1 ± 35.0	39.9 ± 34.0	42.1 ± 30.4	0.78
Random glucose	69.9 ± 23.1	45.6 ± 25.1	50.8 ± 23.9	0.01

Proportion of patients that achieved glycemic targets during the whole follow up. Data are expressed as X ± SD. DM: Diabetes mellitus; HbA1c: Glycosylated hemoglobin.

Table 4 Rate of hypoglycemia among the study groups during the hospitalization

	NPH × 1, *n* = 30	NPH × 2, *n* = 40	NPH × 3, *n* = 35	*P*
Hypoglycemic events (*n*)	13	8	16	
Severe hypoglycemia	–	1	–	0.45
Rate of hypoglycemia (%), (X ± SD)[1]	2.0 ± 3.8	0.7 ± 2.3	1.2 ± 3.1	0.21
Time to the first episode (d), (X ± SD)	6.2 ± 4.0	7.1 ± 1.2	8.2 ± 1.2	0.14
Insulin dose at event (IU/kg), (X ± SD)	0.38 ± 0.13	0.67 ± 0.17	0.94 ± 0.48	< 0.001
Time of presentation, *n* (%)				
Before breakfast	5 (38.5)	2 (25.0)	1 (6.2)	0.11
Before supper	3 (23.1)	3 (37.5)	2 (12.5)	0.37
Before dinner	2 (15.4)	–	7 (43.8)	0.04
Bedtime	3 (23.1)	3 (37.5)	6 (37.5)	0.43

[1]Data are expressed as proportion of events/total glucoses.

regimen (rate 1.1%) and the three times daily regimen (rate 0%) (P = 0.04).

DISCUSSION

NPH insulin administered in a once-daily regimen resulted in improvement in glycemic control with similar rates of hypoglycemia compared to a twice-daily and a three times-daily regimen. This superiority is of particular importance when the duration of diabetes is less than 10 years, HbA1c > 9% (75 mmol/mol), there is pre-hospital insulin use, an absence of infection during hospitalization and the patient has a BMI ⩾ 25 kg/m^2. Furthermore, the use of NPH insulin in a once-daily regimen is associated with lower insulin requirements and lower variability in the insulin dose during follow up.

According to previous studies[4,9,10], glycemic control with levels < 140 mg/dL can be achieved in up to 48%-74% of patients with rates of hypoglycemia of 2%-3.3% when scheduled NPH/regular insulin in a twice-daily protocol is used in non-critically ill patients. We found differences in glucose levels and lower rates of hypoglycemia when a twice-daily regimen was implemented. This could be explained by differences in the target glucose values in previous studies as well as the variability in the basal characteristics of our patients,

who had a longer duration of diabetes, higher HbA1c levels and a higher proportion of individuals using insulin prior to randomization. Furthermore, our population included only Hispanic subjects, which according to Bueno *et al*[10] tend to be significantly leaner, have worse glycemic control and higher HbA1c levels on admission as well as more hypoglycemic events compared to United States population.

In the ambulatory setting, the addition of a single bedtime injection of NPH insulin in those patients who remain poorly controlled with oral agents has been explored[11]. Extrapolated to the hospital setting, this is the first prospective randomized study that evaluates the efficacy of NPH insulin given in a once-daily regimen to inpatients with hyperglycemia. Of note is the observation that compared to the other two study groups, NPH insulin given in a once-daily regimen was associated with a lower dose of total insulin at the end of the study as well as with less variability in the insulin dose during the study period. Despite these differences in total insulin dose, this regimen was related to better glycemic control in selected patients as well as similar rates of hypoglycemia. This measure should be recommended especially when the duration of diabetes is < 10 years, the patients have been treated with insulin prior to hospitalization, HbA1c is > 9% (75 mmol/mol), an absence of infection, and the patient's BMI $\geqslant$ 25 kg/m^2.

Compared to insulin analogs, variability in the serum levels of NPH insulin, secondary to intermediate duration of action and a peak activity at 4-6 h after injection, have questioned its safety and efficacy in the treatment of hyperglycemia. NPH insulin has proved similar rates of glycemic control with a tendency to higher risk of hypoglycemia and greater glycemic variability when it is compared with glargine or detemir[4,11]. Some other studies have concluded similar rates of glycemic control and hypoglycemia[9]. In an attempt to equalize the effect of insulin analogs in terms of glycemic variability, we tried to split the total dose of NPH insulin into 3 equal doses administered during the day. We hypothesized that by splitting the total dose of NPH insulin, we could achieve a flat curve of serum NPH insulin levels similar to that observed with insulin analogs. On the contrary, we found higher rates of a cumulative number of hypoglycemia events and higher doses of insulin required to achieve similar rates of glycemic control. It seems that this measure should not be used as a first-line option in the management of inpatient hyperglycemia. It might be useful when higher doses of total insulin are required during the follow-up of patients treated with a once or twice daily regimen.

Controversy exists whether insulin analogs, such as glargine and detemir, are associated with better glycemic control and a lower risk of hypoglycemia compared to NPH insulin in the management of hospitalized hyperglycemia in the non-crically ill. Yeldandi *et al*[4] showed similar rates of glycemic control with a lower risk of hypoglycemia when insulin glargine was used compared to NPH insulin in a basal/bolus scheme. In the DEAN trial, similar improvements in glycemic control with no differences in hypoglycemia events were found with the use detemir once daily and aspart before meals compared to NPH/regular insulin in a twice daily regimen[9]. Bueno *et al*[10] showed similarly significant improvement in glycemic control without increasing the prevalence of overall hypoglycemia, with higher prevalence of severe hypoglycemia when twice daily NPH/regular insulin was used compared to once daily glargine and glulisine before meals (0.83% *vs* 0.25%, P = 0.01)[10]. In institutions with low- and middle-income resources, such as ours, access to insulin analogs is barely possible. It seems that the benefits of optimal glycemic control outweigh the slightly increased risk of severe hypoglycemia, which of note does not exceed 1% in overall prevalence. We consider that the implementation of protocols of glycemic control that include the use of NPH insulin in the basal regimen are still needed to reduce the complications of severe hyperglycemia and hypoglycemia in hospitalized patients.

There are several limitations in our study to consider: (1) we did not assess the daily oral caloric intake of our patients and the stratification of risk factors of hypoglycemia. Higher risk of hypoglycemia has been observed among subjects with variability in their caloric intake, comorbidities such as liver disease and renal disease, sepsis, malnutrition and drugs such as quinolones and β-agonists[12]; (2) our study was powered to evaluate differences in glycemic control and risk of hypoglycemia instead of mortality and clinical outcomes. Despite the fact that 16% of the randomized patients were lost during follow up, the minimum of 93 subjects to maintain the statistical power of our study was accomplished. In addition, only patients who completed the study were included for the analysis. We believe that in spite of this limitation, our findings provide reliable information to draw conclusions; (3) we included patients with a longer duration of diabetes, higher HbA1c levels on admission and a greater proportion of patients on insulin before hospitalization compared to previous studies. This could underestimate the rates of glycemic control in our patients compared to that of previous studies which included subjects with lower risk of severe hyperglycemia as shown by Pasquel *et al*[13] who proved that patients with higher HbA1c levels have lower odds of having optimal glucose control among hospitalized patients; (4) as it is shown in Table 2, patients in the once-daily regimen had a shorter duration of diabetes and were less prone to insulin use before hospitalization. Additionally, the proportion of patients with unknown history of diabetes was substantially greater in this group as compared to others, the rate of hypoglycemia tended to be higher and the meantime insulin dose at the event was lower, indicating probable greater insulin sensitivity. These features could explain the better glycemic response and lower insulin dose in once-daily regimen group instead of the once-daily regimen itself; (5) we are aware that the comparison of repetitive measurements

could be a better strategy for statistical analysis, however we decided to use average glucose levels since this is the way it has been presented in previous studies that compare different schemes of treatment of inpatient hyperglycemia; and (6) even though subjects were treated with the insulin regimen during the whole hospitalization, the median duration of days for follow up in our study was 6 (2-14) d. This period of maximum 14 d of follow up permitted an adequate titration of insulin dose with achievement of glycemic target in all patients and avoided bias linked to long hospital stay related complications.

Conclusion

In summary, NPH insulin administered in a once-daily regimen resulted in improvement in glycemic control with similar rates of hypoglycemia compared to a twice-daily and a three times-daily regimen. This superiority is of particular importance when the duration of diabetes is less than 10 years, HbA1c is > 9% (75 mmol/mol), there is pre-hospital insulin use, an absence of infection during hospitalization and the patient's BMI $\geqslant$ 25 kg/m^2. Furthermore, the use of NPH insulin in a once-daily regimen is associated with lower requirements as well as lower variability in the insulin dose during follow up. Whether this superiority in glycemic control and insulin dose was related to greater insulin sensitivity among the study subjects in the once-daily regimen needs to be reassessed in further studies. NPH insulin in a three times-daily regimen might not be recommended as a first-line option, because it is associated with a higher cumulative incidence of hypoglycemia and higher insulin doses in spite of an equivalent glycemic control. In this parallel randomized clinical trial, we compared various insulin regimes. Administration of once-daily NPH regimen improved glycemic control with similar rates compared to a twice-daily and a three times daily regimen. Furthermore, the use of NPH insulin in a once-daily regimen is associated with lower requirements as well as lower variability in the insulin dose during follow up.

Despite its limitations, our findings could be useful for changing algorithms for the treatment of inpatient hyperglycemia in addition to current health policies. Further studies are needed to estimate whether NPH insulin in a once-daily regimen can be incorporated as an option in certain populations among the hospitalized patients.

ACKNOWLEDGMENTS

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COMMENTS

Background

Poor glycemic control among hospitalized patients has been established as a risk factor for poor clinical outcome and mortality. The use of a basal-bolus regimen with both insulin analogs and a neutral protamine hagedorn (NPH)/regular insulin has proven efficacy and safety for glycemic control in general medical and surgical patients with hyperglycemia.

Research frontiers

In institutions with low- and middle-income resources, access to insulin analogs is barely possible. The implementation of protocols of glycemic control that include the use of NPH insulin in the basal regimen are still needed to reduce the complications of severe hyperglycemia and hypoglycemia in hospitalized patients.

Innovations and breakthroughs

In this study the authors showed that NPH insulin administered in a once-daily regimen results in improvement in glycemic control with similar rates of hypoglycemia compared to a twice-daily and a three times-daily regimen. Furthermore, it is associated with lower requirements as well as lower variability in the insulin dose during follow up.

Applications

This study provides evidence of an alternative regimen of basal/bolus insulin among the hospitalized patients with diabetes.

Terminology

Glycemic control was defined as the achievement of fasting glucose between 70-140 mg/dL and random glucose levels of < 180 mg/dL. Hypoglycemia was defined as a glucose level < 70 mg/dL. Severe hypoglycemia was defined as a glucose level < 40 mg/dL or the need of assistance.

Peer-review

This is an overall good quality article.

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