ORIGINAL RESEARCH

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Subcutaneous versus intraperitoneal insulin for patients with diabetes mellitus on continuous ambulatory peritoneal dialysis: Meta-analysis of non-randomized clinical trials.

Abstract

Background: Diabetes mellitus is one of the leading causes of end stage renal disease. Use of intraperitoneal (IP) insulin in diabetic patients on peritoneal dialysis (PD) can restore glucose control to near normal values. The safety and efficacy of this method is unclear.

Methods: We performed a meta-analysis to study the safety and efficacy of IP insulin administration in diabetic patients on PD. The primary outcome measures is glycemic control: secondary outcome measures were plasma lipids, insulin dose requirement/day and the risk of peritonitis and hepatic subcapsular steatosis.

Medline, EMBASE, Cochrane Central Register of Controlled Trials, and reference lists of eligible studies were searched. Eligible studies included randomized and non-randomized controlled trials that allocated adult PD diabetic patients to IP insulin and subcutaneous (SC) insulin.

Results: Twenty one citations were identified and three met the eligibility criteria. Glycemic control with IP insulin, as assessed with HbA_{1c}, was equal to or better than that obtained with SC insulin: weighted mean difference was -1.49 % (95% CI: -2.17 to -0.27, p=0.0001). The insulin dose required was more than two-fold higher in the IP treatment. Serum HDL-cholesterol decreased during IP insulin therapy while serum triglyceride (TG) concentration tended to increase, in comparison with levels seen in patients treated with SC insulin.

Conclusions: Use of IP insulin provides adequate glycemic control, which appears superior to that seen following treatment with conventional SC insulin. The plasma lipids are adversely affected by IP insulin, possibly contributing to increased cardiovascular risk. Data are limited and further studies are needed to assess for the long-term safety of this approach.

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Diabetes mellitus remains the leading cause of end-stage renal disease (ESRD) worldwide and, in Canada, accounts for about 35% of new ESRD cases [1]. Adequate glycemic control in diabetic patients is necessary to further reduce morbidity in subjects with diabetes mellitus and ESRD [2].

Hemodialysis (HD) and peritoneal dialysis (PD) are the main forms of replacement therapy in patients with ESRD. Selection between these methods is based on a number of factors including availability and convenience, co-morbid conditions, socioeconomic and dialysis center factors, residual renal function, the level of home support available [3] and patient preference. Although the percentage of patients undergoing HD far exceeds those being maintained on PD [1], PD has some advantages over HD, including steady-state hemodynamics and biochemistry due to daily exchanges, simplicity of the technique, reduced cardiovascular stress, maintenance of optimal blood pressure and volume control [4]. Insulin can also be given in the dialysate in patients on PD rather than via multiple SC injections. PD can be performed either continuously over 24 hours using continuous ambulatory peritoneal dialysis (CAPD) or via automated devices at night known as nocturnal intermittent peritoneal dialysis (NIPD) or continuous cycling peritoneal dialysis (CCPD) [5]. Unlike patients on CAPD, intraperitoneal insulin (IP) is not often used on CCPD patients due to a greater risk of nocturnal hypoglycemia and uncertainty in insulin dosing [6]. CAPD patients are dialyzed with conventional glucose-containing PD solutions, and the glucose that diffuses into the patients' circulation leads to further risk of poor glycemic control. When insulin is administered through the IP route, most of the absorbed insulin is taken up by the portal venous system and delivered directly to the liver, which helps to create a portal-peripheral insulin gradient close to normal [7] and this may result in an improvement in insulin sensitivity [8]. When comparing IP insulin with conventional subcutaneous insulin regimens in patients on CAPD, several potential benefits have been proposed with the IP route including better glycemic control with favorable HbA_{1C} and lower rates of hypoglycemia with IP insulin. There are also some possible drawbacks to IP insulin relative to the SC route including higher insulin requirements, lower HDL cholesterol levels and higher TG levels. The increased insulin requirement using the IP route is related to several factors including hepatic insulin degradation as in physiological circumstances, incomplete peritoneal absorption of insulin (which is concentration- and time-dependent), possible intraperitoneal degradation of insulin by insulinase enzymes, degradation within adipocytes and adsorption of insulin to the surface of fluid containers and connecting tubing [9]. Several studies have

suggested that the IP administration of insulin can restore glucose levels to near normal values [10], but the available evidence is limited either because only a small number of subjects were used or because glycemic control was not the primary outcome. Many observational studies showed positive effects, but observational studies cannot replace randomized trials. As few non-randomized controlled trials comparing IP and SC insulin are available, conducting a meta-analysis using the available data to increase the power of the current studies would help guide health practitioners in choosing IP insulin versus SC insulin in patients with diabetes mellitus on insulin on peritoneal dialysis.

Materials and Methods

The study was conducted to assess safety and efficacy of IP insulin administration in diabetic patients on PD as measured by HbA_{1C} as the primary outcome, with secondary outcomes including HDL, Apo-A1, triglycerides, the insulin dose requirement/day, and the risk of peritonitis and hepatic subcapsular steatosis.

Study eligibility

Studies were eligible if they were randomized or non-randomized trials comparing IP insulin versus SC insulin in PD patients who were 18 years of age and older with either type 1 or type 2 diabetes mellitus. Studies were excluded if they 1) had no comparison group, 2) were reports only of single cases, 3) did not focus on patients with ESRD or 4) used insulin analogues.

Search strategy

The following databases were searched: Medline (1950 to present with daily update), the EMBASE database from (1980 till February 2012) and Cochrane Database of Systematic Reviews 2005 to January 2012, using word elements: diabetes, peritoneal dialysis, insulin administration, and glucose control (Appendices 1-5). The reference lists of the extracted studies were also reviewed to identify references not appearing in the database searches. Unpublished trials and conference abstracts were not included. For trials with duplicate publications, the most complete and/or more recent publication was eligible for consideration and, where possible, for trials with incomplete or missing data, the author was contacted.

TABLE 1. Characteristics of the trials included in the review

	Lahtela [8]	Nevalainen [30]	Nevalainen [31]
Year	1995	2000	1999
Sample size	6	12	11
Type of study	Prospective open/before –after trial	Prospective open/before –after trial	Prospective open/before –after trial
Follow-up period (months)	3	6	6
Mean age (years)	41±3.6yrs.	43.9 ± 2.8	42.9 ± 2.9
Sex; Male/Female	4/2	8/4	7/4
Duration of DM (years)	28.3yrs ±3	30.4 ± 3.5	31.4 ± 3.4
Mode of PD	CAPD	CAPD	CAPD
A1C (mean± SD)			
At the end of the SC period	9.52 ± 1.24	9.36 ± 1.42	9.49 ± 1.43
At the end of the IP period	7.63 ± 1.13	8.01 ± 1.28	8.13 ± 1.29
Insulin dose (unit/day) (mean± SD)			
SC group	43 ± 17.1	39.5 ± 14.2	39.9 ± 13.9
IP group	103 ± 39.2	93.8 ± 33.2	90.9 ± 36.1
Serum Cholesterol (mean± SD)			
HDL-cholesterol (mmol/L)			
SC group	1.35 ± 0.54	1.34 ± 0.49	1.29 ± 0.431
IP group	0.88 ± 0.17	0.953 ± 0.249	0.96 ± 0.199
Triglycerides (mmol/L)			
SC group	1.43 ± 0.76	1.69 ±0.94	1.75 ± 0.93
IP group	1.83 ± 0.66	2.02 ±1.16	2.09 ± 1.16

SC= subcutaneous; IP = Intraperitoneal; ESRD =End stage renal disease; A1C = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR=not reported; SD=standard deviation

Data Abstraction

Two reviewers (M.H.A and M.S.A) independently reviewed all the titles, abstracts and keywords of all recorded studied. Discordant results were resolved by a third reviewer (M.A.A). The data were extracted from the included studies using a standardized extraction form. Data abstracted were age, percentage of male and female study participants, sample size, type of study, duration of diabetes and follow-up period, mode PD, outcomes, main results and variables included in the adjusted model or models.

Statistical analysis

The results were analyzed by using RevMan, version 5.0. For pooling of the results from the three articles included in this systematic review, the standard error of the mean of all the study and outcome variables that were reported in these articles were used. From the standard error, the standard deviation (SD) and variance were derived. As the outcome variables HbA_{1C} level, insulin level, HDL level and TG level are continuous measures, the standardized mean difference (SMD) was used as the effect size. Statistical heterogeneity was assessed

and, based on its significance, either fixed effect models or random effect models Effect size (SMD) was used appropriately to infer the results.

Pooled results are expressed as weighted mean differences (fixed effects model) if studies are clinically homogeneous and there 95% CIs for continuous outcomes. Clinical heterogeneity was observed in some of the outcomes; thus, a random-effects model was used. Heterogeneity was assessed using I-squared statistics with significance set at $P < 0.10$. The I-squared statistic, ranging from 0 to 100%, measures the amount of variation between different studies that is due to heterogeneity. Values over 50% indicate a large degree of heterogeneity [11]. I² can be estimated, along with its confidence intervals, and the confidence intervals are wider when a meta-analysis includes few studies.

Quality assessment

Quality of the included studies was assessed using McMaster Critical Review Form- Quantitative Studies [12]. Sixteen characteristics were assessed: study purpose; relevant background literature; design; sample description; whether sample size was

FIGURE 1. Flow chart showing the number of studies was identified and those excluded

justified; whether outcome measures were reliable and valid; whether intervention was described; whether contamination and co-intervention were avoided; whether the results were reported in terms of significance; whether the analysis method(s) was/were appropriate; whether clinical importance and dropouts were reported; and whether the conclusions were appropriate given the study methods and results. Each characteristic was awarded a score of one. Two independent reviewers assessed the trials (M.H.A, M.S.A) and disagreement was resolved through discussion with third reviewer (M.A.A). Some characteristics were not applicable to all studies and hence the overall quality score varied (Appendix 6).

Results

The initial search (Fig. 1) yielded 21 studies. After review of the abstracts, 18 studies were excluded: one was a duplicate publi-

cation [13], three were review articles [14-16], one used oral hypoglycemic agent but no insulin [17], four did not involve patients on dialysis [18-21], one studied patients on nighttime IPD [22], one used analogue insulin on non-dialysis subjects [23], two studies had no comparison group [24, 25], two were case reports [26, 27] and two did not contain adequate information (no HbA_{1C}) [10]. The first author /corresponding author of one study [28] was contacted for additional data, but the database was no longer available. One study included non-diabetic patients [29]. Ultimately, only three non-randomized controlled trials were appropriate for inclusion in the meta-analysis [8, 30, 31] (Fig. 1). All three had study populations including patients who had long-standing diabetes and who were treated with insulin.

Demographics

The three trials involved 29 participants, all with type 1 diabetes mellitus. The mean age was 42.6 ± 3.1 years. Diabetes duration was 30 ± 3.2 years. Trial duration ranged from 3 to 6 months. During the subcutaneous insulin phase, the insulin was given either as multiple daily injections (MDI) or through an insulin pump. After switching to IP insulin, patients injected regular insulin into the dialysis bags four times per day prior to fluid exchange. Three of these daily doses were equal but the nightly dose was reduced by 20%. Insulin was titrated whenever necessary. Table 1 summaries the characteristics of the trials included in the review.

Effect of insulin route of administration on HbA_{1C}

In non-randomized studies of diabetic patient on PD, glycemic control with IP insulin treatment, as assessed with HbA_{1C}, was better than that obtained with SC insulin [8, 9, 19, 30]. The analysis of the results of three studies showed that the HbA_{1C} was -1.49 % lower in the IP group (SMD -1.49 % CI -2.17 to -0.27, $p=0.0001$) with no heterogeneity ($I^2=0.80$ and $I^2=0\%$). (Fig. 2)

FIGURE 2. Change in HbA_{1C} level

FIGURE 3. Change in insulin dose

FIGURE 4. Change in HDL level

FIGURE 5. Change in TG level

Effect of insulin route of administration on daily insulin dose

The change from SC to IP insulin therapy resulted in an increase in insulin dose of more than two-fold in the IP group as compared with the SC group. When the data from the three studies was combined, the mean insulin dose was higher with IP insulin treatment than with SC insulin, with the pooled SMD in insulin dose (units per day) being 54.02 (95% C.I: 40.10 to 67.94). The test for heterogeneity was not statistically significant ($p=0.91$) and $I^2 = 0\%$. (Fig. 3)

It is important to recognize that both the insulin dose and HbA_{1C} may be affected by patient weight. The change in the subject weight before and after insulin administration in different phases was not reported, thus potentially affecting both

total daily insulin with IP route and HbA_{1C} results secondary to increased insulin resistance with weight gain. This could bias the noted significant difference between different routes of administration.

Effect of insulin route of administration on other metabolic parameters

Serum HDL-cholesterol was lower with IP insulin therapy than with SC therapy (SMD -0.38; 95% C.I:- $p=0.00001$). As low HDL levels are considered a cardiovascular risk factor, this difference would favor SC insulin administration and was not related to patient heterogeneity ($p = 0.87$ and $I^2 = 0\%$). (Fig. 4)

Serum TG concentration tended to be lower during SC insulin as compared with IP insulin. Analysis of the results of three studies showed that the pooled SMD was 0.36 (95% CI: -0.13 to 0.84, $p=0.15$). This trend was not related to patient heterogeneity ($p=0.99$, $I^2 = 0\%$). As high triglycerides are potentially deleterious to the vasculature, this difference also favors SC insulin administration. (Fig. 5)

LDL-cholesterol was evaluated in three trials, although but actual data was reported in only two [8, 31], and showed a modest increase in LDL cholesterol in the IP group (not statistically significant). Apo lipoprotein A-1 and B did not change significantly during the study period in either study [8, 17]

The rates of peritonitis events, hepatic subcapsular steatosis and hypoglycemia are important safety outcomes that may be increased in patients using IP insulin relative to those on SC insulin, and were unfortunately not reported in selected studies.

Discussion

This meta-analysis of three clinical trials of subjects with type 1 diabetes has shown that HbA_{1C} is improved in patients on IP insulin relative to those on SC insulin. As daily insulin doses differ with the two routes of administration, it cannot be determined with confidence whether the change in HbA_{1C} is related to the altered route of administration or to the higher insulin dose used in the IP patients. While this is useful information, it is important to note that there are no studies in the PD population that address the relationship between HbA_{1C} and cardiovascular outcomes.

Of note, the HbA_{1C} may overestimate glycemic control in patients with ESRD on replacement therapy due to the presence of hemoglobin like carbamylated hemoglobin [32]. Using HbA_{1C} assays with higher specificity for glycated hemoglobin may be a more precise monitoring tool for such patients.

In this review, the effect of IP insulin on serum lipids was reported in three trials. Decreased HDL-cholesterol has been reported during IP insulin therapy in all studies, along with slight decrease in ApoA-1 in one study [31]. There was a modest increase in TG after switching from SC to IP insulin, which was consistent in all studies. It has been suggested that IP insulin enhances triglyceride synthesis by a direct action on the liver rather than by inhibiting the removal of TG [21].

A slight increase in LDL-cholesterol occurred during CAPD while continuing on IP insulin. Mild increases in serum Apo-B were noted during the IP insulin period, but these changes were not statistically significant. It is not clear whether these lipoprotein abnormalities in patients receiving IP insulin would translate into additional risk for cardiovascular disease.

Moreover, there is no evidence that an improvement in the lipid parameters could lead to an improvement in the cardiovascular outcomes.

Safety issues are of concern with IP insulin. Although there is a potential risk of peritonitis, this has not been a consistent finding in clinical trials. In one study [4] of 11 patients, one episode of peritonitis was recorded during IP insulin treatment. In another study [28] of 30 patients, the incidence of peritonitis was four-fold greater in the IP group.

None of the selected studies reported hepatic subcapsular steatosis, but this condition has been reported in patients receiving IP during CAPD [33-35]. The impact of these potential safety concerns on patient survival is unknown and warrants further study. Unfortunately, the trials meeting the criteria for this Meta analysis did not report safety parameters and further data are needed to fully define the risks of the IP insulin approach.

The potential limitation of this review is that all trials were non-randomized. In addition, most trials were of short duration and small subject numbers, which could limit assessment of long-term safety and efficacy of IP insulin versus SC insulin: assessment for heterogeneity was used to attempt to control for this. Unpublished trials were not included in this study; hence, publication bias may be a limitation to the findings of this study.

Conclusions

IP insulin results in improved HbA_{1C} relative to SC insulin but has some deleterious effects on other metabolic parameters such as HDL and TG. The impact of IP insulin on peritonitis rates and hepatic subcapsular steatosis is not well defined. Long-term efficacy and safety trials are required to see if improvement in the glycemic control noted when PD patients are switched from SC to IP insulin translates into a reduction in diabetes related and cardiovascular morbidity. It is clear that more information on this important topic is needed given that the prevalence of diabetes in the ESRF population is 40% and PD usage accounts for 30-50% of renal replacement therapy.

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Appendices 1-5: Detailed Medline searches

Appendix 1: Database: Ovid MEDLINE(R) 1950 to Present with Daily Update

Search Strategy: for meta-analysis-1

1 Diabetes Mellitus/ (78452)	21 subcutaneous insulin.mp. (1730)
2 diabetes mellitu\$.mp. (239668)	22 subcutaneous insulin\$.mp. (1733)
3 diabetes mellitus.mp. (239658)	23 intraperitoneal insulin.mp. (222)
4 diabetes mellitu\$.mp. (239668)	24 intraperitoneal insulin\$.mp. (222)
5 Diabetes Mellitus, Type 1/ (53944)	25 intraperitoneal insulin\$.tw. (222)
6 type 1 diabetes mellitus.mp. (4372)	26 21 or 22 or 23 or 24 or 25 (1894)
7 type 1 diabetes mellitu\$.tw. (4372)	27 glycemic control.mp. (8748)
8 type 1 diabetes mellitu\$.mp. (4373)	28 glycemic control\$.mp. (8760)
9 Diabetes Mellitus, Type 2/ (63392)	29 SMBG.mp. (370)
10 type 2 diabetes mellitu\$.mp. (11494)	30 Blood Glucose Self-Monitoring/ (3269)
11 type 2 diabetes mellitus.mp. (11494)	31 Hemoglobin A, Glycosylated/ (17085)
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (239668)	32 Hemoglobin A, Glycosylated.mp. (17086)
13 Peritoneal Dialysis/ (12828)	33 A1C.mp. (5428)
14 peritoneal Dialysis\$.mp. (23166)	34 Hyperglycemia/ (16174)
15 peritoneal Dialysis.mp. (23164)	35 hyperglycemia.mp. (29467)
16 Peritoneal Dialysis, Continuous Ambulatory/ (9100)	36 Hypoglycemia/ (18794)
17 Peritoneal Dialysis, Continuous Ambulatory.mp. (9103)	37 hypoglycemia.mp. (26394)
18 peritoneal dialysis\$.tw. (16710)	38 hypoglycemia\$.tw. (16278)
19 CAPD.mp. (5820)	39 glucose control.mp. (4095)
20 13 or 14 or 15 or 16 or 17 or 18 or 19 (23372)	40 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (76758)

- 41 12 and 20 and 26 and 40 (12)
- 42 Meta-Analysis as Topic/ (10961)
- 43 meta analy\$.tw. (31755)
- 44 Meta-Analysis/ (27592)
- 45 (systematic adj (review\$1 or overview\$1)).tw. (24141)
- 46 42 or 43 or 44 or 45 (62640)
- 47 cochrane.ab. (15520)
- 48 embase.ab. (12915)
- 49 (cinahl or cinhal).ab. (5024)
- 50 science citation index.ab. (1233)
- 51 bids.ab. (293)
- 52 cancerlit.ab. (489)
- 53 47 or 48 or 49 or 50 or 51 or 52 (21741)
- 54 reference list\$.ab. (5898)
- 55 bibliograph\$.ab. (8768)
- 56 hand-search\$.ab. (2540)
- 57 relevant journals.ab. (455)
- 58 manual search\$.ab. (1433)
- 59 54 or 55 or 56 or 57 or 58 (17122)
- 60 selection criteria.ab. (13899)
- 61 data extraction.ab. (6375)
- 62 60 or 61 (19154)
- 63 "Review"/ (1582922)
- 64 Comment/ (429168)
- 65 Letter/ (699919)
- 66 Editorial/ (267515)
- 67 63 or 64 or 65 or 66 (2595680)
- 68 46 or 53 or 59 or 62 or 67 (2631396)
- 69 41 and 68 (1) →(review article)

Appendix 2: Database: Ovid MEDLINE(R) 1950 to Present with Daily Update

Search Strategy: RCTS and Observational study -2

- 1 Diabetes Mellitus/ (78452)
- 2 diabetes mellitu\$.mp. (239668)
- 3 diabetes mellitus.mp. (239658)
- 4 diabetes mellitu\$.mp. (239668)
- 5 Diabetes Mellitus, Type 1/ (53944)
- 6 type 1 diabetes mellitus.mp. (4372)
- 7 type 1 diabetes mellitu\$.tw. (4372)
- 8 type 1 diabetes mellitu\$.mp. (4373)
- 9 Diabetes Mellitus, Type 2/ (63392)
- 10 type 2 diabetes mellitu\$.mp. (11494)
- 11 type 2 diabetes mellitus.mp. (11494)
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (239668)
- 13 Peritoneal Dialysis/ (12828)
- 14 peritoneal Dialysi\$.mp. (23166)
- 15 peritoneal Dialysis.mp. (23164)
- 16 Peritoneal Dialysis, Continuous Ambulatory/ (9100)
- 17 Peritoneal Dialysis, Continuous Ambulatory.mp. (9103)
- 18 peritoneal dialysi\$.tw. (16710)
- 19 CAPD.mp. (5820)
- 20 13 or 14 or 15 or 16 or 17 or 18 or 19 (23372)
- 21 subcutaneous insulin.mp. (1730)
- 22 subcutaneous insulin\$.mp. (1733)
- 23 intraperitoneal insulin.mp. (222)
- 24 intraperitoneal insulin\$.mp. (222)
- 25 intraperitoneal insulin\$.tw. (222)
- 26 21 or 22 or 23 or 24 or 25 (1894)
- 27 glycemic control.mp. (8748)
- 28 glycemic control\$.mp. (8760)
- 29 SMBG.mp. (370)
- 30 Blood Glucose Self-Monitoring/ (3269)
- 31 Hemoglobin A, Glycosylated/ (17085)
- 32 Hemoglobin A, Glycosylated.mp. (17086)
- 33 A1C.mp. (5428)
- 34 Hyperglycemia/ (16174)
- 35 hyperglycemia.mp. (29467)
- 36 Hypoglycemia/ (18794)
- 37 hypoglycemia.mp. (26394)
- 38 hypoglycemia\$.tw. (16278)
- 39 glucose control.mp. (4095)
- 40 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (76758)
- 41 12 and 20 and 26 and 40 (12)
- 42 Randomized Controlled Trials as Topic/ (71567)
- 43 Randomized Controlled Trial/ (305522)
- 44 Random Allocation/ (70957)
- 45 Double-Blind Method/ (110497)
- 46 Single-Blind Method/ (14768)
- 47 Clinical Trial/ (469362)
- 48 controlled clinical trial.pt. (83352)
- 49 randomized controlled trial.pt. (305522)
- 50 multicenter study.pt. (128936)
- 51 clinical trial.pt. (469362)
- 52 exp Clinical Trials as topic/ (237992)
- 53 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 (843291)

- 54 (clinical adj trial\$.tw. (151022)
- 55 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (107671)
- 56 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (107671)
- 57 PLACEBOS/ (29751)
- 58 placebo\$.tw. (128808)
- 59 randomly allocated.tw. (12508)
- 60 (allocated adj2 random\$).tw. (14758)
- 61 case report.tw. (155734)
- 62 Letter/ (699919)
- 63 Historical Article/ (270799)
- 64 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 (1434442)
- 65 Epidemiologic Studies/ (4989)
- 66 exp case control studies/ (493169)
- 67 exp cohort studies/ (799136)
- 68 Case control.tw. (54632)
- 69 (cohort adj (study or studies)).tw. (50761)
- 70 Cohort analy\$.tw. (2394)
- 71 (Follow up adj (study or studies)).tw. (31428)
- 72 (observational adj (study or studies)).tw. (25002)
- 73 Longitudinal.tw. (98492)
- 74 Retrospective.tw. (187377)
- 75 Cross sectional.tw. (105338)
- 76 Cross-Sectional Studies/ (119931)
- 77 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 (1431600)
- 78 53 or 64 or 77 (3208118)
- 79 41 and 78 (5)

Appendix 3: Database: EMBASE <1980 to February 2012 >

Search Strategy: for meta-analysis-3

- 1 Diabetes Mellitus/ (222040)
- 2 diabetes mellitu\$.mp. (380390)
- 3 diabetes mellitus.mp. (380387)
- 4 diabetes mellitu\$.mp. (380390)
- 5 Diabetes Mellitus, Type 1/ (59983)
- 6 type 1 diabetes mellitus.mp. (5534)
- 7 type 1 diabetes mellitu\$.tw. (5464)
- 8 type 1 diabetes mellitu\$.mp. (5536)
- 9 Diabetes Mellitus, Type 2/ (90145)
- 10 type 2 diabetes mellitu\$.mp. (15538)
- 11 type 2 diabetes mellitus.mp. (15538)
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (380390)
- 13 Peritoneal Dialysis/ (17405)
- 14 peritoneal Dialysi\$.mp. (28108)
- 15 peritoneal Dialysis.mp. (28107)
- 16 Peritoneal Dialysis, Continuous Ambulatory/ (10341)
- 17 Peritoneal Dialysis, Continuous Ambulatory.mp. (8)
- 18 peritoneal dialysi\$.tw. (18751)
- 19 CAPD.mp. (6826)
- 20 13 or 14 or 15 or 16 or 17 or 18 or 19 (28383)
- 21 subcutaneous insulin.mp. (2276)
- 22 subcutaneous insulin\$.mp. (2280)
- 23 intraperitoneal insulin.mp. (267)
- 24 intraperitoneal insulin\$.mp. (267)
- 25 intraperitoneal insulin\$.tw. (265)
- 26 21 or 22 or 23 or 24 or 25 (2478)
- 27 glycemic control.mp. (17049)
- 28 glycemic control\$.mp. (17064)
- 29 SMBG.mp. (543)
- 30 blood glucose monitoring/ (8322)
- 31 Hemoglobin A, Glycosylated/ (11266)
- 32 Hemoglobin A, Glycosylated.mp. (21)
- 33 A1C.mp. (24587)
- 34 Hyperglycemia/ (39273)
- 35 hyperglycemia.mp. (47924)
- 36 Hypoglycemia/ (36022)
- 37 hypoglycemia.mp. (41596)
- 38 hypoglycemia\$.tw. (18442)
- 39 hypoglycemia\$.tw. (18442)
- 40 glucose control.mp. (5344)
- 41 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (121545)
- 42 12 and 20 and 26 and 41 (19)
- 43 exp Meta Analysis/ (51594)
- 44 ((meta adj analy\$) or metaanalys\$).tw. (40599)
- 45 (systematic adj (review\$1 or overview\$1)).tw. (29540)
- 46 cancerlit.ab. (585)
- 47 cochrane.ab. (19386)
- 48 embase.ab. (15923)
- 49 (cinahl or cinhal).ab. (5852)
- 50 science citation index.ab. (1469)
- 51 bids.ab. (353)
- 52 reference lists.ab. (6441)
- 53 bibliograph\$.ab. (10731)
- 54 hand-search\$.ab. (2931)

- 55 manual search\$.ab. (1645)
- 56 relevant journals.ab. (587)
- 57 relevant journals.ab. (587)
- 58 data extraction.ab. (8358)
- 59 selection criteria.ab. (16463)
- 60 review.pt. (1652078)
- 61 editorial.pt. (358354)
- 62 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 (2070750)
- 63 42 and 62 (1) →(review article)

Appendix 4: Database: EMBASE <1980 to February 2012 >

Search Strategy: RCTS and Observational study-4

- 1 Diabetes Mellitus/ (222040)
- 2 diabetes mellitu\$.mp. (380390)
- 3 diabetes mellitus.mp. (380387)
- 4 diabetes mellitu\$.mp. (380390)
- 5 Diabetes Mellitus, Type 1/ (59983)
- 6 type 1 diabetes mellitus.mp. (5534)
- 7 type 1 diabetes mellitu\$.tw. (5464)
- 8 type 1 diabetes mellitu\$.mp. (5536)
- 9 Diabetes Mellitus, Type 2/ (90145)
- 10 type 2 diabetes mellitu\$.mp. (15538)
- 11 type 2 diabetes mellitus.mp. (15538)
- 12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (380390)
- 13 Peritoneal Dialysis/ (17405)
- 14 peritoneal Dialysi\$.mp. (28108)
- 15 peritoneal Dialysis.mp. (28107)
- 16 Peritoneal Dialysis, Continuous Ambulatory/ (10341)
- 17 Peritoneal Dialysis, Continuous Ambulatory.mp. (8)
- 18 peritoneal dialysi\$.tw. (18751)
- 19 CAPD.mp. (6826)
- 20 13 or 14 or 15 or 16 or 17 or 18 or 19 (28383)
- 21 subcutaneous insulin.mp. (2276)
- 22 subcutaneous insulin\$.mp. (2280)
- 23 intraperitoneal insulin.mp. (267)
- 24 intraperitoneal insulin\$.mp. (267)
- 25 intraperitoneal insulin\$.tw. (265)
- 26 21 or 22 or 23 or 24 or 25 (2478)
- 27 glycemic control.mp. (17049)
- 28 glycemic control\$.mp. (17064)
- 29 SMBG.mp. (543)
- 30 blood glucose monitoring/ (8322)
- 31 Hemoglobin A, Glycosylated/ (11266)
- 32 Hemoglobin A, Glycosylated.mp. (21)
- 33 A1C.mp. (24587)
- 34 Hyperglycemia/ (39273)
- 35 hyperglycemia.mp. (47924)
- 36 Hypoglycemia/ (36022)
- 37 hypoglycemia.mp. (41596)
- 38 hypoglycemia\$.tw. (18442)
- 39 hypoglycemia\$.tw. (18442)
- 40 glucose control.mp. (5344)
- 41 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 (121545)
- 42 12 and 20 and 26 and 41 (19)
- 43 Clinical trial/ (815265)
- 44 Randomization/ (52851)
- 45 Crossover procedure/ (29559)
- 46 Randomized controlled trial\$.tw. (57394)
- 47 Rct.tw. (6101)
- 48 Random allocation.tw. (998)
- 49 Randomly allocated.tw. (14840)
- 50 Allocated randomly.tw. (1679)
- 51 Single blind\$.tw. (10503)
- 52 Placebo\$.tw. (152155)
- 53 Prospective study/ (158218)
- 54 Case study/ (10547)
- 55 Abstract report/ or letter/ (759204)
- 56 Case report.tw. (193062)
- 57 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 (1976587)
- 58 Clinical study/ (28445)
- 59 case control study/ (49451)
- 60 Family study/ (8883)
- 61 Longitudinal study/ (41648)
- 62 Retrospective study/ (216717)
- 63 Prospective study/ (158218)
- 64 Randomized controlled trials/ (284101)
- 65 Cohort analysis/ (89976)
- 66 (Cohort adj (study or studies)).mp. (57595)
- 67 (follow up adj (study or studies)).tw. (34108)
- 68 (observational adj (study or studies)).tw. (31070)
- 69 (epidemiologic\$ adj (study or studies)).tw. (55263)
- 70 (cross sectional adj (study or studies)).tw. (44678)

71 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 (951912) 72 57 or 71 (2469961)
73 42 and 72 (5)

Appendix 5: Database: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to January 2012.

1 diabetes mellitus.mp.(395) 7 subcutaneous insulin.mp.(10)
2 diabetes.mp.(985) 8 glucose control.mp.(53)
3 1 or 2(985) 9 A1C.mp.(46)
4 peritoneal dialysis.mp.(55) 10 glucose control.mp.(53)
5 3 and 4 (21) 11 8 or 9 or 10(82)
6 intraperitoneal insulin.mp.(0) 12 5 and 7 and 11(0)

Appendix-6 Checklists to assess study quality.

	Lahtela [8]	Nevalainen [30]	Nevalainen [31]
Study purpose stated clearly	Yes	Yes	Yes
Was relevant background literature reviewed?	Yes	Yes	Yes
Design	Prospective open/before –after trial	Prospective open/before –after trial	Prospective open/before –after trial
Sample size	6	12	11
Was the sample described in detail?	No	No	No
Was sample size justified?	No	No	No
Were the outcome measures reliable?	Yes	Yes	Yes
Were the outcome measures valid?	NA	NA	NA
Intervention was described in detail?	Yes	Yes	Yes
Contamination was avoided?	Yes	Yes	Yes
Co-intervention was avoided?	NA	NA	NA
Results were reported in terms of statistical significance?	Yes	Yes	Yes
Were the analysis method(s) appropriate?	NA	NA	NA
Clinical importance was reported?	Yes	Yes	Yes
Dropouts were reported?	No	No	No
Conclusions were appropriate given study methods and results	Yes	Yes	Yes
NA: Not addressed			