"Finding the right route for insulin delivery – an overview of implantable pump therapy"

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ABSTRACT

Introduction

Implantable pump therapy adopting intraperitoneal route of insulin delivery has been available for the past three decades. The key rationale for implantable pump therapy is the restoration of the portal-peripheral insulin gradient of the normal physiology. Uptake in clinical practice is limited to specialised centres and selected patient populations.

Areas covered

Implantable pump therapy is discussed including technical aspects, rationale for its use, and glycaemic and non-glycaemic effects. Target populations, summaries of clinical studies and issues related to implantable pump therapy are highlighted. Limitations of implantable pump therapy and its future outlook in clinical practice are presented.

Expert opinion

Although intraperitoneal insulin delivery appears closer to the normal physiology, technical, pharmacological, and costs barriers prevent a wider adoption. Evidence from clinical studies remains scarce and inconclusive. As a consequence, the use of implantable pump therapy will be confined to a small population unless considerable technological progress is made and well-conducted studies can demonstrate glycaemic and/or non-glycaemic benefits justifying wider application.

Article highlights

- Key rationale of implantable pump therapy is the restoration of the portal-peripheral insulin gradient of the normal physiology
- Although implantable pump therapy has been available for over three decades, data from randomised controlled trials remain limited
- The use of implantable pump systems remains restricted due to technical, pharmacological and cost barriers and the need for specialist input
- Advances in implantable pump therapy technology has made it more reliable with fewer technical failures and clinical adverse events
- Well-conducted studies demonstrating beneficial effects of implantable pump therapy on glycaemic and/or non-glycaemic outcomes are still needed to justify wider adoption in clinical practice

1. Introduction

Type 1 diabetes is a chronic autoimmune condition characterised by destruction of beta cells and consequential insulin deficiency[1]. Insulin replacement therapy is the mainstay of treatment aiming to replicate physiological levels of circulating insulin attained by the healthy pancreas. Modern clinical management is by multiple daily insulin injections to cover basal insulin and prandial requirements, and insulin pump therapy which delivers insulin by applying pre-programmed basal rates and insulin boluses at meal times allowing greater flexibility[2].

The first externally worn insulin pump devices were developed in 1977 and delivered insulin subcutaneously[3]. The rationale for implantable pump (IP) therapy was instigated by the need for a more physiological route of insulin delivery, whilst mitigating body wear issues and device burden. The first implantable pump was applied in 1979[4] with the expected progress towards the implantable artificial pancreas, which unfortunately failed

to materialise. Early generations of IP utilised either intravenous or intraperitoneal routes, depending on the IP model used[5]. However, due to the greater risk of thrombosis and infection observed with the latter, the intraperitoneal route has prevailed[6].

Although from a physiological standpoint, IP insulin delivery appears to be an attractive alternative and closer to the normal physiology, its clinical application remains limited to selected groups of patients and restricted to specialised clinical centres[7-10]. The technical properties of the IP systems, physiological aspects related to intraperitoneal insulin delivery, clinical evidence, limitations and outlook are discussed in this review, with focus on intraperitoneal IP systems. An electronic search of Medline (via Pubmed) and the public register of clinical trials (www.clinicaltrials.org) was conducted. Keywords (implantable pump, intraperitoneal insulin delivery, type 1 diabetes, clinical trials) combined with relevant MeSH terms were used. A secondary search strategy was conducted using these keywords and terms in the abstract databases, and the bibliographies of retrieved papers were searched. Additional papers known to the authors were used.

2. Technical description and overview of implantable pumps

The first generation of commercial intraperitoneal IP systems developed in the 1980's and 1990's included the MIP 2001 pump (Minimed), the Promedos ID1/ID3 pump (Siemens AG), and the Model 1000 pump (Infusaid)[5, 6, 11]. The MIP 2007D pump (Medtronic Minimed, Northridge, CA, USA) is currently the only available commercial IP system. Its clinical use is limited to Europe.

IP systems are implanted at the lower quadrants of the abdomen under general anaesthesia[12] (Figure 1). The MIP 2007D pump has a diameter of 8cm, thickness of 2cm and contains up to 15ml of insulin which is delivered via a catheter placed within the peritoneal cavity. The tip of the catheter is directed towards the liver. Post-procedure, patients are required to undergo 24 hours of strict bedrest, followed by wearing a supportive belt for 4 to 6 weeks. They are restricted from lifting heavy weights and strenuous physical activity for 6 weeks post-procedure. Insulin delivery is remotely controlled by the user using a pager-sized hand-held device which allows for bolus delivery at mealtime and to correct high glucose values with pre-programmed basal infusion rates (Figure 2). The insulin reservoir is refilled transcutaneously through a central insulin refill port at a dedicated outpatient clinic at least every 3 months, depending on individual insulin requirements. The IP device components are biocompatible to avoid rejection and adverse reactions, and currently have a power source lasting up to 7-10 years. The IP insulin reservoir has an additional side-port to support technical maintenance such as rinsing in case of catheter occlusion.

Apart from the technical equipment and the need for specialist input and expertise, intraperitoneal insulin delivery imposes specific challenges on insulin formulation. Increased insulin stability is required compared to subcutaneous delivery due to factors which aggravate the risk of insulin precipitation such as higher ambient temperature, fluid turbulence related to the pumping mechanism and interactions with surface materials[13]. A highly concentrated formulation such as U-400 is normally used to prolong the interval between reservoir refills.

Widespread pump failures in 1994[14] were attributed to precipitation of a new insulin formulation in the pump reservoir, highlighting issues associated with insulin stability during intraperitoneal delivery. A follow-up semisynthetic neutral human insulin preparation Hoe 21 GH (Hoechst AG, Frankfurt, West Germany) was marketed in 1998 as Insuplant (U-400). Insuplant contains a surface-active agent (polyethylene-polypropylene glycol) which increases its stability[15]. The move to human recombinant insulin synthesis has led to the development of Insuman implantable insulin (U-400; Sanofi-Aventis, Frankfurt Germany) in 2012, and is currently the only available insulin for intraperitoneal insulin delivery. Rapid acting insulin analogues are not approved for intraperitoneal delivery. Insuman has been shown to be non-inferior to Insuplant in terms of HbA1c change from baseline and the accuracy of pump delivery[16]. The pivotal study also showed comparable insulin doses, rates of hypoglycaemia, and technical and metabolic adverse events between the two insulin preparations.

3. Physiological justification of intraperitoneal insulin delivery

Endogenous insulin secretion into the portal vein results in preferential exposure of the liver to insulin. Studies in humans and animal models have shown that insulin concentrations during steady state conditions are typically two- to fourfold higher in the portal vein than in the periphery following rapidly pulsating insulin delivery by the pancreas[17-19]. A positive portal to systemic insulin gradient assists in balancing hepatic glucose output and peripheral glucose disposal, thereby maintaining glucose homeostasis in both postprandial and postabsorptive periods[20]. Conventional subcutaneous insulin delivery attains glycaemic control in a less favourable physiological manner as the positive portal to systemic insulin gradient and the pulsatile insulin concentration in the portal system are lost given that insulin is diffused from a subcutaneous depot into the central circulation. Subcutaneous insulin administration needed to regulate hepatic glucose production results in higher-than-physiological insulin concentrations at the peripheral tissues (Figure 3).

It has been argued that the resulting peripheral overinsulinization by subcutaneous insulin shifts the primary site of insulin action away from the liver towards the skeletal

muscle, predisposing to hypoglycaemia. This is compounded by the skeletal muscle being a larger glucose sink than the liver due to the higher percentage of total mass which takes up glucose regardless of glycaemic levels. In contrast, hepatic glucose uptake is diminished under hypoglycaemic conditions, and is moderate under euglycaemic conditions[21]. Thus, relative hepatic hypoinsulinaema shifts glucose storage away from the liver towards the muscle contributing to excess hepatic glucose output[22].

Subcutaneously administered regular insulin has a slower absorption rate compared to intraperitoneally delivered insulin[23]. However, this advantage may be lost with rapid insulin analogues which are approved for subcutaneous but not for intraperitoneal delivery, and also due to the high insulin concentration needed for intraperitoneal delivery, which is known to slow down the rate of insulin absorption. A number of factors such as the anatomical region, the depth of the insulin injection, the degree of fibrosis, and the local blood flow may contribute up to 35% variability in insulin absorption of rapid insulin analogues from the subcutaneous tissue. It is hypothesised that this variability could be ameliorated by the application of intraperitoneal insulin delivery although exact data for the latter are yet to be quantified[24].

Intraperitoneal insulin delivery has been suggested to restore partially the positive portal to systemic insulin gradient. Intraperitoneal insulin delivery infuses insulin directly into the intraperitoneal space. Insulin is then absorbed via the capillaries of the visceral peritoneum into the portal vein[25]. The integrated rise in plasma insulin is notably reduced by 50% with intraperitoneal insulin delivery, suggesting a considerable first pass effect with significantly lower peripheral insulin levels.

The differential effects of portal and peripheral insulin delivery on glucose turnover have been investigated in several studies using stable isotopes. A recent proof of concept study demonstrated that in the setting of induced hypoglycaemia, by either dose-matched portal or peripheral insulin administration, glucose utilisation and the consequent fall in glucose levels were significantly more pronounced by the subcutaneous as opposed to portal route[26]. Although the effect of portal compared to subcutaneous insulin delivery on glucose disposal is known, the evidence of its effect on hepatic glucose output is inconsistent. Whereas some studies have shown decreased hepatic glucose output, others have not been able to reproduce these findings[27-29].

4. Endocrine effects of intraperitoneal insulin delivery– beyond glycaemia

Due to the higher portal and lower systemic insulin levels, several non-glycaemic and endocrine effects have been associated with intraperitoneal insulin delivery.

Intraperitoneal insulin delivery has been suggested to augment glucagon response as reported in one study where subjects with type 1 diabetes receiving subcutaneous and intraperitoneal insulin pump therapy underwent identical hyperinsulinaemic challenges[30]. Whilst a significant increase in the plasma glucagon concentration was observed during the latter, no such increase was seen during the former.

Portal insulin is critical for hepatic glycogen storage[31]. This may be an important mitigation against hypoglycaemia. To date, no clinical studies have investigated liver glycogen metabolism in subjects receiving portal insulin delivery. As peripheral over-insulinisation has been linked to an increase in body weight and fat mass, emulating the physiological portal to systemic insulin gradient through portal insulin delivery may be beneficial for weight management[32].

Portal insulin delivery has been shown to normalize altered IGF-1 axis in individuals with type 1 diabetes with an observed increase in IGF-1 bioactivity, IGF-I and IGF-II levels as well as a decrease in IGF1BP-1 levels following intraperitoneal insulin delivery[33]. The clinical significance of these effects remains unclear but may include reversal of peripheral insulin resistance as well as anabolic effects on IGF-1 sensitive tissues such as the skeletal muscle and bone.

Portal insulin delivery has also been shown to influence sex hormone binding globulin (SHBG) levels. Decreased levels of SHBG in males with type 1 diabetes during portal insulin delivery have been reported[34]. However, the clinical relevance of these findings remains unclear and requires further investigations. The lower peripheral insulin concentrations associated with intraperitoneal insulin delivery are known to affect the lipid profile[35-37]. Lower VLDL triglycerides and VLDL apolipoprotein B and higher HDL and HDL3 cholesterol during portal insulin delivery have been reported in one study suggesting a lower atherogenic potential[37]. Vitamin D activation with resulting higher levels of plasma 25-hydroxyl vitamin D[38] has been linked to portal insulin delivery further highlighting its potential endocrine and metabolic effects.

It is important to note that the aforementioned studies which reported on endocrine and metabolic findings of intraperitoneal insulin delivery were relatively small and underpowered. Any clinical significance of the suggested effects is therefore speculative and requires further investigations.

5. Target population for “last-resort” treatment

Experts in the field including the EVAluation dans le Diabète des Implants ACtifs (EVADIAC) group[39] and others have reviewed available evidence and published guidelines based on clinical experience and consensus for patient selection for intraperitoneal insulin delivery[7]:

- The failure to reach adequate glycaemic control or occurrence of frequent hypoglycaemic episodes including recurrent severe hypoglycaemia (often combined with hypoglycaemia unawareness). Patients who experience fear of hypoglycaemia and consequently have maladaptive behaviours leading to a chronic hyperglycaemic state may also benefit from implantable pump therapy;
- Impaired subcutaneous insulin absorption (e.g. due to skin reactions, allergies, or extensive lipohypertrophy)[40];
- Frequent hospital admissions as a result of suboptimal metabolic control due to poor acceptance and management of insulin therapy[41].

The contra-indications listed below should also be considered by healthcare providers when prescribing intraperitoneal insulin delivery:

- Health conditions or work environments incompatible with portal insulin delivery (e.g. immunodeficiency syndromes, exposure to high-intensity magnetic field or very low/high atmospheric pressure);
- Children or adolescents;
- Pregnancy (due to lack of clinical data and regulatory approval of the insulin formulation).

In cases where the expected benefits are unclear, the indication of IP therapy should be based on a comprehensive assessment of the individual's clinical and psychological status by experienced staff and a careful risk/benefit assessment.

6. Evidences from clinical studies

6.1 Pilot and early feasibility studies

An early feasibility study using the stabilised Hoe 21 GH insulin in the Promedos ID 1 implantable pump (Siemens AG, Erlangen, West Germany) which delivered insulin via the intravenous and intraperitoneal route was assessed over a one-year period in twenty adults with type 1 diabetes[5]. The authors combined findings from intraperitoneal and intravenous routes as no significant differences in glucose levels and HbA1c between the two approaches were observed. The authors reported that 63% of self-monitoring blood glucose measurements were within the range 3.3 to 8.9mmol/l, with three glucose measurements per patient-month below 2.8mmol/l and 0.22 hypoglycaemia episodes per patient year requiring medical attention. Due to the inherent issues related to intravenous access, thrombosis and the risk of blood-borne infections[42], intravenous insulin delivery has not been deemed feasible for ambulatory implantable pump use.

Intraperitoneal insulin delivery has since become the preferred route for the IP use, and early clinical studies have been performed to evaluate its feasibility in type 1 diabetes (Table 1).

A pilot study in 18 participants receiving IP over 28-patient years showed that glycaemic control was sustained (mean HbA1c 8%) and glucose variability reduced without episodes of severe hypoglycaemia or diabetic ketoacidosis[11]. Four users experienced catheter-occlusions and the authors reported that approximately 80 percent of implantable catheters were useable for up to 1.5 years.

A large (N=224) non-randomised multicentre prospective study reported on technical issues and related outcomes of the IP use[39]. The authors showed that over the 1.5 year follow-up period, catheter obstructions were still relatively common (47 events) with nine pump failures requiring replacement. However, glycaemic control as measured by HbA1c and mean glucose were significantly improved compared to baseline ($p<0.001$ for both). Long-term feasibility studies by the same group showed that technical improvements reduced the frequency of insulin under-delivery caused by insulin aggregation and increased accuracy of pump delivery[43].

6.2 Randomised controlled trials

Although IP therapy has been available in clinical practice for several decades, data from randomised controlled trials remain limited. Results related to glycaemic control and hypoglycaemic outcomes have been mixed due to the heterogeneous population of the comparator group in these studies (i.e. subcutaneous insulin pump and multiple daily injection users, various insulin preparations used such as human insulin and rapid-acting analogues by the comparator group) and glucose measures used (intermittent capillary glucose and continuous glucose monitoring), making interpretation of the results challenging. The small number of participants limited statistical power especially for hypoglycaemia-related outcomes. The small number of participant may be partly attributable to the highly selected patient population deemed appropriate for this therapy, and the low number of specialist centres with clinical expertise and skills to manage IP devices which required input both from the diabetes and surgical teams.

An early randomised controlled parallel design study compared IP delivering intraperitoneal insulin against optimised subcutaneous insulin therapy administered by either multiple daily injections or subcutaneous insulin pump[44]. There were no significant differences in HbA1c levels or severe hypoglycaemia events between the two groups, with both groups achieving a comparable HbA1c reduction relative to baseline. Longitudinal within group comparisons showed that glycaemic variability as measured by the standard deviation of capillary glucose was notably reduced by IP [4.3±0.4 vs.

3.2±0.5mmol/l in the IP group (p<0.005) and 3.7±0.3 vs. 4.0±0.4mmol/l in the subcutaneous insulin group (p>0.05)]. Conversely, a randomised controlled cross-over design study comparing intraperitoneal insulin infusion via IP to subcutaneous insulin via multiple daily injections showed that IP users had significantly lower HbA1c (7.2±0.2 vs. 8.5±0.7%, p=0.02), glycaemic variability as measured by the standard deviation of capillary glucose (3.4±0.2 vs. 4.6±0.2mmol/l, p<0.01) and hypoglycaemic events (5.7±2.0 vs. 10.0±3.1 events/month, p=0.02)[45].

A single centre randomised cross-over design study compared IP delivering intraperitoneal insulin in 24 suboptimally controlled adults with type 1 diabetes (mean baseline HbA1c 8.6%) against a heterogeneous group of subcutaneous insulin therapy users (insulin pump and multiple daily injection)[8]. There were no reported differences between the groups in the study's primary endpoint (the number of hypoglycaemic events, p=0.13), although IP use reduced HbA1c levels by 0.76% (p=0.03) without significantly increasing total daily insulin (p=0.57). Quality of life was notably improved in IP compared to subcutaneous insulin therapy users.

6.3 Long-term follow-up clinical studies

Limitations of randomised controlled trials involving IP include the relatively short duration of studies ranging from 9 to 16 months, and a small number of participants. Long-term observational studies have provided insights into the safety, efficacy, and tolerability of IP therapy over prolonged use as well as its impact on quality of life in larger patient populations[10, 46].

In one of the longest follow-up study to date, no significant difference in HbA1c was found among 19 of 23 patients who received IP for 6 years, compared to their pre-IP period, following optimisation of subcutaneous insulin therapy [mean estimated change of HbA1c −0.1mmol/mol, 95%CI (-10.5, 10.3); p=1.0][9]. Although a significant reduction in the number of capillary glucose values below 3.5mmol/l was observed, continuous glucose monitoring sensor measurements showed significantly greater time spent in the hyperglycaemic range at the 6-year follow-up [mean change 19.8% (95% CI 3.0, 36.6), p=0.013].

Treatment satisfaction, as measured by the Diabetes Treatment Satisfaction Questionnaire (DTSQ), was reportedly higher at follow-up with IP than subcutaneous insulin therapy, albeit with notably higher perceived hyperglycaemic score of the DTSQ. Health-related quality of life measures remained high and stable throughout the study. There were three reported technical pump failures over a mean study duration of 5 years, and 4 users required either laparoscopic procedures or operations for catheter-related complications. There was no reported mortality over the whole study period.

7. Challenges and issues related to implantable pump therapy

In spite of the reported benefits on treatment satisfaction, studies evaluating IP therapy have reported issues and technical limitations such as pump malfunctions which are generally more difficult to resolve compared to subcutaneous insulin pump therapy. Modern IP devices present fewer of these issues[43, 47]. The most common are local complications at the abdominal implantation site and insulin under-delivery. Reported occurrences of local complications, which included pump site infections, fluid collections as well as skin atrophy or erosions, have decreased from eight to less than two per 100 patient-years, from the early 1990s to present[43, 48-50]. Most infections are related to bacterial seeding from the skin during surgical and maintenance-related procedures, e.g. repeated transcutaneous punctures of the pump pocket for insulin refill. Suggested approaches to mitigate against local infections include peri-procedural antibiotic coverage and antiseptic cleaning of the surrounding skin.

Insulin under-delivery may develop steadily over time[51] and is reflected by an increase in insulin requirements needed to maintain glucose control. This may be related to occlusions in the pumping system caused by either biological materials such as fibrin clots or encapsulation, or insulin aggregation. As the latter has been thought to be a common cause of insulin under-delivery, a pragmatic solution includes regular rinsing of the tubing system with sodium hydroxide[52].

Several studies in the 1990s reported an increase of anti-insulin antibody levels during IP use[53-55], which occurred as early as the third month following implantation. The increased immunogenicity was attributed to factors such as the insulin formulation (HOE 21 PH insulin), the route of delivery - the peritoneum is a macrophage-rich area which may bolster lymphocytes activation and antibody production - as well as insulin aggregates formed in the pumping system[56]. Of note, this immune reaction is highly variable and the only identifiable predictive factor appears to be the anti-insulin antibody level before implantation, however, its clinical significance is unclear.

8. DiaPort – intraperitoneal insulin delivery with externally worn pump

Due to the invasive nature and associated risks of IP, DiaPort (Roche Diagnostics, Mannheim, Germany) has been developed, which is an alternative approach for intraperitoneal insulin delivery[57]. DiaPort utilises a percutaneous insulin port connected to an external pump device. It consists of a small titanium-encased body which is biocompatible and is implanted into the subcutaneous tissue. DiaPort has made intraperitoneal insulin delivery more feasible in clinical practice due to its less invasive application procedure compared to IP[32]. In a multi-centre cross-over design study,

sixty participants with type 1 diabetes were randomised to intraperitoneal insulin infusion using DiaPort with regular insulin (Insuman U-100) or to subcutaneous insulin pump therapy with lispro for 12 months[32]. The primary endpoint based on intention to treat analysis showed that the incidence of hypoglycaemia was comparable between the treatments (p=0.91) whereas the number of severe hypoglycaemia events was halved during the DiaPort use (34.8 vs. 86.1 events / 100 patient years, p=0.013). The number of dropouts during the study was relatively high (24/30 and 12/30 participants in the DiaPort and subcutaneous insulin pump group, respectively), which the authors attributed to participants' fear of potential complications of intraperitoneal delivery, leading to reluctance to use it.

The second-generation DiaPort system was introduced in 2011. Information obtained from the manufacturer suggests that compared to its predecessor, improvements have been made to the implantation method, design and materials. These modifications were implemented to simplify the implantation procedure and to reduce further the risk of infection and catheter obstruction. There are no randomised clinical trials of the second generation DiaPort system currently available. Non-randomised single-arm studies with a relatively small number of participants have been performed (i.e. ClinicalTrials.gov NCT01483352) and results are yet to be published.

9. Implantable pump and artificial pancreas

Closed-loop systems, also known as the Artificial Pancreas, are considered a bridge to a biological cure. A closed-loop system consists of an insulin pump, a continuous glucose monitoring sensor and a control algorithm[2]. Insulin delivery is directed by the control algorithm in a glucose-responsive fashion. Closed-loop systems have been tested in up to 6-month home studies using the subcutaneous route for both glucose sensing and insulin delivery[58-61]. The first closed-loop insulin delivery system adopting subcutaneous insulin delivery route has been approved by the US Food and Drug Administration based on a recent pivotal study[62]. Limitations remain with regards to delays in insulin absorption and action inherently linked to the subcutaneous route of insulin delivery. If intraperitoneal insulin infusion from IP therapy could provide faster and less variable insulin action, integrating IP into closed-loop system would be a promising approach. However, the lack of rapid acting insulin analogues for intraperitoneal delivery remains an obstacle. The feasibility of closed-loop IP insulin delivery system adopting intravenous[63] and subcutaneous glucose sensors has been demonstrated. A non-randomised controlled trial of closed-loop intraperitoneal insulin delivery via DiaPort was recently completed but results are yet to be published (ClinicalTrials.gov NCT01555788).

10. Expert – Outlook and future of implantable pump therapy

The development and interest of IP therapy stemmed from the conjecture that intraperitoneal insulin delivery may restore the physiological portal-systemic insulin gradient thereby circumnavigating the unfavourable effects of subcutaneous insulin which impedes satisfactory postprandial control and may lead to delayed postprandial hypoglycaemia and increased glycaemic variability. Portal insulin delivery, with *potentially* faster time-to-peak insulin action and return-to-baseline ("on-and-off" of insulin action) and better reproducibility of insulin absorption could improve the efficacy and safety of present management approaches. This may also enhance closed-loop performance, which is currently hampered by delayed subcutaneous insulin kinetics[59, 60]. Studies have provided insights into both glycaemic and non-glycaemic outcomes of intraperitoneal/portal insulin delivery, showing potential amelioration of metabolic and endocrine dysregulation in type 1 diabetes, although data supporting the clinical significance of these observations are lacking. In addition, most evidence justifying the pharmacokinetic benefits of IP insulin delivery is based on outdated studies in the pre-insulin analogue era[23]. Research in the field is limited by the lack of innovation, the lack of rapid acting insulin analogues for intraperitoneal delivery, and the small niche target population which may deter commercial interest.

Findings from clinical studies have overall been inconclusive and challenging to interpret due to the inherent limitations of study designs and populations, various insulin preparations and regimes used. The limited numbers of prospective randomised controlled trials have shown modest reductions in HbA1c and glycaemic variability. Most recent studies of IP, or intraperitoneal insulin delivery via DiaPort, have yet to be published. The scientific progress inertia in this field is in contrast with the rapid advances and innovations surrounding subcutaneous insulin pump technology and associated rapid acting insulin analogues[62, 64]. Hypoglycaemia outcomes have been inconsistent, likely due to the small sample size and limited continuous glucose monitoring available in early studies. Regulatory approval of IP is currently restricted to Europe, and used in clinical practice in Belgium, France, Sweden and the Netherlands. Several groups with extensive experience of IP use, such as the EVADIAC group, have formulated clinical guidelines and patient selection criteria.

Cost implications have limited the wider clinical use and availability of IP in many countries. The estimated direct pump and procedure-related (i.e. filling and rinsing procedures) costs in 2010 for IP therapy were approximately 31,000 Euros in the first year, and 7,500 Euros for the following 6 years[65]. Other incurred costs such as the

specific insulin formulation used and the need for specialist teams which include technical and surgical input. This results in IP therapy being costlier than conventional subcutaneous insulin therapy, either by multiple daily injections or insulin pumps. The annual costs of IP is approximately 6,000 Euros higher than subcutaneous insulin pump therapy[10].

Based on the aforementioned limitations such as the risk of complications, the need for more clinical evidence, higher costs, and the rapid development of subcutaneous insulin-based therapies (i.e. ultra-fasting acting analogues) and non-insulin adjunctive therapies, the incremental benefits of IP in the wider population of people with type 1 diabetes remain debatable. Well-conducted studies supporting the clinical benefits from glycaemic and non-glycaemic, endocrine and metabolic effects of IP are needed to provide stronger justification for its wider use in clinical practice but it is unclear whether there is sufficient appetite and justification to do so.

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Table 1. Summary of studies comparing implantable pump therapy with subcutaneous insulin therapy.

	Study design	Intervention	Comparator	N	Study duration	Main findings	Reference
Early feasibility studies	Single-arm observational study	IP	-	20	1-year	62·9% capillary glucose measurements between 3·3-8·9mmol/l. 3.3 glucose measurements per patient-month in the hypoglycaemic range (<2·8mmol/l) and 2·6 episodes of hypoglycaemia per patient-month, 0·22 severe hypoglycaemia episodes per patient-year. Median HbA1c at baseline 7.6%, and 7·0% at the end of the trial (p <0·05).	[5]
	Single-arm observational study	IP	-	18	4-25 months (mean 18 months)	Mean plasma glucose level 7.3mmol/l; mean HbA1c 8% and significantly reduced glycaemic fluctuations during IP therapy. Total mean daily insulin dose did not change compared to baseline. No surgical complications, or severe hypoglycaemia or diabetic ketoacidosis episodes. Four patients had catheter blockages, one pump had manufacturing defect.	[11]
	Single-arm observational study	Post-IP	Pre-IP	224	1 – 40 months (353 patient-years)	Mean HbA1c decreased from 7.4 to 6.8% (p<0.001). Mean glucose decreased from 8.7 to 7.8mmol/l (p<0.001).	[39]
Randomised controlled studies	Randomised, prospective, cross-over design.	IP	MDI, CSII	21	6 months	No significant differences in HbA1c or severe hypoglycaemia events between groups.	[44]
	Randomised, prospective, cross-over design.	IP	MDI	10	6 months	IP significantly decreased HbA1c (7.2 ± 0.2 vs. 8.5 ± 0.7%, p =0.02), reduced glycaemic variability (SD of capillary glucose 3.4 ± 0.2 vs. 4.6 ± 0.2mmol/l, p<0.01).	[45]
	Randomised, prospective, cross-over design	IP	MDI, CSII	24	16 months	No significant difference in incidence of hypoglycaemia. IP significantly decreased HbA1c by -0.76% (95% CI -1.41 to -0.11, p=0.03). and increased time spent euglycaemic by 11% (p=0.003) with no difference in total daily insulin use.	[8]
Long-term follow-up studies	Prospective, observational, case control design	IP	MDI, CSII	183	26 weeks	HbA1c did not significantly change within IP group, and significantly decreased within control group by -0.09% (95% CI -0.17 to -0.01). Difference between treatment groups was -0.27% (95% CI -0.46 to -0.09). Number of blood glucose <4.0mmol/l decreased by 1.2(95% CI -1.7 to -0.7) within control group, and was non-significant in the IP group.	[10]
	Non-randomised, retrospective design	IP	-	181	5 years	HbA1c decreased from 7.9±1.2 to 7.6±1.2% (p<0.01) after the first year of implantation, and remained significant lower than baseline (p<0.05) throughout subsequent years.	[46]

IP = intraperitoneal pump, MDI= multiple daily injections, CSII= continuous subcutaneous insulin infusion

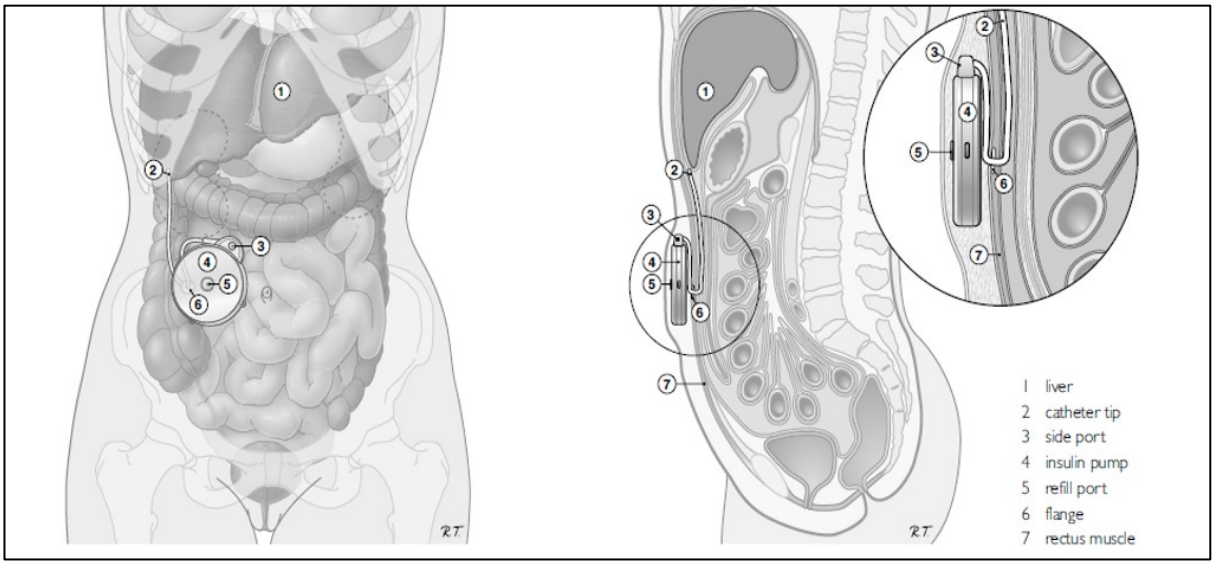

Figure 1. Anatomical location and components of implanted pump device (*Copyright © 2009 American Diabetes Association. From: Diabetes Care 2009 Aug; 32(8): 1372-1377. Reprinted with permission from The American Diabetes Association).*

Figure 2. The MIP 2007D implantable pump with hand-held device ***(reprinted with permission by Medtronic).***

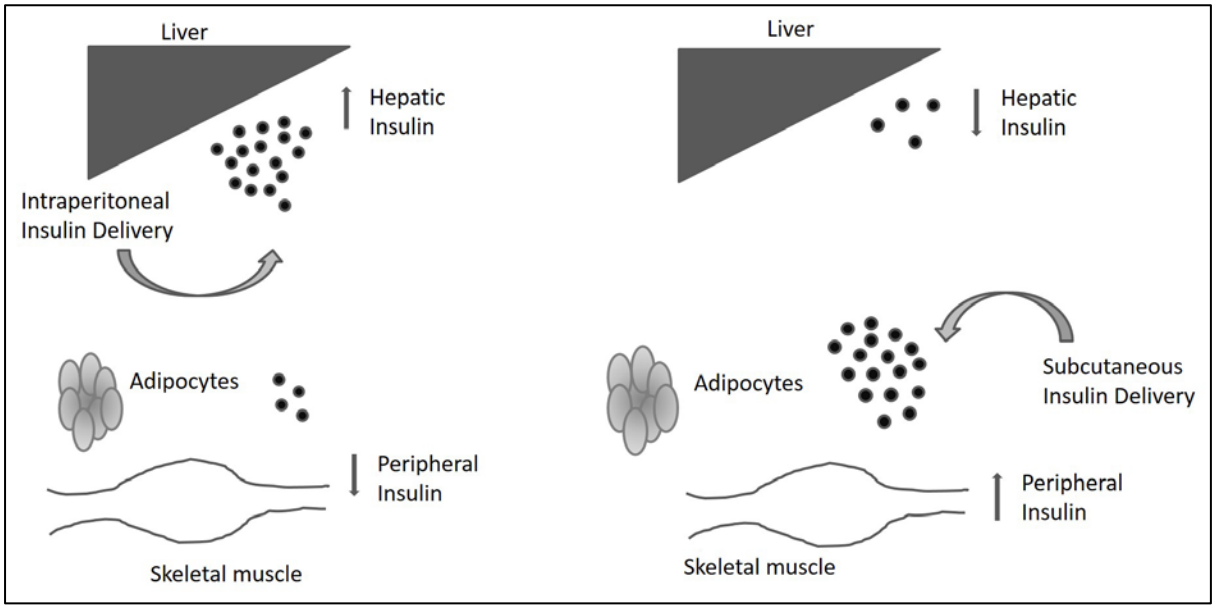

Figure 3. Schematic outline of the pharmacological and physiological properties of intraperitoneal and subcutaneous insulin delivery.