CHAPTER 11

Discussion and perspectives

PARTS OF THIS CHAPTER WERE PUBLISHED AS

Van Dijk PR, Logtenberg SJJ, Gans ROB, Bilo HJG, Kleefstra N. Intraperitoneal insulin infusion: treatment option for type 1 diabetes resulting in beneficial endocrine effects beyond glycaemia. Clin Endocrinol (Oxf) 2014; 81: 488-97.

This thesis aims to provide an update and extension about the knowledge of continuous intraperitoneal insulin infusion (CIPII) therapy in type 1 diabetes mellitus (T1DM) by investigating several important and relative new aspects of this treatment modality. The first part of this thesis describes the complications of CIPII therapy using an implanted pump. In the second part, the effects of long-term CIPII therapy on glycaemia, quality of life and treatment satisfaction, also in comparison with subcutaneous (SC) insulin administration, were studied. Furthermore, as the effect of insulin administration via the intraperitoneal (IP) route reaches beyond glycaemia, the influence of CIPII on the growth hormone (GH) - insulin-like growth factor -1 (IGF1) axis was studied in the third part of this thesis. In this chapter the most important findings will be highlighted. Furthermore, after discussing study limitations, the implications of the results and future perspectives on both the use of CIPII in clinical practice and in research will be discussed.

1. Main findings

1.1 PART I - COMPLICATIONS OF CIPII THERAPY USING AN IMPLANTABLE PUMP

As demonstrated in *Chapter 2*, CIPII therapy with an implantable pump is associated with complications at a rate of one complication per four patient years. In the studied group of 56 patients, almost two-thirds of patients experience at least one complication during the period 2000-2011. Occlusion of the catheter attached to the pump (8.1 per 100 patient years), dysfunction of the pump (4.2 per 100 patient years) and pain at the pump site (3.9 per 100 patient years) are the most frequently observed complications. Complications resulted in 50 re-operations and 69 hospital re-admissions. Among the patients in which re-operation was necessary, the period between implantation of the pump and the first re-operation was 4.5 years (95% confidence interval (CI) 4.1, 4.8 years) and stayed stable over the last decade. A total number of 5 patients stopped CIPII therapy due to infections (n=2), pain (n=1), inadequate glycaemic control (n=1) or at own choice (n=1). One episode of peritonitis and no pump-related mortality has been reported.

1.2 PART II - EFFECTS OF INTRAPERITONEAL INSULIN THERAPY - GLYCAEMIA, QUALITY OF LIFE AND TREATMENT SATISFACTION.

The baseline situation concerning glycaemic control, prior to initiating CIPII, is demonstrated in *Chapter 3*. Overall, patients are poorly controlled, with a median HbA1c of 70 mmol/mol (8.6%), spending only 47% of time in euglycaemia and experiencing a median of 4 episodes of grade 1 (blood glucose reading <4.0 mmol/l) and 3 episodes of grade 2

(blood glucose reading <3.5 mmol/l) hypoglycaemic episodes per week.

Additionally, in *Chapter 3* it is shown that after 6 years of CIPII therapy, patients have a more hyperglycaemic profile and the initial HbA1c improvement reached after 6 months of CIPII disappears. Nevertheless, HbA1c concentrations are still comparable to that of prior intensive SC insulin therapy under trial circumstances while the number of grade 2 hypoglycaemic episodes was significantly lower during CIPII.

As compared to a population of T1DM patients in poor glycaemic control treated with SC insulin therapy, the number of hypoglycaemic episodes is substantially lower with CIPII therapy over a 7-year period despite the fact that HbA1c levels do not show differences (*Chapter 4*). Nevertheless, as presented in *Chapter 5*, T1DM patients using CIPII spend more time in hyperglycaemia and less in euglycaemia than matched subjects using SC insulin therapy, but CIPII therapy appeared to be non-inferior to SC insulin therapy with respect to HbA1c. Additionally, in *Chapter 7* it is demonstrated that, despite higher mean blood glucose concentrations, CIPII therapy seem to have a modest positive effect on glycaemic variability as compared to SC insulin therapy.

The results of *Chapters 3* and *4* demonstrate that prior to initiating CIPII, health status, general quality of life and treatment satisfaction are poor, also in comparison to a reference group of SC treated patients in poor glycaemic control: most scores are only two-third of the optimal scores. After 6-years of follow-up the treatment satisfaction remains higher than before despite health status and general quality of life remaining poor. The longitudinal comparisons between T1DM patients treated with CIPII and SC insulin therapy made in *Chapter 4* show that the course of general quality of life does not seem to differ between both treatment groups. In the 26-week study period, described in *Chapter 6*, the difference in health status and general quality of life between CIPII and SC treated patients remained present while treatment satisfaction was higher among CIPII treated patients. After adjustment for baseline differences, health status was worse but there were no differences regarding general and diabetes-related quality of life and treatment satisfaction between both treatments .

1.3 PART III - EFFECTS OF INTRAPERITONEAL INSULIN THERAPY - BEYOND GLYCAEMIA

In *Chapter 8*, *9* and *10* the effects of CIPII on the GH-IGF1 axis, as compared to SC insulin therapy are investigated. In *Chapter 8*, CIPII during a period of 6 months resulted in lower levels of IGF binding protein (IGFBP)-1, the production of which is acutely down regulated

by the presence of insulin in the portal vein and suggested to regulate IGF1 bioactivity, as compared to SC insulin therapy [1]. Nevertheless, no significant differences in IGF1 between CIPII and SC treatment were observed. In *Chapter 9* the course of IGF1 concentrations over a period of 6 years are described in a CIPII treated population. Results demonstrate an ongoing improvement of IGF1 during the studied period. In addition, although the use of different IGF1 assays should be taken into account, concentrations of IGF1 were higher than during previous intensive SC insulin therapy among these patients. Finally, in order to gain a more comprehensive view, more parameters of the GH-IGF1 axis were investigated in a larger population of T1DM patients during a 26-week observational study (*Chapter 10*). During this period, concentrations of IGF1 among CIPII treated T1DM patients were stable, at a level that is near-normal as compared to a non-DM reference population and significantly higher as compared to patients treated with SC insulin therapy. In addition, concentrations of IGFBP1 and GH were lower among CIPII treated patients as compared to patients treated with SC insulin therapy. Only IGFBP1 concentrations continued to decrease during the 26-week study period with CIPII as compared to SC insulin therapy.

2. Study limitations

At present, CIPII using an implantable pump is a last-resort treatment option for selected patients with T1DM who do not tolerate or do not sufficiently respond to SC insulin therapy and therefore fail to reach adequate and stable glycaemic control. It is also considered only as a last-resort because of restricted pump availability in recent years, a rather high complication rate and the associated costs.

Consequently, patients using CIPII are a small, heterogeneous and at the same time very selective and complex group of patients who are beyond the stage of intensified SC insulin therapy. Amongst others, this is reflected by the observation that T1DM patients in poor glycaemic control (defined as HbA1c≥ 58 mmol/mol (7.5%) and/or ≥ 5 incidents of hypo-glycaemia per week) who initiate CIPII therapy have more often microvascular complications, experience more hypoglycaemic episodes and have a lower quality of life as compared to patients with the same HbA1c level that remained on SC insulin therapy (*Chapter 4*). These considerations have important consequences for the internal- and external validity of the studies in this thesis.

2.1. INTERNAL VALIDITY

First, the studies in this thesis are limited by the small number of patients. In *Chapters 3*, *4* and *8* the small number of CIPII treated patients, at most n=21, and patients that were eligible to function as controls could well have led to relatively wide confidence intervals and not enough power to detect differences. It could be hypothesized that, in particular, the quality of life questionnaires, used in *Chapters 3* and *4*, and IGF1 concentrations, described in *Chapter 8*, which both seemed to increase in the CIPII group during the study period could become significant if there were more (CIPII treated) patients available.

Second, due to both the selected and heterogeneous nature of patients treated with CIPII, relevant differences in (baseline) characteristics were present as compared to subjects treated with SC insulin therapy. These differences may well have influenced the results. In *Chapter 4*, for example, subjects initiating CIPII experienced more episodes of hypoglycaemia at baseline, as compared to the reference group of SC treated subjects and thus a more pronounced effect of CIPII on the number of hypoglycaemic episodes could be expected. Nevertheless, in *Chapter 4*, differences in HbA1c and indices of quality of life between the CIPII and SC treatment groups were adjusted for the number of hypoglycaemic episodes at baseline and the change in hypoglycaemic episodes between groups was adjusted for HbA1c. Furthermore, subgroup analysis were performed to make separate comparisons within groups of patients with a high HbA1c and those with frequent hypoglycaemic episodes at baseline. Although the decrease of HbA1c within the CIPII treated group was no longer present in subgroup analysis, the decrease in hypoglycaemic episodes with CIPII was.

In order to overcome aforementioned limitations, i.e. small numbers, selected and heterogeneous nature of CIPII treated patients, related to the last-resort use of CIPII therapy and subsequent difficulties in comparing CIPII with SC treated patients, ideally, a randomized controlled trial with sufficient follow-up would be performed to reveal the effects of long-term CIPII and SC therapy. However, due to the limited number of implantable pumps, costs and the consideration that it would be undesirable and unethical to interrupt the IP insulin administration in patients who are currently treated with CIPII, a randomized controlled trial is impossible at present.

Given these considerations, a prospective matched-control study was seen as most suited to compare the long-term effects of CIPII with SC insulin therapy among T1DM in poor glycaemic control (*Chapters 5*, *6*, *7* and *10*). Furthermore, since patients treated with CIPII, the last-resort treatment option, are considered to be in general far more complex

than patients using SC insulin therapy regarding glycaemic control, a hypothesis of non-inferiority regarding the primary outcome, HbA1c, was chosen. While fully acknowledging the drawbacks of a non-inferiority assessment, the rationale for the use of this method is based on the consideration that finding non-inferiority of CIPII as compared to SC insulin would be an outcome that would support the use of CIPII in this selected population, given the complexity of the diabetes of patients selected for CIPII and the last-resort character of CIPII relative to SC insulin therapy and, importantly, the presence of advantages of CIPII with respect to e.g. hypoglycaemic episodes, quality of life and hospital admissions as reported in *Chapters 3, 4* and during previous studies [2–7]. This is in accordance with consolidated standards of reporting trials (CONSORT) point of view regarding the rationale and use of non-inferiority in studies [8]. Furthermore, the non-invasive and observational nature of study and the clear predefined study-protocol, including a non-inferiority margin based on previous literature and the use of both an intention-to-treat and per-protocol analysis, also support the use of the current study design [8,9].

The group of currently treated CIPII patients is heterogeneous, consisting of both patients with a high frequency of hypoglycaemic episodes with (relatively) low HbA1c concentrations and patients without hypoglycaemic episodes but high HbA1c concentrations [10]. In order to gain more resemblance (i.e. prevent baseline imbalance) between CIPII treated patients and controls on SC insulin therapy regarding hypoglycaemic episodes, a lower HbA1c inclusion criterion was chosen for patients using SC insulin therapy. Additionally, patients were matched on age and gender, had to use their current mode of therapy for more than 4 years in order to reflect a stable situation, measurements were made on 2 points in time and outcomes were adjusted for baseline imbalance using analysis of covariance.

2.2. EXTERNAL VALIDITY

It should be stressed that the population under investigation in this thesis is highly selected. Taken together with the aforementioned limitations regarding the internal validity of the results, the external validity of the studies, in particular those concerning glycaemic control and those making comparisons between CIPII and SC insulin therapy, is limited.

3. Implications of the results

In this paragraph, the implications of this thesis, taking the current situation of CIPII in clinical practice into account, will be discussed.

3.1 PART I - COMPLICATIONS OF CIPII THERAPY USING AN IMPLANTABLE PUMP

As demonstrated in *Chapter 2*, most of the complications of CIPII with an implanted pump are due to the device and not the IP insulin. Subsequently, the question can be raised whether there is a way to avoid the disadvantages of the current implantable pump and catheter, while retaining the benefits associated with the IP mode of insulin delivery. One such way could be insulin delivery by means of an externally placed pump which delivers insulin IP.

Such a method is currently available: the so-called Diaport system which consists of a metal body with a catheter that is placed transcutaneously in the peritoneal space. A catheter is attached to the metal body inserted in the abdominal wall and delivers insulin from an externally placed pump into the Diaport system and eventually the IP space. A randomized cross-over study among 60 T1DM patients by Liebl *et al*. demonstrated effectiveness of this system with respect to reducing the number of severe hypoglycaemic episodes as compared to patients using continuous subcutaneous insulin infusion (CSII). Nevertheless, complications of this method, in particular the high number of infections of the port (47 per 100 patient years) related to the use of a catheter, and the limited long-term results are drawbacks hampering a more widespread use of this system. Thus, it seems that an implanted pump is, at the moment, the best available option for delivering IP insulin.

Another way to keep the advantages of IP insulin delivery without the disadvantages of the current implanted implanted device would be to update the currently used insulin pump or develop a new model. Bearing the most frequent complications mentioned in *Chapter 2* in mind several adjustments could be suggested. In paragraph 4 of this chapter these suggestions will be discussed in more detail.

As CIPII treatment is continued with the currently used implantable pump, measures should be taken to reduce the number of complications. In coincidence with the introduction of a new insulin formulation for IP infusion in the year 2011 (400 IU/ml; human insulin of E. Coli origin, trade name: Insuman Implantable®, Sanofi-Aventis), a shorter interval to perform a refill of insulin (previously: at least every 3 months, now: at least every 6 weeks) and a

rinse procedures (previously: every 9 months, now: every 6 months) had to be acquainted according to European Medicines Agency's regulation [11]. Additionally, a lower threshold for insulin underdelivery necessitating a rinse procedure (the ratio between programmed and actually infused insulin volume upon programmed insulin, previously: 20%, now: 12%) was set. In theory, this should results in a decrease in the number of catheter obstructions due to insulin aggregate [4]. On the other hand, these measures will translate into higher costs, more procedure related risks and may decrease treatment satisfaction. Altogether, it should be concluded that ongoing monitoring of CIPII related complications is of utmost importance.

3.2 PART II - EFFECTS OF INTRAPERITONEAL INSULIN THERAPY - GLYCAEMIA, QUALITY OF LIFE AND TREATMENT SATISFACTION

The most pronounced effect of long-term CIPII therapy is the reduction of hypoglycaemic episodes (*Chapters 3* and *4*). This finding can in part be explained by the pharmacokinetic and pharmacodynamic properties of insulin administration in the IP space. In *Chapter 7* of this thesis it is demonstrated that there is indeed less blood glucose variability during continuous glucose measurements among CIPII treated patients as compared to subjects treated with SC insulin. The high treatment satisfaction on the subscale "perceived hypoglycaemia", found in *Chapter 6* among CIPII treated patients emphasizes the relevance of reduced blood glucose variability. In addition, a reduction in hypoglycaemic episodes may reduce the risk of a range hypoglycaemia associated clinical adverse events and mortality [12]. Nevertheless, as the clinical importance of glycaemic variability with respect to diabetes related complications (including quality of life) is unsure, the relevance of this specific finding with respect to clinical outcomes is unknown [13–16]. Taken together, these findings emphasize that high blood glucose variability is positively influenced by CIPII therapy and should be one of the more prominent selection criterion for CIPII therapy.

In T1DM patients using CIPII, health status is poor and worse as compared to patients using SC insulin. The discrepancy between the poor general quality of life and health status and the relatively normal and stable measures of diabetes specific quality of life among CIPIII treated patients, found in *Chapter 6*, suggests that the poor health status among these patients is not due to their diabetes *per se* but that probably other factors have an important influence. In the present thesis, possible factors such as poor social functioning, limited peer support or more (perceived) physical limitations and pain have been suggested. Additionally, the presence of physical comorbidity and psychiatric symptoms, in particular depression, could be hypothesized as a determinant of the poor health status [17].

Nevertheless, although these suggested factors may not be directly related to diabetes at the present, an indirect relation with diabetes such as problems with social functioning at present due to unemployment after frequent hypoglycaemic episodes or previous frequent hospitalization during childhood, may still be present. As quality of life is an important outcome in the management of T1DM and influences glycaemic control, the need for ongoing psychological support for a substantial portion of CIPII treated patients is evident [18,19]. Additionally, a psychological assessment prior to starting CIPII therapy could not only be advocated to screen for amongst others depression and fear for hypoglycaemia, but also to identify psychosocial or psychological barriers to reach adequate glycaemic control.

3.3 PART III - EFFECTS OF INTRAPERITONEAL INSULIN THERAPY - BEYOND GLYCAEMIA

Among T1DM patients it has been suggested previously, that low concentrations of insulin in the portal vein catchment area would lead to insufficient hepatic insulinization and subsequent low IGF1 and IGFBP3 concentrations and high concentrations of IGFBP1 and GH [20–25]. Since CIPII results in higher levels of insulin in the portal vein catchment area, it was hypothesized in the present thesis that the GH-IGF1 axis is affected by the route of insulin administration and that CIPII has a more pronounced effect than SC insulin therapy [26–30].

The findings of *Chapters 8*, *9* and *10* indicate that CIPII is more beneficial than SC insulin in correcting the altered GH-IGF1 axis in T1DM. IGF1 concentrations even increased to a near-normal level as compared to non-DM subjects. The higher IGF1 concentrations in combination with lower GH concentrations among CIPII treated patients as compared to SC treated patients, found in *Chapter 10*, provide clinical support for hypothesis that increased hepatic insulinization due to IP insulin administration results in increased hepatic GH sensitivity and, subsequently, higher IGF1 levels. Accordingly, as GH secretion is under negative feedback by concentrations of IGF1, the lower GH concentrations among CIPII treated patients could well be the results of a near-normalization of IGF1 concentrations. Moreover, as IGFBP1 is regulated directly by insulin levels in the portal vein, the finding of lower IGFBP1 levels with CIPII are compatible with an enhanced hepatic effect of insulin and, furthermore, IP insulin may cause higher IGF1-bioactivity in addition to the change in total IGF1 enhancing the effect of IGF1 and the feed-back on GH-secretion [31–33].

Since GH has insulin antagonizing and IGF1 insulin sensitizing effects, some restoration of the GH-IGF1 axis could beneficially influence the whole body insulin resistance and the subsequent development of T1DM related complications [34,35]. Additionally, altered IGF1 concentrations have been suggested to be involved in carcinogenesis in T1DM patients [36].

It should be noticed however, that the clinical relevance of these findings is not clear at the moment. Nevertheless, the observations made in the present thesis may provide insight in the effects of insulin and it's route of administration on the GH-IGF1 axis.

3.4 CURRENT USE OF CIPII

At present, the use of CIPII is largely restricted to Europe, especially Belgium, France, Sweden and the Netherlands. In the Netherlands there are two centers (Isala, Zwolle and Medical Centre Haaglanden, The Hague) that provide this treatment option: only 70 T1DM patients, on a total approximately 85.000 T1DM patients, are currently treated with CIPII. In 2007, the Dutch Internist Associated acknowledged the following indications for starting and using CIPII [37]:

- Subcutaneous insulin resistance
- 'Brittle' diabetes
- Hypoglycaemia unawareness
- Delayed insulin absorption
- Allergies
- Lipohypertrophy or lipoatrophy
- Very lean subjects
- Needle phobia
- Severe skin scarring or chronic dermatologic problems.

Alternative current last-resort treatments with overlapping patient criteria include pancreas- and beta-cell transplantation. Although both treatments are emerging and yield the promise of curing diabetes, the risk-benefit ratio is unfavorable at present for most patients. Also, there is limited availability. The need for a surgical procedure in case of a pancreas transplantation with possible severe peri- and post transplantation complications, the need for donor tissue, possible rejection and the use of prolonged systemic immunosuppression are factors which have to be taken into account when weighing in the possible effects like insulin independence and diminishing the chance of occurrence or deterioration of diabetes related complications [38–40]. It should also be mentioned that both procedures are still in development, costs are high (approximately an average of 77,745 euro for the procedure and the subsequent year) and the amount of evidence and clinical experience is scarce but growing [40,41]. Although direct comparisons are lacking, it can well be advocated that CIPII using an implantable pump is more viable as a last-resort alternative for T1DM patients than pancreas- and beta-cell transplantation.

It should be concluded that, based on the complications and effects on glycaemic control as described in the present thesis, lack of other literature, current costs and available alternatives, there are insufficient arguments to extent the indications or the use of CIPII to a wider range of patients. Nevertheless, future developments, in particular those regarding incorporation of IP insulin administration in a closed-loop system, and more research towards the effects of IP insulin beyond glycaemic control may change this point of view (see paragraph 4.4).

4. Future research, developments and use of CIPII

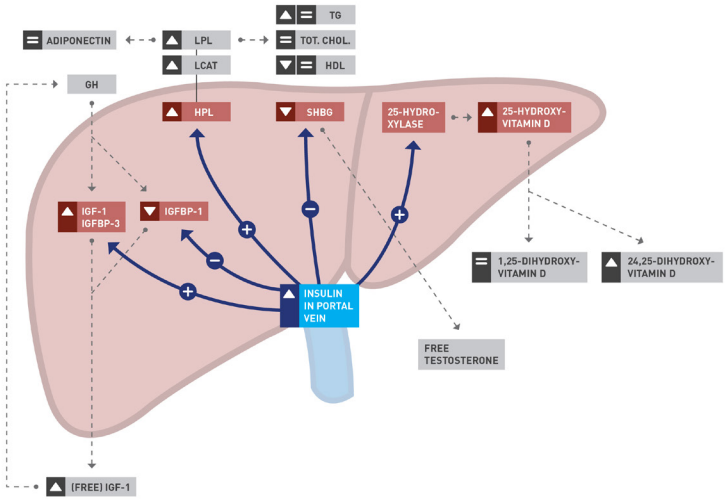
CIPII provides unique in vivo research opportunities to study the effects of IP insulin administration, relative to SC insulin therapy, on glycaemia and beyond. In this paragraph several lines of possible research are discussed. Finally, a point of view on possible developments on the implanted pump and future use of CIPII therapy is given.

4.1 RESEARCH BEYOND GLYCAEMIA

As known, insulin does not only have effects on glucose control but influences a wide range of endocrine and metabolic processes. Because IP insulin is to a large extent absorbed in the portal vein catchment area, the insulin concentration in the portal vein and the peripheral plasma insulin concentration are much more physiological compared to SC administered insulin [26–29]. In this thesis the effects of CIPII on the GH-IGF1 axis were investigated. Additionally, IP insulin could also alter, and even improve, several other metabolic parameters (see Figure 1).

Higher insulin concentrations in the portal vein inhibit the production of the hepatic glycoprotein sex hormone-binding globulin (SHBG), irrespective of glycaemic control [42]. In the presence of higher SHBG- and normal testosterone concentrations, lower concentrations of free testosterone are present among T1DM men using SC insulin therapy [43]. Lassmann-Vague *et al*. tested the hypothesis that IP insulin lowers SHBG concentrations among T1DM patients who switched from SC insulin therapy to CIPII. Indeed, during IP insulin infusion there was a significant decrease of SHBG concentrations [44]. Therefore, a switch to treatment with IP insulin could offer an advantage. Further testing of this hypothesis needs to be performed and the clinical significance, e.g. on the reproductive function, of this finding remains to be investigated.

FIGURE 1 Alterations in GH-IGF1 axis in T1DM



The (+) and (-) indicate positive and negative associations, respectively. The (▲) and (▼) indicate increases and decreases of concentrations as found in previous studies 9–16. Abbreviations: GH, growth hormone; IGF1, insulin-like growth factor-1, IGFBP1/-3, insulin-like growth factor binding protein -1/-3.

Insulin influences the lipoprotein metabolism by activation of lipoprotein lipase (LPL) and hepatic lipase and by inhibition of the hepatic very low density lipoprotein (VLDL) production [45]. Among individual with T1DM and poor glycaemic control there is an increased plasma concentration of triglycerides (TG) as a result of an increased VLDL production and an increased circulation of free fatty acids secondary to insulin deficiency. Furthermore, low density lipoprotein (LDL) may be increased, with, formation of small, dense oxydated particles [45]. In well-regulated T1DM patients both TG and LDL levels are (virtually) normal due to VLDL down regulation secondary to insulin use [46]. The lower peripheral plasma insulin concentrations due to IP insulin are associated with a normalization of the activity of the enzymes cholesteryl-ester-transferase and LPL in comparison with SC insulin therapy [30,47,48]. Furthermore, there is an increase in hepatic lipase activity [49]. The hypothesis that IP insulin administration leads to further beneficial modification of lipids and lipoproteins has been tested in a few studies. In one report, there was an increase in TG, whereas TG were unchanged in 3 other studies [47,49–51]. Total cholesterol and apolipoprotein B were also unchanged, while high density lipoprotein (HDL) cholesterol decreased or remained the same [47,49–51]. It should be mentioned, however, that in all these studies the number of patients was small (n<14), the degree of glycaemic control was variable and the duration of IP

treatment was limited (ranging from a few days to 9 months). Although it has been reported that high concentrations of IP administered insulin can reverse focal hepatic steatosis in T1DM patients, the clinical relevance of the effects of IP insulin on lipid metabolism is as yet unclear [52].

Adiponectin, an adipocyte-released peptide hormone, is regarded as a marker for insulin sensitivity with anti-inflammatory and -atherosclerotic properties. In T1DM, adiponectin concentrations are increased and these raised concentrations are positively associated with insulin resistance [53]. In 2 recent studies, increased adiponectin concentrations were found to be related to the presence of microvascular complications and an increased all cause and cardiovascular mortality in patients with T1DM [54,55]. Adiponectin concentrations are positively associated with LPL activity and inversely associated with plasma hepatic lipase activity [56,57]. Thus, one could hypothesize that CIPII lowers adiponectin concentrations as compared to SC insulin administration. However, the only study testing this hypothesis found no differences among 7 T1DM patients with almost 2 years of IP insulin therapy in adiponectin concentrations as compared to the situation during SC insulin use [50].

Considering metabolic consequences, it was shown by Freyse *et al*. that IP insulin administration in an insulin-dependent dog model increased energy expenditure as compared with systemic insulin administration [58]. In addition, synthesis of hepatic production of proteins such as albumin, fibrinogen as well as tissue proteins resembled more closely the non-diabetic situation during pre-portal insulin administration [58].

In a small study by Colette *et al*. differences in vitamin D metabolism were present between patients using SC insulin and CIPII therapy [59]. Although there were no differences in 1,25-dihydroxyvitamin D (calcitriol) concentrations, CIPII treated T1DM patients had higher concentrations of plasma 25-hydroxyvitamin D (calcidiol), also after correction for glycaemic control, and 24,25-dihydroxyvitamin D (inactive metabolite) as compared to SC insulin users. These findings may indicate that higher concentrations of insulin as present with use of IP insulin stimulate the activity of the hepatic enzyme 25-hydroxylase, which in turn promotes the turnover of cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) to calcidiol.

4.2 RESEARCH REGARDING GLYCAEMIC CONTROL

It should be acknowledged that the amount and level of evidence strongly supporting the use of CIPII therapy as a method to substantially improve metabolic control is rather low. Further evidence concerning the effectiveness of CIPII in comparison to other emerging

(last-resort) treatment options is necessary in order to get a better understanding regarding indications and most eligible patients. In particular a trial comparing the effects of CIPII with sensor augmented CSII insulin therapy, currently the most frequently used kind of SC insulin therapy prior to CIPII therapy, could give further insight in the kind of and magnitude of differences between both treatment modes.

If the outcomes of such as study would point out to positive effects of CIPII, further study should be performed towards the actual cost-effectiveness and the number of patients who would be eligible for CIPII therapy, given the specific category of patients that would profit most from CIPII therapy, as these two points are largely unknown at the present or, at best, estimated using expert based opinion. Of course, patient preferences should be taken into account.

The effect of CIPII on hypoglycaemia incidence should also be focus of additional investigations. Previous research suggested that IP insulin improves the previously impaired glucagon secretion, also during exercise, and enhances hepatic glucose production in response to hypoglycaemia [29,60–63]. Investigating details regarding the possible underlying mechanism hypothesized to be due to restoration of the glucagon release or hepatic glucose utilization during hypoglycaemia, should be encouraged [60]. The finding of less glycaemic variability in *Chapter 7*, suggest perpetuating of this mechanism during long-term therapy, and may be of importance in the current patient population with frequent hypoglycaemia (unawareness). Additionally, this finding may be relevant for developing a closed-loop system (see paragraph 4.4).

4.3 FURTHER DEVELOPMENT OF THE IMPLANTABLE INSULIN PUMP

As demonstrated in *Chapter 2*, most complications of CIPII with an implanted pump are due to the device and not the IP insulin. Another way to keep the advantages of IP insulin delivery without the disadvantages of an implanted device would be to update the present insulin pump or develop a new model. Bearing the most frequent complications in mind several adjustments could be suggested. First, the electronics should be updated to modern's day technologic standards. Such a development could contribute to a decrease in the number of pump dysfunctions, add to minimization of the size of the implanted pump and may offer means for communication with other devices, i.e. smartphones. This latter could also make the present patient-pump communicator redundant and would aid to the incorporation of the implanted insulin pump in a closed-loop system. Second, the size or shape of the present discus-shaped pump with a diameter of approximately 8 cm diameter

and a thickness of 1.8 cm should be reduced. A smaller, more convex-shaped pump could diminish the complaints of pain and cutaneous erosions. In addition, alteration in the size and shape of the pump could offer an improved esthetics.

4.4 FUTURE USE OF CIPII THERAPY

Future use of CIPII will partly depend on further development regarding the pump. Whether proposed research and developments will take place depends on several factors.

First, as there is only one manufacturer of the implantable pump at present, improvements by renewal and updates is not stimulated very much. Developing a new (implantable) device for IP insulin administration is challenging, in particular for interested new parties, due to the considerable amount of knowledge, time and, very important, resources needed. These matters are closely related to the amount of patients which would be eligible for such a (re)new(ed) model for CIPII. At present, CIPII with in implantable pump is a treatment option for a niche of T1DM patients. Second, it should be emphasized that the current evidence supporting a more extensive use of for CIPII treatment is virtually absent. Third, as alternative treatment options for T1DM, i.e. islet transplantation and the closed-loop system, are developing in fast pace, the urgency for further development of the current implantable pump system could be questioned.

Further development of IP insulin infusion will also be dependent of the possibility of incorporating IP insulin administration in a closed-loop system. Over the last decade considerable advances have been made in the development of closed-loop systems. Aiming towards optimal blood glucose regulation in various situations without patient involvement, the present research on closed-loop systems combines continuous glucose sensing, mono- (insulin) or bihormonal (insulin and glucagon) SC delivery devices and control algorithms with automated data transfer, real-time control action and automated command of the insulin delivery device [64]. After showing safety and efficacy of closed-loop systems in controlled (overnight) clinical settings, the field of research has progressed to study the ability for the closed-loop systems to function in ambulant, non-clinical environments [65,66]. Nevertheless, as SC insulin is absorbed slower than ingested glucose, current closed-loop systems using SC insulin are unable to reach postprandial normoglycaemia, and the delayed insulin action may sometimes result in hypoglycaemia in the hours following a meal [64,67–69]. Theoretically, with fast insulin action to peak and fast return to baseline, the near physiological portal:systemic insulin ratio and the reproducibility of insulin absorption the IP route of insulin delivery could be able to overcome these challenges posed by the

SC administration [70]. Furthermore, one could hypothesize that the use of IP insulin would diminish the need for glucagon, as a counter regulatory hormone in the closed-loop system. A recent feasibility study among 8 T1DM patients in which a 2-day closed-loop CIPII driven by a SC glucose sensor via a proportional-integral-derivative algorithm found almost 40% of the time spent with blood glucose levels between 4.4 and 6.6 mmol/l (as compared to 28% during self-monitoring data). This was mostly due to better glycaemic regulation during the non-postprandial period [71]. As speculated upon by the authors, this problem may be resolved by further developments of the control algorithm, used in combination with CIPII, with handling of (pre)meal insulin requirements. Another solution may include faster glucose sensing by using an IP or intravenous (instead of a SC) placed glucose sensor, in combination with IP insulin delivery [72].

In addition to these positive effects on glycaemic regulation, the historical drawbacks of CIPII such as complications, limited experience and data on long-term efficacy have, to a certain extent, been overcome in the recent years. Nevertheless, there is still a need for more research focusing on the effects of CIPII, as compared to intensive SC insulin therapy, with specific attention for glycaemic control, glucose variability and aforementioned endocrine and metabolic effects beyond glycaemic control. If such large-scale, (randomized) studies among T1DM patients in intermediate to good glycaemic control would yield relevant positive results and patient preferences would still be in favor of CIPII, costs would be lowered and availability would be sufficient, a shift in focus from SC to IP insulin as the preferred route of insulin administration in the closed-loop system may ultimately be advocated on sufficiently validated ground.

In the meantime, CIPII using an implantable pump remains a feasible last-resort treatment option in selected patients who fail to reach adequate glycaemic control with intensive SC insulin therapy and experience high blood glucose variability.

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