Chapter

Intensive Management of Type 1 Diabetes in Adults: One Centre Experience 1970–2022

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Abstract

This chapter deals with clinical trials and routine management of persons with type 1 diabetes (PWD1) carried out at the Teaching Hospital and Palacký University Olomouc since 1970 in cooperation with experts from other centres. The following outcomes are presented: (1) physical training resulted in (a) enhancement of physical working capacity; (b) increased insulin effectiveness (c) increased S-HDL cholesterol; (d) improvement of neuropathy, memory, attention and general condition of PWD1. (2) Intensive basal and prandial insulin substitution with only short-acting insulin given seven times a day and night appeared to be the most effective approach to the conventional insulin substitution; group education and pens motivated to the intensification of insulin therapy. (3) Continuous subcutaneous insulin infusion, conventional self-monitoring, continuous/flush glucose monitoring and prolongation of time in range opened new horizons. Intensive education, early application of hybrid insulin pumps and specialised prevention of late diabetes complications are deemed to improve the life expectancy and quality. Cooperation with insurance companies should be acknowledged.

Keywords: insulin, glucose monitoring, insulin pen, insulin pump, diabetes education, life style, food, muscular exercise

1. Introduction

Type 1 diabetes (T1D) is a chronic syndrome of disturbed metabolism of saccharides, proteins and fat. This syndrome is characterised by the destruction of insulin-producing B-cells of the pancreas which is mostly (in 80%) due to a lasting influence of autoantibodies of uncertain origin. Multiple factors could simultaneously explain the increasing T1D incidence [1]. Impact of HLA phenotype and previous contact with viral antigens should be mentioned [2, 3].

Clinical signs and symptoms of insulin deficiency comprise abundant passing of water, thirst, loss of body mass (up to several kilograms per week), hunger, overeating, weakness, loss of appetite and finally nausea, vomiting, dehydration, breathlessness, abdominal pain, disturbed consciousness, coma and death. These signs are

accompanied by fasting hyperglycaemia ≥ 7 mmol/l and high or low plasma concentrations of minerals and lactate; acidosis, uraemia and infections may also be present [4, 5]. The only possibility how to interrupt this deleterious chain is to recover the homeostasis with adequate amounts of fluids, the substitution of missing insulin combatting the acidosis.

The exciting milestones of the insulin era have already been described [6–12]. In the year 1922, the pharma industry started production of short-acting bovine/porcine insulin (Iletin, Eli Lilly, Indianapolis, USA). Long-acting Protamin Insulin was discovered by Hagedorn in 1934 [13]. In the year 1940, NPH (Neutral Protamin Hagedorn, Nordisk, Denmark) was discovered by Rosenberg and Krayenbühl in Hagedorn´s laboratories and published after the war in 1946 [11]. Human insulins have been produced since 1980. Short-acting insulin analogues lispro, aspart and glulisine have been used since 2000 [14], followed by long-acting analogues (glargine, detemir), ultralong analogue degludec and biosimilars. The pharmacokinetics of individual insulin preparations were studied [15]. Insulin concentrations were unified from 20 IU/ml or 40 IU/ml or 80 IU/ml to the mandatory concentration of 100 IU/ml. However, in disposable pens, there are some exceptions: glargine (Toujeo) 300 IU/ml, degludec (Tresiba) 200 IU/ml. Faster-acting insulin (FIASP) has been used since 2017 [16].

The evolution of technologies for insulin application enhanced the flexibility of insulin substitution which became more physiologic [17]. In the seventies, glass syringes were replaced by plastic disposable syringes. Continuous subcutaneous insulin substitution (CSII) using Mill Hill Infuser as a personal insulin pump was described in Guy´s Hospital London in 1978 [18]. Convenient pocket insulin syringes appeared in England before 1980. According to personal communication, Dr. Ireland in Glasgow, following an idea of Dr. Reith, invented an insulin pen injector produced then by Hypoguard ([17, 19], personal communication). Development of insulin pens (later they have received the name MADI) was supported by Palacký University Olomouc, Czech Republic. Their production started in 1983 (Meta Ostrava, Czech Republic) [20–22] . The NOVO Laboratories, Copenhagen, Denmark, started the production of Novopen [23, 24]. Their technical evolution continued up to the smart pens of today [25]. Haemoglobin A1c [26], Dextrostix and Glucometer-strips systems followed by continuous glucose monitoring (CGM) [27–31], flash glucose monitoring (FGM) [32] and by the assessment of time in range (TIR) [33] became prerequisites for effective metabolic control.

Primary insulin regimens were based on insulin boluses prescribed by a physician. These “mandatory” insulin doses resulted in diabetic diets with fixed amounts of nutrients. Then, limitations of muscular exercise were a measure for the prevention of hypoglycaemias [34]. In contradiction, a few specialists emphasised a liberalised approach to food consumption which was based on adaptations of frequent prandial boluses of regular insulin [35, 36]. The vital mission of insulin and the harmful angiopathic consequences of hyperinsulinaemia and hyperglycaemia [37–41] should be considered. Potential risks of hypoglycaemia are always worthy of attention [42].

In healthy people, the insulin production was found to be mostly 30–40 IU per 24 h [43]. So, the daily amount of injected insulin needs to be “as high as necessary and simultaneously as low as possible” [44]. This paradigm became the leading idea of our therapeutic strategy.

Active individual and/or group therapeutic education was suggested in Genf and Düsseldorf [45, 46]. A series of teaching letters was issued by the Diabetes Education Study Group of the European Association for the Study of Diabetes (DESG/EASD). Scheduled educational programmes of various structures were applied in diabetes centres all over the world [47–54].

This chapter is focused on selected clinical trials and routine management of people with type 1 diabetes (PWD1) carried out since the year 1970 at the Teaching Hospital and Palacký University Olomouc [55, 56], mostly in cooperation with experts from diabetes centres in the Czech and Slovak Republics [57], Institute of Diabetes G. Katsch Karlsburg [58–76], Heinrich Heine Universität Düsseldorf [77], Royal Infirmary Edinburgh [62] and St. Thomas Hospital London [62, 78].

The targets of the presented topics and single-centre "real world trials" have been to encourage physicians and health care professionals to implement flexible insulin substitution along with adequate exercise into routine management of PWD1. Sensor-augmented CSII and/or recent insulin analogues are going to be the core of this intention.

2. Influence of dynamic physical training on metabolic, hormonal and clinical parameters in adolescents and men with Type 1 diabetes mellitus (1978 to 1982)

A prospective single-centre study with 19 PWD1 males (age 15–35 years, diabetes duration from 2 months to 20 years (mean 6,8 years) improved insights on the effects of physical training [62]. The study protocol was based on several previous studies [79–88] At the beginning of the training period, proband was admitted to the hospital for one week. His Physical Working Capacity (PWC 170) was investigated using the bicycle ergometer Zimmermann [89]. At the end of the following outdoor training period (duration 157 ± 43 days), the second and third tests were performed whereas a one-week quiet break between them without any exercise was included into the study schedule (**Figure 1**). Each test was performed one hour after breakfast in the morning. PWC 170 and other parameters at the first, second and third tests were compared (**Figures 2** and **3**).

Here are the effects of the 5–6-month dynamic training (athletics, cycling and swimming) in PWD1:

1. Increase of PWC 170. PWC 170 is the submaximal ergometer load resulting in a heart rate of 170 beats/min which is reached at the 4th step. This load was calculated using linear extrapolation of heart rates at previous steps. Each step lasted 10 min (In future studies maximum oxygen capacity VO2 max. has been used instead of PWC 170).

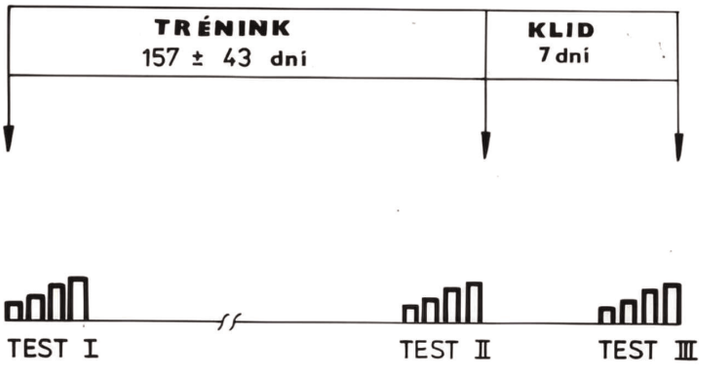


Figure 1.
Design of the training and quiet (klid) period with three ergometer tests.

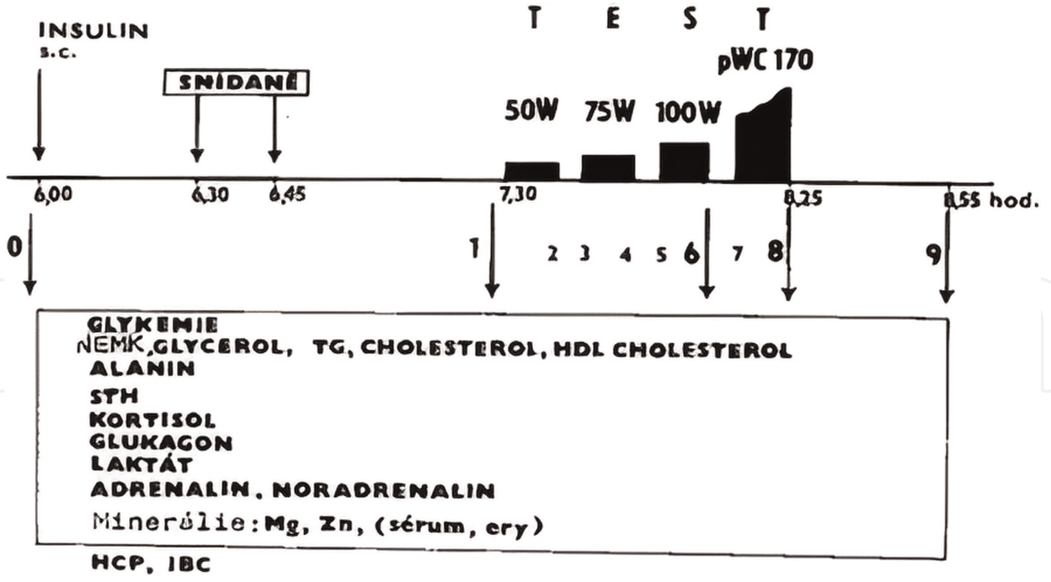


Figure 2.
Schedule of PWC 170 ergometer step test [89] and respective investigations.

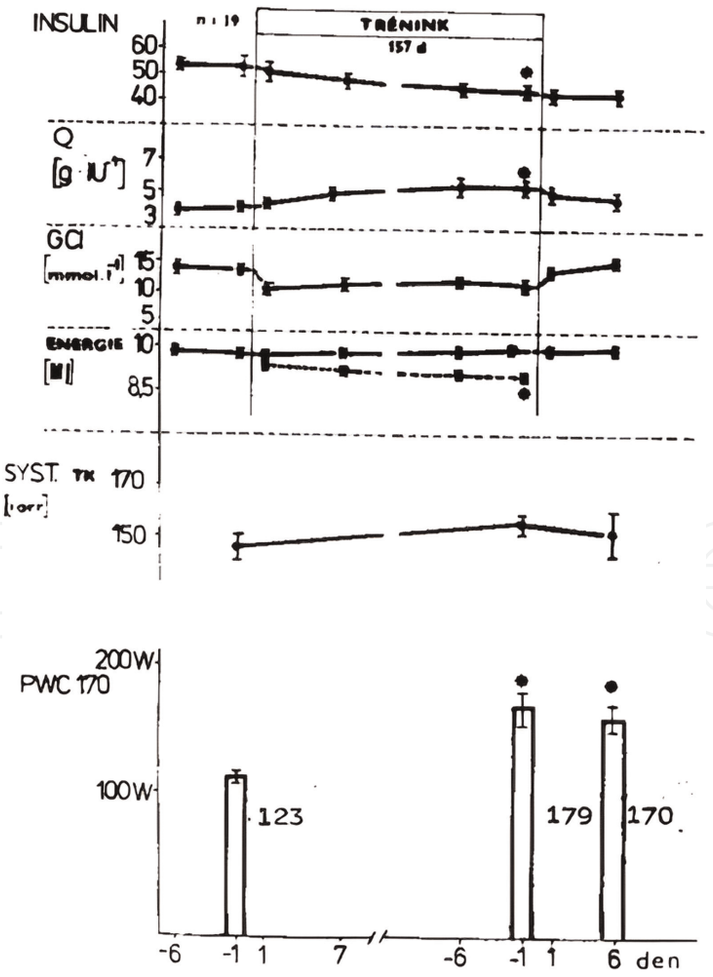


Figure 3.
Amount of injected insulin [IU/d], quotient Q [g Carb/IU] (saccharide relation), Michaelis glycaemic control index GCI [90] estimated energy expenditure [MJ/d], systolic blood pressure (syst TK) at the 3rd step (100 W) of ergometer test and PWC 170 [W] over the study n = 19.

2. An improvement of saccharide (carbohydrate) metabolism was demonstrated by increased insulin effectiveness (quotient Q) without any change in blood glucose control. Quotient Q describes how many grams of consumed carbohydrates are metabolised due to 1 IU of injected insulin. An approximate relation between insulin effectiveness Q and physical working capacity PWC 170 can be calculated using a new formula derived from our observations:

$$Q\ [\text{g Carb./IU}] = 0{,}03\ \text{PWC}\ 170\ [\text{W}] - 0{,}5,$$

(where PWC 170 reached values 90 W <PWC 170 <295 W).

The increase of PWC 170 depends on the amount of estimated energy expended for the submaximal training. Following training interruption (as it may happen e.g. after admission to the hospital) the insulin effectiveness drops in relation to the decrease of PWC 170 due to reduced physical exercise (**Figure 3**).

The insulin effectiveness Q in this study reached values ranging from 2.5 to 22.4 g Carb./IU. Its evolution appears to be related to the value of the physical working capacity PWC 170 (**Figure 4**).

No influence of training either on venous blood glucose concentration (vBG) at the beginning of ergometer test or on the speed of vBG reduction in the course of tests I, II and III was shown. The reduction of vBG became significant ($p < 0{,}05$) as soon as at the end of step 2 (75 W) (**Figure 5**).

An improvement of lipoprotein metabolism was recognised by an increase in HDL cholesterol concentration (1.19 ± 0.08 vs 1.86 ± 0.22 mmol/l, $p < 0.05$) (**Figure 6**) and by a decrease in the index of total cholesterol/HDL cholesterol. These significant changes could also be found 7 days after the end of the training [58].

A beneficial influence on some signs of neuropathy [59], on memory, attention and on the general condition of diabetic patients could also be demonstrated [60].

The important results of our study are comprised in the Abstract book (**Figure 7**).

Hence, based on this study, a submaximal dynamic physical training may be recommended as an additive treatment of type 1 diabetic patients with no signs of

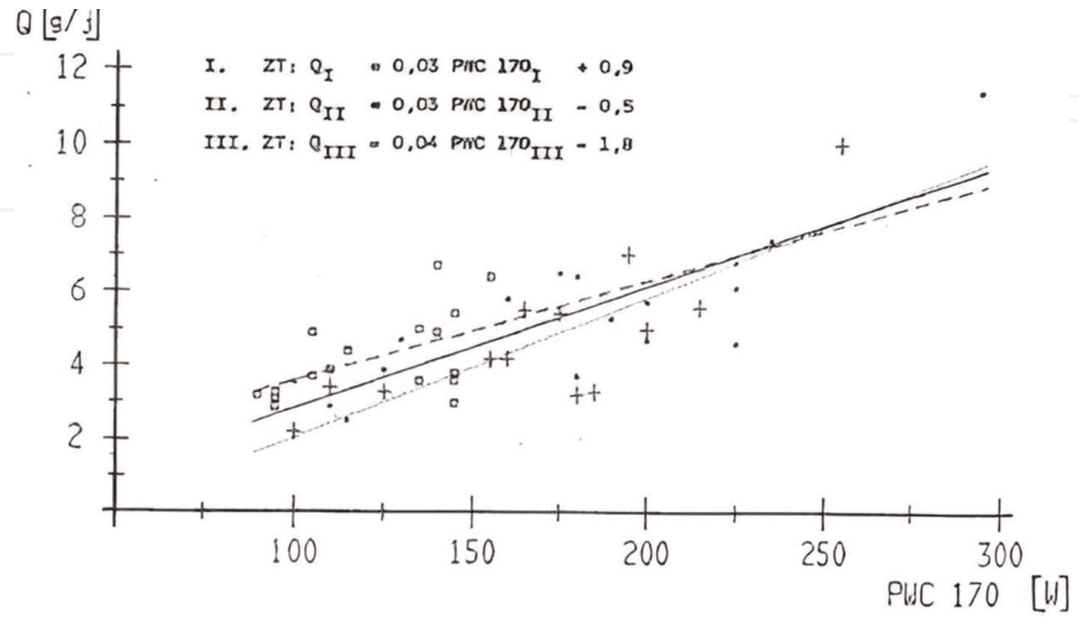


Figure 4.
Relation of insulin effectiveness Q_I, Q_{II}, Q_{III} and respective PWC 170.

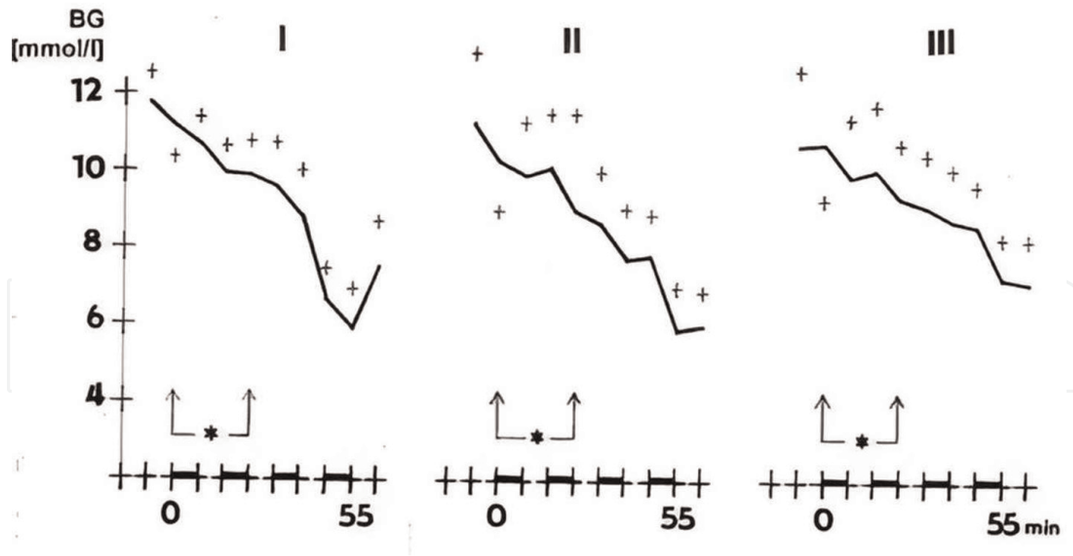


Figure 5.
Development of vBG in the course of the bicycle ergometer test I (before training), II (end of training) and III (after 6 days of quiet) n = 19.

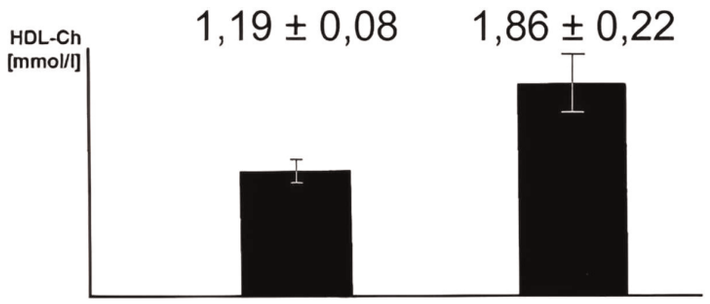


Figure 6.
Increase of serum HDL cholesterol concentration between the start and end of the 6-month training (n = 19).

catabolism. At the beginning, the insulin should be reduced or the amount of carbohydrates in food increased along with the change of insulin effectiveness. Even in patients with high physical working capacity, it is not possible to replace insulin by physical exercise. Following the training cessation, the amount of injected insulin should be increased or the amount of carbohydrates in food reduced along with the decrease of insulin effectiveness.

3. Randomised cross-over clinical trial on metabolic effectiveness and feasibility of three intensive insulin regimens with particular consideration of night period in PWD 1 (Institute of Diabetes Karlsburg, Germany, 1989–1990) [63]

Subjects: A group of 36 T1D (males, age 18 to 50 years, duration of diabetes at least 3 years, C-peptide 0,037 ± 0,013 nmol/l, BMI 23,6 ± 0,5 kg/m^2, PWC 170 172,5 ± 6,8 W, retinopathy 1st grade in 7 and 2nd grade in 7 of them, traces of proteinuria in 11 of them, proteinuria > 2 g/d in one of them) completed the study.

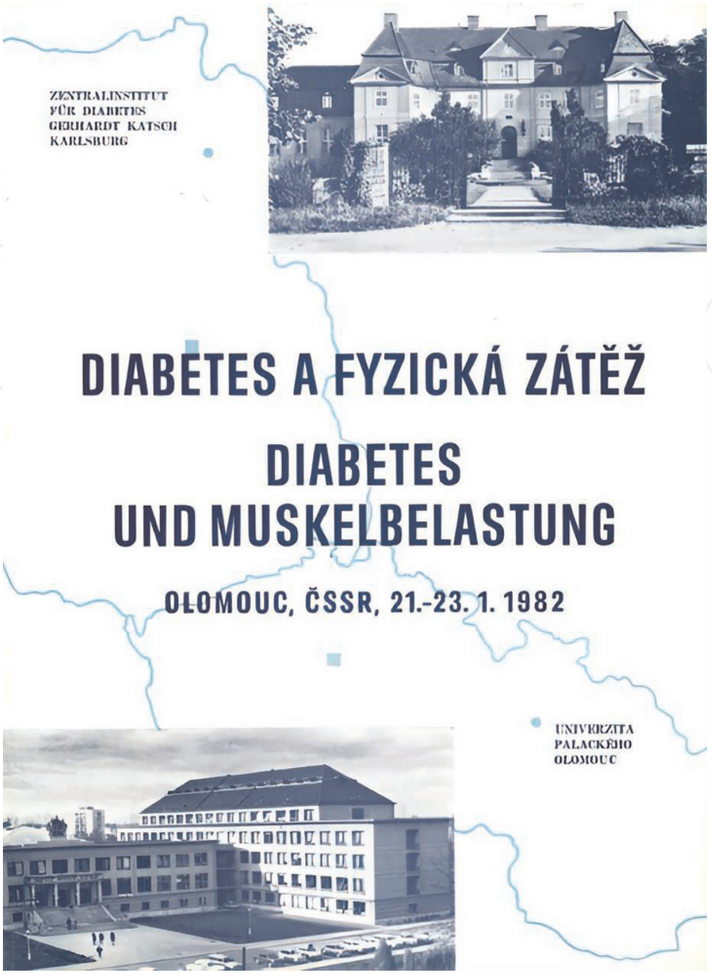


Figure 7.
Abstract book Symposium on Diabetes and exercise, 21.-23.1.1982, Olomouc, Czechoslovakia, organised by Palacký University Olomouc and Central Institute of Diabetes G. Katsch Karlsburg; Olomouc, 1982 p 102 [91–96].

Study design: The suggested protocol considered our previous experience and outcomes of other studies on dawn phenomena and pharmacokinetics of various insulin preparations [97–105]. After admission, each of the three insulin regimens A, B, and C (**Tables 1** and **2**) was randomly tested over two weeks and then replaced by another one. At discharge (6 weeks after admission) the tested person could choose the preferred regimen for the 8-week treatment period at home/at work. Final in-patient examination targeted to the complex assessment of respective clinical and laboratory parameters.

Results: The basal and prandial insulin substitution with only purified porcine shortacting insulin (SNC, Berlin Chemie) given seven times a day (regimen A) was the most effective kind of the conventional insulin therapy as assessed by the mean cBG (MBG 16) of 16-point BG profiles at the end of the respective test period (**Figure 8**).

The regimen A led to the best metabolic control in 21/36 (58%) of patients (**Figures 9** and **10**).

The insulin regimen B with one animal intermediate insulin preparation (BS, Berlin Chemie) at 10 p.m. or the regimen C with a long-acting insulin (Ultratard HM, NovoNordisk) at 5.30 p.m. led to the best control in 6/36 (17 %) or in 9/36 (25%) of all patients, respectively.

Randomisation	**Hospital**			**At home**	**Hospital**
Each PWD was randomized to 1 of 6 subgroups	12 d	14 d	14 d	8 weeks	3 days
	A	B	C	Individually selected insulin regimen A or B or C	
	A	C	B		
	B	A	C		
	B	*C*	*A*		
	C	A	B		
	C	B	A		
Diet				Free adopted diet	
BG-profiles					
FIRI-profil					
Fruktosamin					
Lipoproteins					
C-peptid, IBC					
STH					
Psychology					
PWC 170					
HbA_1					
U-glucose, U-aceton					
Selfmonitoring	Strips for capillary blood measurements				

Table 1
Schedule of PWD randomisation into six groups with different sequences of insulin regimens; hospital and home study periods; clinical and laboratory check-ups.

Time	**6,30**	**9,00**	**11,30**	**15,00**	**17,30**	**22,00**	**2,30**
Regimen A	R	R	R	R	R	R	R
Regimen B	R	R	R	R	R	B intermediate	
Regimen C	R	R	R	R	R + Ultratard		

Table 2.
Tested insulin regimens: A (regular insulin R only), B (R in the course of day plus intermediate insulin at 10 p.m.), C (R in the course of day combined with Ultratard insulin at 5.30 p.m.).

Even though the capillary FIRI concentrations (which were investigated parallel with cBG) were significantly higher than in healthy men (**Figure 11**), the cBG values in the best PWD when compared to a group of 9 healthy men remain significantly higher.

In addition, in the last two regimens (B and C), the total daily insulin dose was higher than in regimen A. On the other hand, the fasting BG concentrations were in regimen A 60 of 72 BG measurements below 10 mmol/l. In regimen B, it was only in

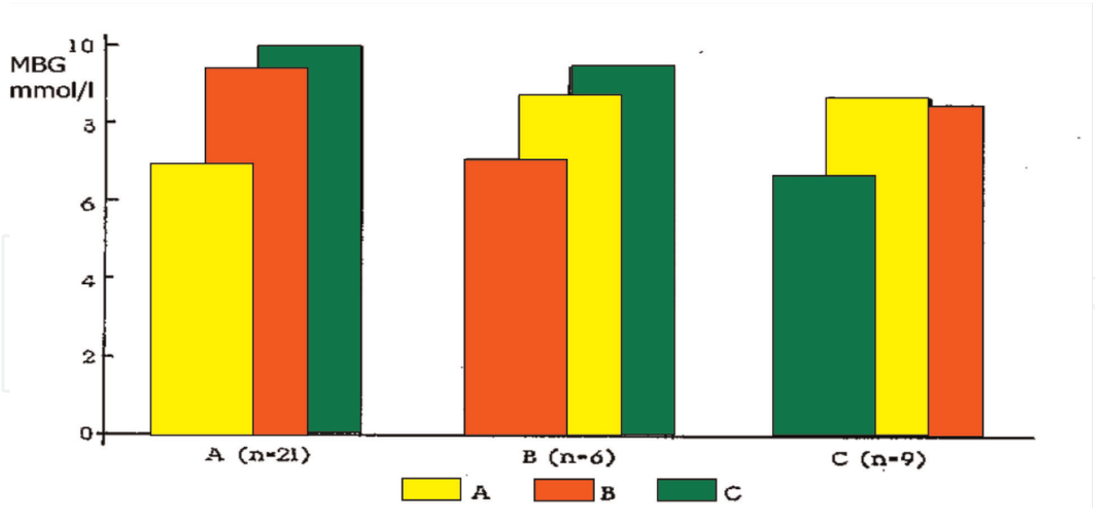


Figure 8.
MBG 16 in the group with the best regimen A (n=21)—left, in the group with the best regimen B (n = 6) — middle, and in the group with the best regimen C (n = 9)—right, in comparison with MBG 16 of other two regimens in the respective group.

14 of 72 measurements and in regimen C in 19 of 70 measurements (2 values were missing) (**Figure 12**).

The group education and an insulin pen motivated the diabetic patients to an intensification of insulin therapy including injections of insulin at 2.30 a.m. [73]. The feasibility (acceptance) of night injections (insulin regimen A) increased from 2/36 (6 %) at the beginning to 15/36 (42 %) at the end of the study. On the contrary, the optimistic patients´ hopes expecting the best effects from the long-acting insulin preparation Ultratard declined from 26/36 (72 %) on recruitment to 12/36 (33 %) on the final assessment at the end (**Figure 13**).

Neither the intensive insulin treatment enabled a long-lasting normalisation of B-glucose and B-FIRI concentrations.

A significant impact of regimen A on MBG 16 was only seen in a subgroup of 19 PWD who on discharge preferred regimen A for their future treatment.

No metabolic differences were seen when using the MADI 7/2ml needle pen (**Figure 14**) or catheter pen [78, 106]. The needle pen was preferred in 54 % of all patient days.

4. Continuous subcutaneous insulin infusion (CSII)

Since the year 1978 CSII by means of an external insulin pump became the best near-physiological way of insulin substitution [18, 107–115].

CSII supported by intensive self-monitoring mostly resulted in improved metabolic control as well as in increased satisfaction and quality of life in thousands of PWD1.

In our diabetes centre the first pump (Promedos E 1, Siemens, Germany) was introduced in December 1981 (**Figure 15**) [115]. From 2003 to 2012, DAHEDI Elektronics (**Figure 16**), H tron (**Figure 17**), Minimed (**Figure 18**) and Animas IR 1000, 1200 and 2020 (**Figure 19**) were inserted and regularly upgraded beyond the date of their 4-year expiry period. There were two pumps produced in Czechoslovakia: Insulin Injektor Kovo Brno developed by Hirš, Institute of Physiology, Academy

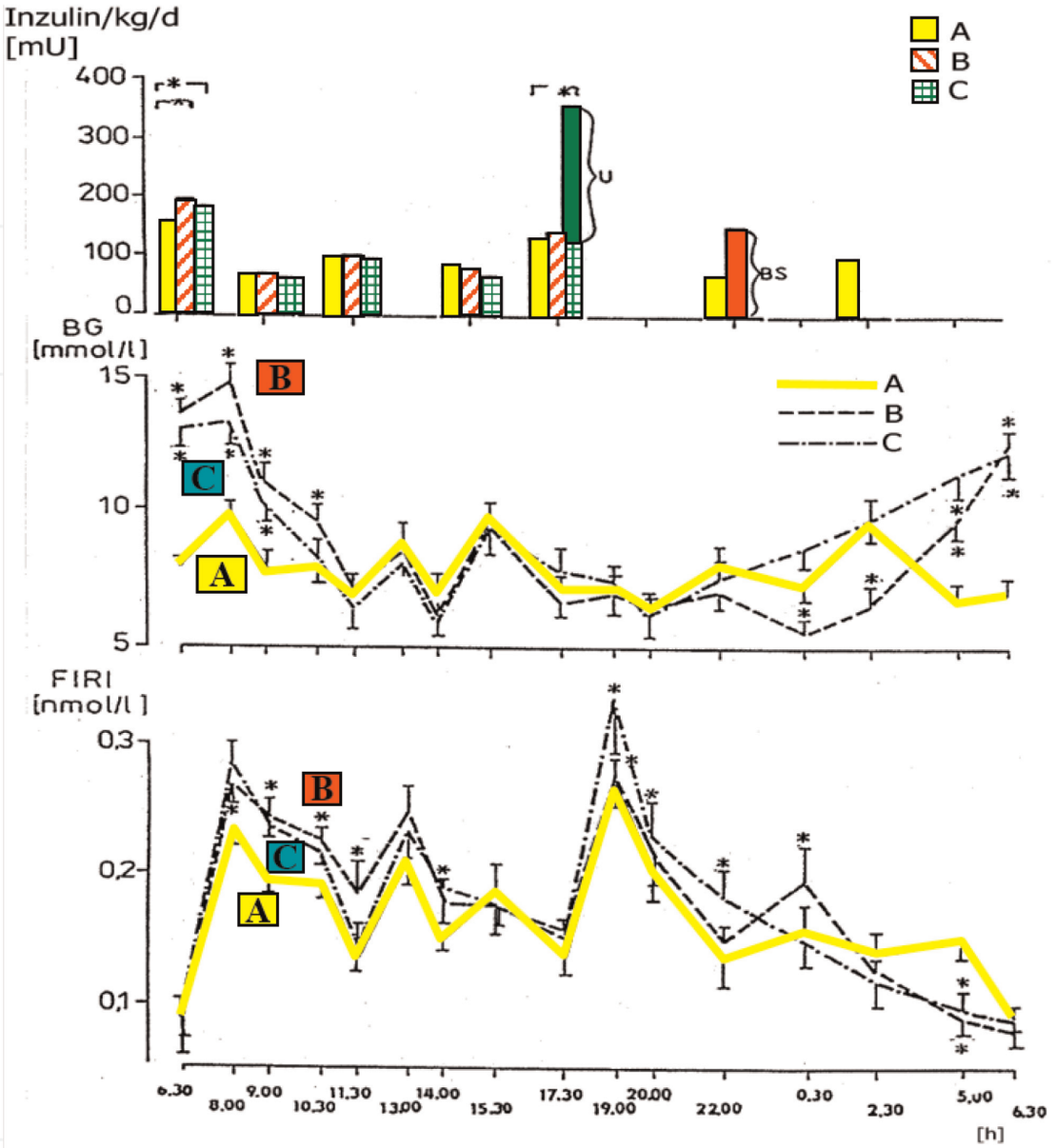


Figure 9.
*Comparison of insulin doses, 16-point cBG profiles and 16-point free immunoreactive insulin (FIRI) profiles at the end of respective insulin regimen period. See **Figures 9** and **10** for further details.*

of Sciences, Prague (**Figure 20**) [108–112] and programmable pump DI2 PC, developed by Vojtek, MEDIPO Brno. Thirty prototypes of this pump were produced, seven of them successfully tested in 1991–1993 in Olomouc (**Figure 21**) [53].

Paradigm 712, 722, 522, VEO 754 and 554 enabled the "low glucose suspend" if connected to CGM (**Figure 22**).

4.1 Single centre pilot study on metabolic effectiveness of CSII in PWD1 (1993–1998)

Subjects: Thirteen PWD1 males and females were put on an insulin pump (Dahedi, H-Tron, Minimed) in the period of years 1993–1998 demonstrated that the continuous subcutaneous insulin infusion resulted as soon as in 72 days in a decrease of concentrations of HbA1c in blood (NGSP scale 9.3 ± 0.46 vs 7.6 ± 0.28 %, $p < 0.05$)

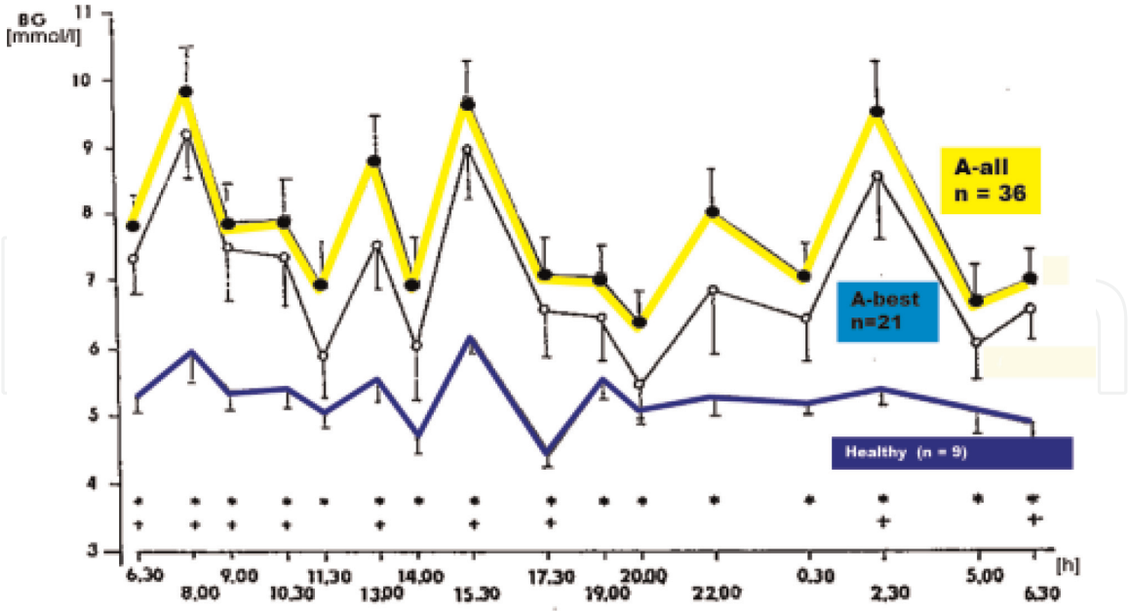


Figure 10.
The 16-point cBG profiles at the end of insulin regimen A in 36 PWD (A) and in 21 of them who reached the best BG values with regimen A (A-best). cBG values in the group A-best remain significantly higher than in a control group of 9 healthy men. See also ***Figure 11****.*

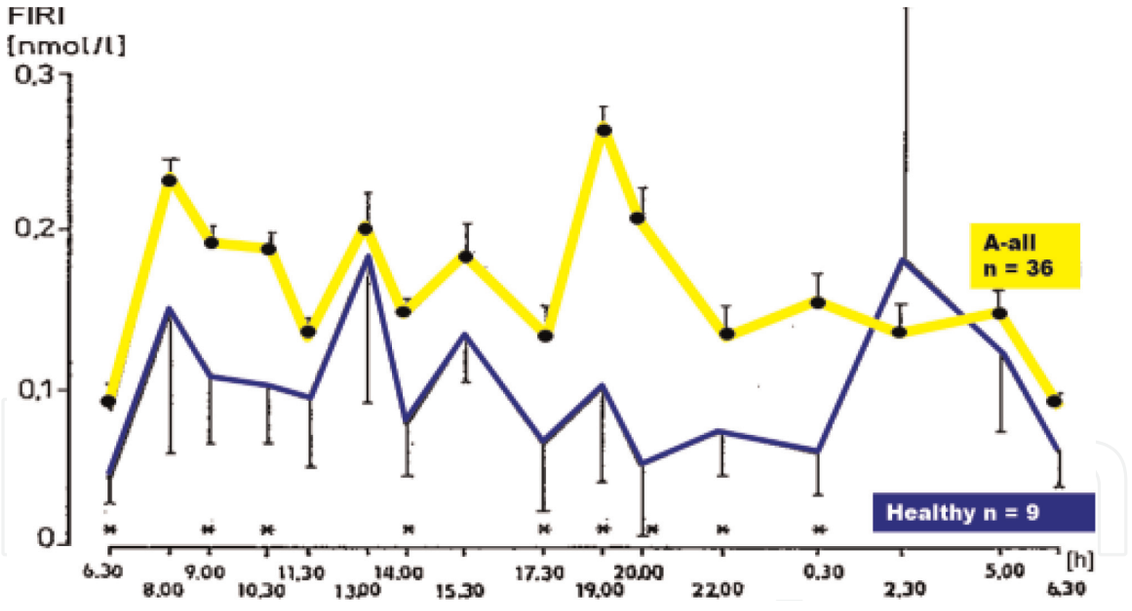


Figure 11.
*The 16-point FIRI profiles at the end of insulin regimen A in 36 men (A-all) and in a control group of 9 healthy men. * $p < 0.05$.*

(**Figure 23**), of total serum cholesterol (5.47 ± 0.29 vs 4.85 ± 0.19 mmol/l, $p < 0.05$) (**Figure 24**) and triacylglycerols (1.58 ± 0.24 vs 1.13 ± 0.15 mmol/l, $p < 0.05$). The total daily dose of insulin was reduced (47.8 ± 2.75 vs 41.3 ± 2.3 IU/d, $p < 0.05$) and the body mass did not change. An improved metabolic control was also found in a check-up 554 days later. There were no serious complications resulting from the usage of a pump.

In the third milenium, insulin pumps enable adaptation of basal rate up to 48 times per 24 h. Based on the biorhythm of insulin sensitivity and

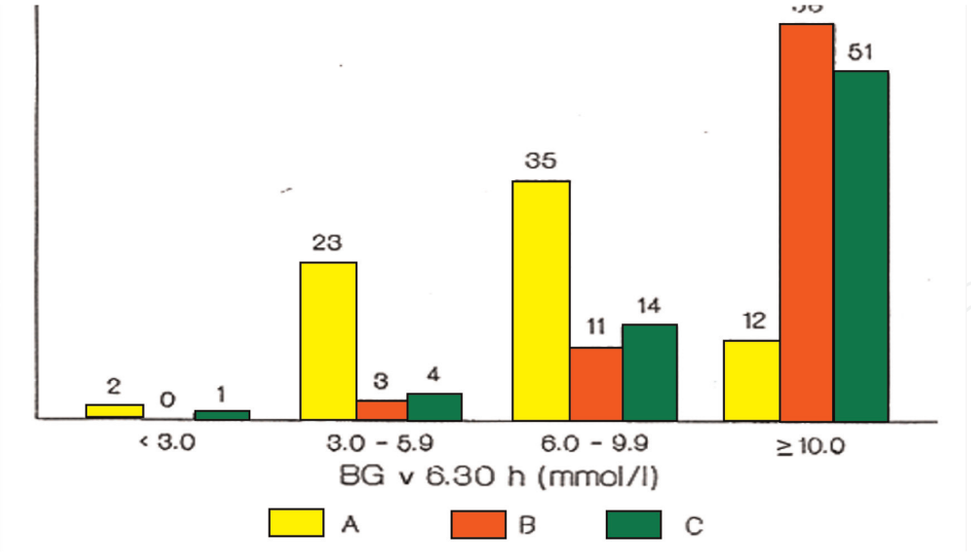


Figure 12.
Frequency of fasting cBG concentrations at BG profiles in the course of respective regimen.

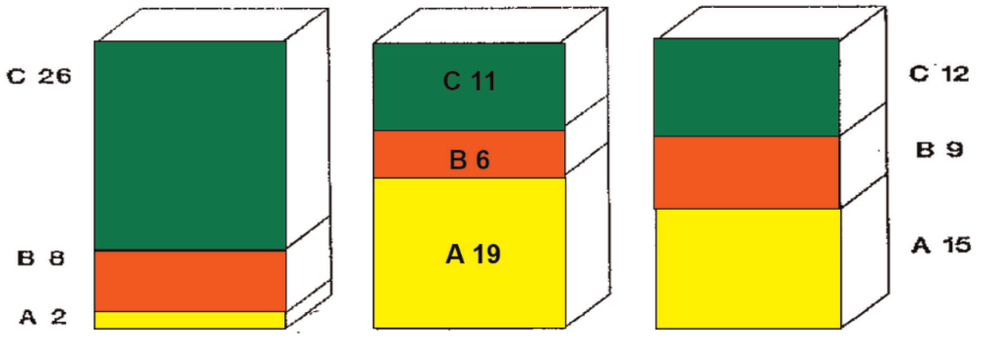


Figure 13.
Preference of regimens A, B, C at the beginning, at the end of the in-patient period and after 8-week home therapy with self-selected regimen.

Figure 14.
First insulin pens MADI (MAnual Device for Insulin) developed at Palacký University Olomouc in 1983–1990 [20, 21, 78] MADI 5/5 ml (above), MADI 7/2 ml—used in this study (middle), MADI 8/3 ml (below). Photo V. Kupčík, www.diabetesmuseum.cz.

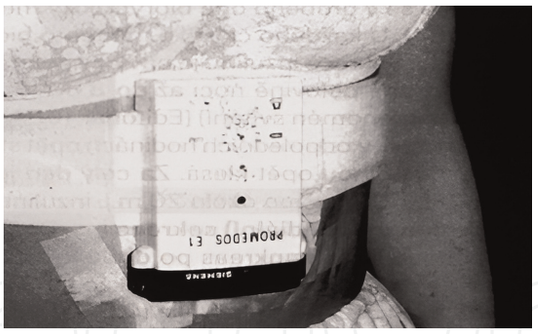


Figure 15.
Promedos E 1, Siemens, Germany [115].

Figure 16.
Dahedi Elektroniks, Netherlands.

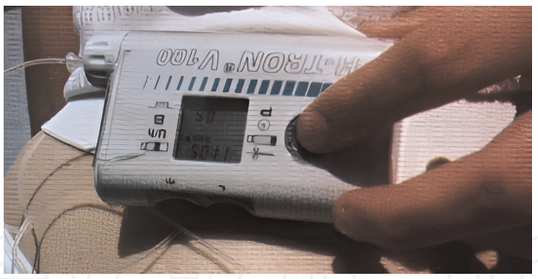


Figure 17.
H tron, Disetronic, Switzerland.

Figure 18.
Medtronic-Minimed 506, CA, USA.

Figure 19.
Animas IR.

Figure 20.
Osobní Injektor, Institute of Physiology Prague, Kovo Brno, CR. Hundreds of pumps were widely used in Prague, Brno and Hradec Králové in the period of years 1984–1991 [108–112]. Photo V. Kupčík, www.diabetesmuseum.cz

Figure 21.
DI2 PC, MEDIPO Brno, CR.

carbohydrate ratio and on our clinical experience with CGM-augmented CSII (**Figure 25**) [65, 98, 100, 103, 116], we have introduced a dynamic schedule of basal rates (**Figure 26**). This schedule we have used in PWD1 at the beginning of CSII therapy, to be adopted individually. Intensive conventional self-monitoring or CGM or FGM are prerequisites for an effective CSII.

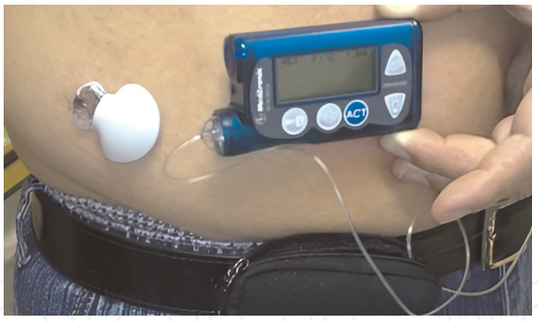


Figure 22.
Paradigm 722, Sensor and transmitter, Minimed-Medtronic, CA, USA. These sensor-augmented pumps [116] opened the door for the effective application of CGM or FGM in metabolic control and prevention of late complications in PWD1.

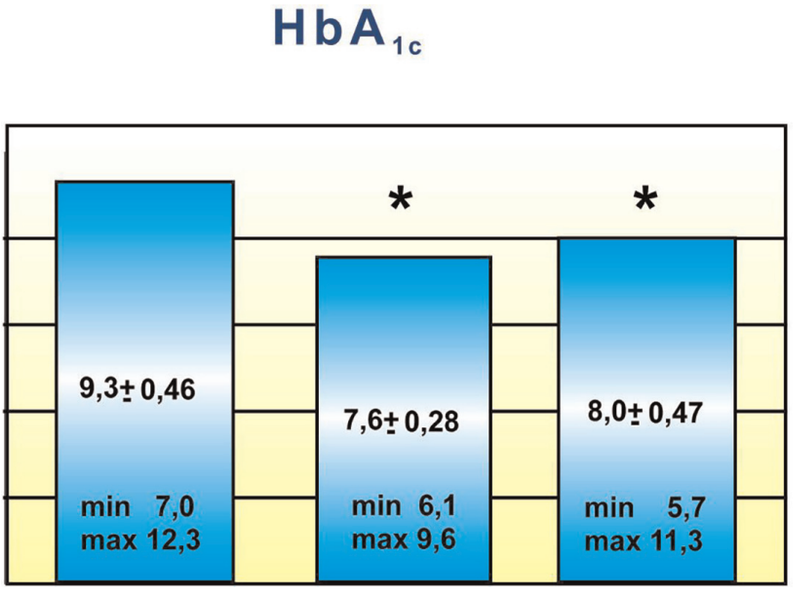


Figure 23.
HbA1c (NGSP %) at baseline, after 72 d and 554 d on CSII n = 13.

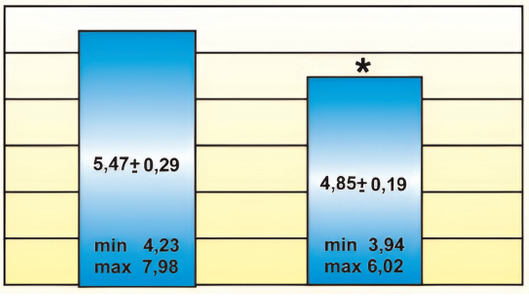
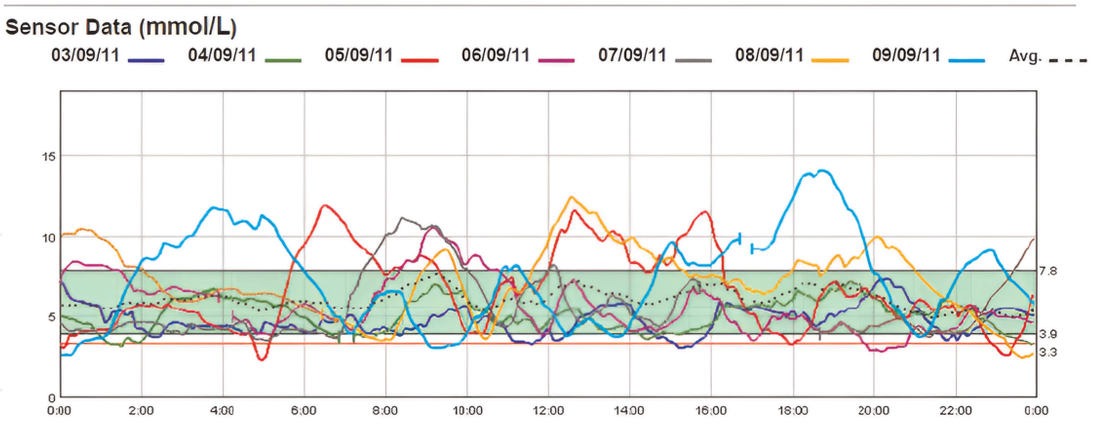


Figure 24.
Total cholesterol (mmol/l) at baseline and after 72 d on CSII n = 13.

4.2 Retrospective single centre study on feasibility of CSII in PWD1 and PWD2 (1981–2013)

In a period of 31 years we summarised our observations (**Figures 27** and **28**) [117]:

- a total of 185 PWDs (113 type 1, 72 type 2), aged 18–78 years, duration of diabetes from 0 to 56 years, were put on insulin pumps;



	Sat 3 Sep	Sun 4 Sep	Mon 5 Sep	Tue 6 Sep	Wed 7 Sep	Thu 8 Sep	Fri 9 Sep	Average / Total
# Sensor Values	288	284	288	285	254	285	285	1,969
High SG (mmol/L)	7.3	7.2	11.9	10.6	11.2	12.3	14.1	14.1
Low SG (mmol/L)	3.1	3.1	2.3	2.8	3.5	2.4	2.6	2.3
Average SG (mmol/L)	4.8	5.1	6.6	5.7	5.6	7.2	7.3	6.0
Standard Dev.	0.9	1.0	2.4	1.7	2.0	2.2	2.9	2.2
MAD %	19.5	8.9	25.1	3.6	1.5	9.8	5.5	13.4
# Valid Calibrations	4	3	3	3	2	2	3	20

Figure 25.
Continuous glucose monitoring (CGM) using a transcutaneous sensor in the course of 7 days. Each day has a different colour. Up to 288 sensor values per day.

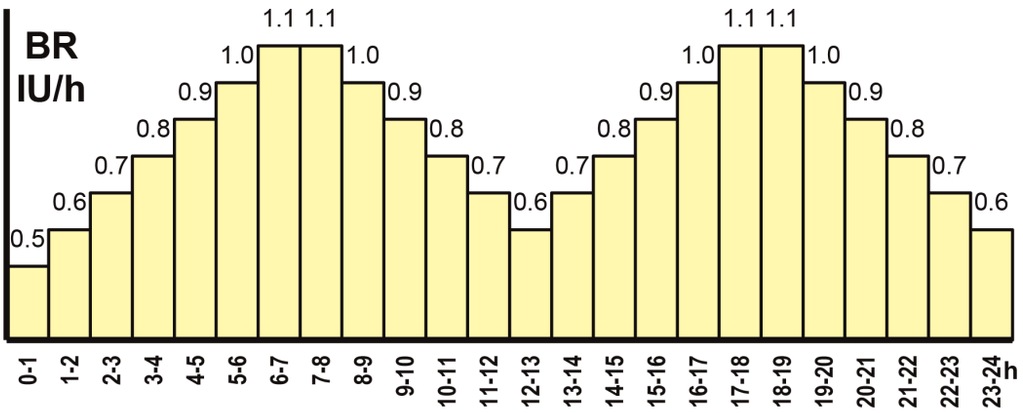


Figure 26.
CSII start: suggested distribution of basal rates over 24 h; to be individually adopted according to glycaemic profiles and clinical experience.

- six PWDs (3%) rejected the pump within 6 years after the commencement of use due to stress related to new technologies.

- seven PWDs (4%) were switched to other treatments (pancreas transplantation 2, liraglutide 2, multiple daily insulin 3).

- twenty pump-treated PWDs (11 %) died (heart failure 12, stroke 2, renal failure 2, pneumonia 2, M. Alzheimer 2).

- in the year 2013, 152 of 185 (82 %) CSII-treated PWDs registered in our working group PARASEN (since 1981) have been profiting from insulin pumps.

Insulin pumps are the optimum available and safe means for insulin substitution in PWD1 [117, 118]. From insulin pumps may also profit some PWD 2 [106, 119].

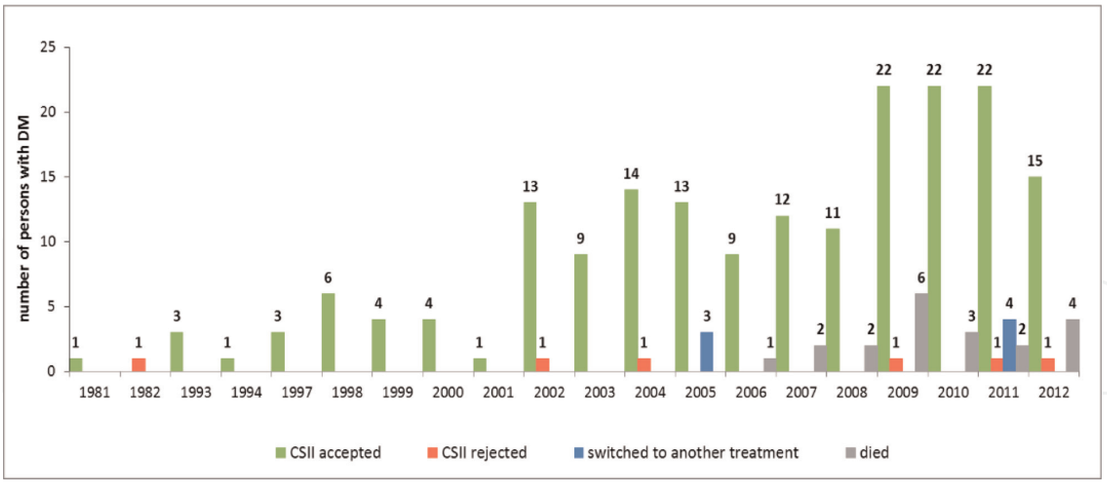


Figure 27.
Distribution of PWD (PARASEN Group) with accepted or rejected insulin pump or switched to other treatments or decreased over the period of 31 y.

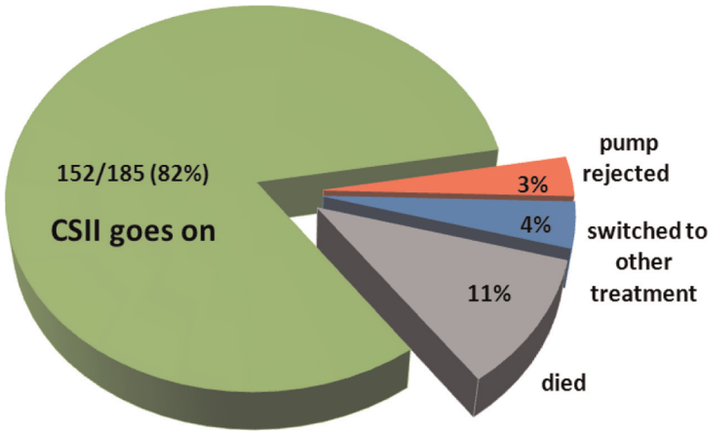


Figure 28.
Summary of outcomes from insulin pump treatment of PWD (PARASEN Group) over the 31-year period 1981–2012.

However, in PWD2 incretins and gliflozins recently appear to offer better cardioprotective and nephroprotective perspectives.

4.3 Retrospective single centre study on the safety and microbial hazards of prolonged transcutaneous sensor insertion (2004–2007)

Inflammation is a potential adverse event at the site of sensor insertion. In eight studies, there were 364 transcutaneous sensors used in 169 men and women with diabetes and in 40 healthy persons. The skin was sprayed with an antiseptic before sensor insertion. In the course of 2117 sensor days, there was only one serious complication: an abscess in the gluteal region. We demonstrate this case report [120].

History: A man born in 1972 with T1D from 1981, on insulin pump since 2002, from 2003 he used 15 sensors without any complication except occasional slight redness and increased sensitivity at the site of insertion. On 14.3.07, the patient inserted a sensor in the middle of the right gluteal area 14 cm below spina illiaca posterior superior. Before insertion, the site was sprayed by antiseptic. The third day

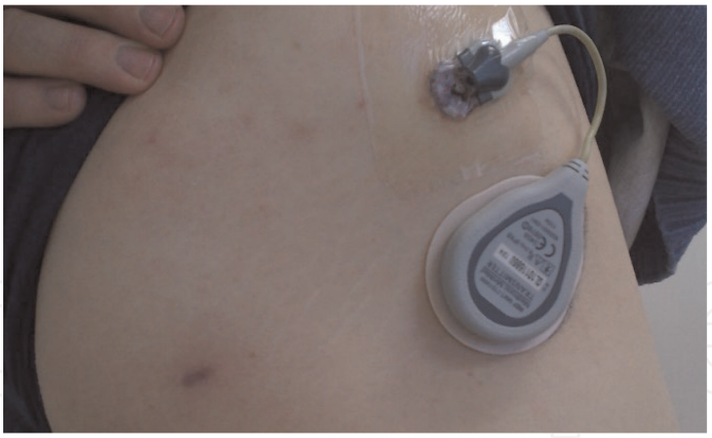


Figure 29.
Healing serious adverse events after sensor insertion. Scar after the abscess drain (left lower corner). New sensor and transmitter (right upper corner).

after insertion pain and aedema appeared, the fourth day the sensor was removed, the pain became more severe so 5 days later (23.3.07) he contacted the diabetes centre.

On examination: Redness and infiltration 5 cm of diameter. Small incision in local anaesthesia (Mesocain 1%) was performed, 10–20 ml of purulent fluid was evacuated. The wound rinsed using physiological solution and drained. New sensor was inserted (**Figure 29**).

Microbial culture: Streptococcus pyogenes. No antibiotics were given. Within 14 days after surgical intervention, the local redness and pain disappeared and no signs of secretion or retention were seen. A small scar remains.

Conclusions: In the course of the FDA-approved period for sensor insertion only one serious adverse event occurred. There were no other serious adverse events in sensors used for up to 9 days. Hence, from the point of view of potential microbial hazards prolonged insertion of sensors appears to be safe. These conclusions are supported by other studies [72].

4.4 Interests in long-term continuous glucose monitoring in persons on insulin pumps-one centre experience (2006–2012)

The purpose of this prospective study [57] was to assess the real patient´s interest in routine use of transcutaneous sensors related to hypothetic optimum state of "always on CGM".

Methods and results: In the course of 7 years (from 2006 to 2012), the sensor augmentation of Continuous Subcutaneous Insulin Infusion (CSII) was repeatedly offered free of charge to all PWD on pumps (n=123) attending the regular check-ups supported by Carelink Personal software. The CGM was accepted for a variable number of days by 63 (51%) of them. The real percentage of time spent on CGM shows the present study (**Table 3**).

SPSS v 15.0, SPSS Inc., Chicago, IL, was used for statistical analysis. $P < 0.05$ was considered significant. Fisher´s exact test and Mann–Whitney U test revealed no significant differences in number of PWD, duration of diabetes, duration of CSII, duration of offer of CGM, total number of days with real use of CGM and rates of real use of CGM compared between PWD1 vs. PWD2 and men vs. women, except the age of PWD1 vs. PWD2 at start of CSII ($P = 0.0001$). The interests of PWD on CGM augmented CSII and their real-life conditions resulted in median of up to 14.1 % time

Parameter	Unit	PWD1 Men	PWD1 Women	PWD1 M+W	PWD2 M+W
N	#	26	27	53	10
Age at the start of CSII	y	30.5 (23.2, 52.2)	31.7 (23.8, 45.2)	31.0 (24, 48)	57.7 (52, 66)
Duration of DM at CSII start	y	18.5 (5.8, 29.0)	9.0 (3.0, 20.0)	12.0 (3.5, 25.0)	7.0 (3.8, 21.5)
Duration of CSII	y	4.1 (2.4, 10.3)	6.3 (2.4, 12.1)	5,8 (2.4, 10.9)	3.2 (2.5, 4.5)
Unlimited offer of CGM	d	1491 (868, 2147)	1491 (883, 2252)	1491 (883, 2221)	1123 (746, 1499)
Real use of CGM	d	154 (72, 339)	189 (27, 337)	175 (56, 333)	66 (6, 137)
Days on CGM/ Days of offer	%	10.9 (5,1, 26.9)	14.1 (4.1, 28.0)	12.1 (5, 26.1)	7.7 (0.4, 12.2)

Table 3.
Characteristics of PWD on insulin pumps and their interest in sensor-augmented CSII (median, percentile 25 and 75).

of CGM use. So, having made available sensors and CGM education for unlimited time for all 123 PWD on insulin pumps in our centre, their attitudes and motivation remained to be adopted.

5. Prevention, early diagnosis and treatment of gestational diabetes, T1D and late complications in PWD1 at Teaching Hospital Olomouc (2014–2022)

5.1 Gestational diabetes mellitus (GDM)

GDM is transient glucose intolerance first detected during pregnancy. Manifestation usually occurs in the second and third trimesters. After delivery, the impaired glucose metabolism is corrected, and the glucose level moves within the normal range.

At the beginning of pregnancy, the main goal of the mother's metabolism is to build up sufficient reserves of energy to be used for foetal growth [121]. With the end of the first trimester, insulin resistance of muscle and adipose tissue gradually begins to develop, reaching its peak during the third trimester. The volume of adipose tissue decreases and the supply of free fatty acids increases, which newly become the main source of energy for the maternal organism. Glucose is redirected by the placenta to the foetus. Despite significant insulin resistance development of diabetes in pregnancy usually does not occur.

The HAPO study in 2008 demonstrated a strong association between glycaemia values and the perinatal complications which was almost linear and already evident at the level of glycaemia, which until then was considered completely physiological [122]. This study led to the development of a new guideline for screening and diagnosis of gestational diabetes [123]. Our centre, like others in the Czech Republic, adopted these criteria in 2015 (**Table 4**).

The primary treatment of GDM consists of dietary control, adequate physical activity and weight management remain the cornerstones of GDM treatment.

First antenatal visit	24– 28 week of gestation (75g oGTT)
FPG ≥5,1mmol/l[1]	PG ≥ 5,1mmol/l (fasting) PG ≥ 10,0mmol/l (1h) PG ≥ 8,5 mmol/l (2h)

FPG=fasting plasma glucose; PG=plasma glucose; 75g oGTT=oral glucose tolerance test with 75g of glucose. [1] At least 2 measurements on separate days.

Table 4.
Diagnostic criteria for GDM (adopted from IADPSG).

FPG	<5,3 mmol/l
PPG (1h)	<7,8 mmol/l
PPG (2h)	<6,7 mmol/l

FPG=fasting plasma glucose; PPG=postprandial plasma glucose.

Table 5.
Glucose targets recommended for GDM treatment [124].

Pharmacological (mainly insulin) treatment of GDM is considered in cases where we are unable to achieve the treatment goals through dietary modification and lifestyle management. Insulin is indicated when glycaemia exceeds the recommended range (**Table 5**).

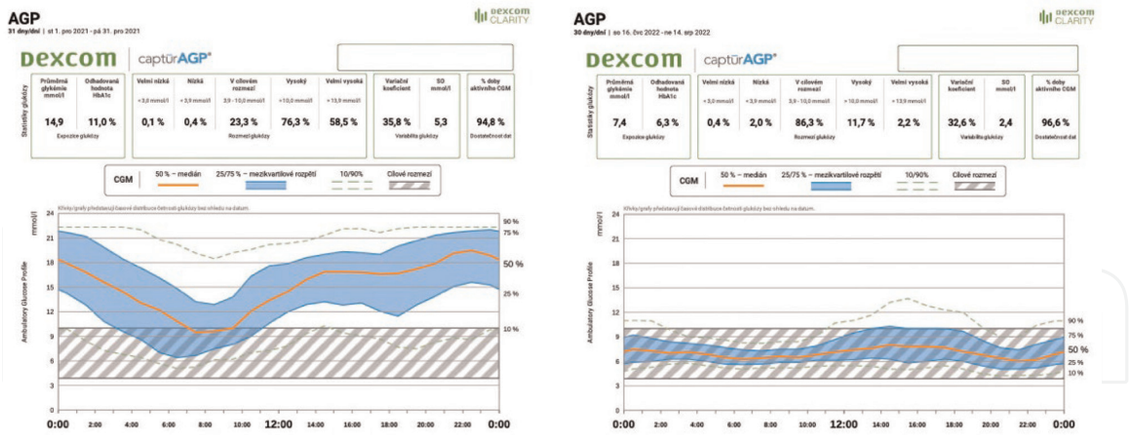
In GDM, the reason for insulin preference dominance is good efficacy in glycaemic control and the low risk of foetal harm with the negligible transplacental transfer. Metformin has the most experience worldwide. However, in our centre, metformin is not currently recommended in the management of GDM. It is known to cross placenta and a long-term safety for offspring is still of some concern [124].

The relationship between hyperglycaemia at 24–28 weeks of pregnancy and the incidence of perinatal complications is well established. This is not entirely true for the detection of hyperglycaemia in early pregnancy. We have insufficient data to establish target glycaemic values for the diagnosis and treatment of early onset gestational diabetes. However, increased fasting glycaemia in early pregnancy has shown to be closely associated with higher body mass and BMI in the initial weeks of pregnancy [125]. Women with GDM had more pronounced features of metabolic syndrome than pregnant women without GDM in terms of lipid profiles (triglycerides) and increased insulin production (C-peptide) [126]. Women with early onset GDM also showed altered adipokine production. Increased A-FABP and decreased adiponectin levels are correlating with visceral adiposity and glucose control and may be affected by treatment later in pregnancy [127].

It turns out that gestational diabetes is a heterogeneous condition. Further research is now focusing on finding potential different screening strategies and diagnostic criteria in early and late pregnancy. At the same time, it is necessary to look for appropriate treatment approaches for women with hyperglycaemia at different stages of pregnancy in terms of efficacy and safety [128].

5.2 Sensor-augmented insulin pumps

Continuous subcutaneous insulin infusion (CSII) represents the most physiological substitution of insulin in PWD1. However, without frequent glycaemic control



A) TIR (3.9-10.0mmol/l) 23,3%

B) TIR (3.9-10.0mmol/l) 86,3%

Figure 30.
A—Ambulatory glucose profile (AGP) on multiple-dose injection regiment (MDI) with real-time glucose monitoring. B—Ambulatory glucose profile (AGP) after 6 months of sensor-augmented pump therapy with a hybrid close loop system (Control-IQ ™; t:slim X2 ™).

and insulin dose correction, it fails to keep glycaemia within the recommended range. Real-time continuous glycaemic monitoring system (rtCGM) on the other hand improves the metabolic outcomes regardless of insulin delivery method [31]. Sensor-augmented pump therapy (SAP) integrates these two technologies into one functional system. In the course of the last few years, it has been further improved by a mathematical algorithm that allows semi-autonomous adjustments of subcutaneous insulin infusion according to the current glycaemia (hybrid close loop system—HCL). For the last 2 years, we have been using the Minimed™ 780G system (Medtronic) with the SmartGuard™ and also t:slim X2™ (Tandem) with the Control-IQ™. Those systems have been certified and fully approved for the treatment of T1DM in the Czech Republic. Our experience with the HCL system shows that it is possible to achieve very good results, surprisingly not only in well-cooperating and trained PWD1. **Figure 30** shows the increase of the TIR (Time In Range) and the enormous improvement of daily glucose pattern in a woman, who has been using Control-IQ hybrid close loop function of t:slim X2 inuslin pump for 6 months.

5.3 Prospective uncontrolled single-centre study ROXINEGLYD (Contribution of Retinal OXimetry to the assessment of impact of INternal Environment, GLYcaemia and Diabetes control on retinal vessel oxygen saturation in PWD) (2016–2020)

Retinal oximetry is a method for measuring retinal oxygen saturation ($SatO_2$). Changes of retinal oxygen saturation were described in various clinical conditions such as retinal vein occlusion, retinitis pigmentosa, glaucoma, cataract, after pars plana vitrectomy, Alzheimer´s disease and also in diabetic retinopathy [129, 130]. An increase in venous oxygen saturation was shown to be related to the severity of retinopathy [131–133]. Lower arteriovenous difference of oxygen saturation reflects reduced oxygen delivery to tissues [134]. The question is whether early regular investigations of retinal oxygen saturation might help to assess the risk and progress of diabetic retinopathy.

Purpose of the pilot study [135] was to find an association of retinal oxygen saturation with acid-base balance, carboxyhaemoglobin concentration, current

plasma glucose concentration (PG), mean PG and PG variability over the last 72 hrs, HbA_{1c}. and other conditions.

Methods: Forty-one adults (17 men) with T1D (n=14) or T2D (n=27), age 48.6±13.5 years, diabetes duration 9 (0.1–36) years, BMI 29.4±6.3 kg/m^2, HbA_{1c} 52±12.7 mmol/mol completed the study. The 4-day study comprised two visits (Day l, Day 4) including 72 hrs of CGM by iPro®2 Professional CGM (Medtronic, MiniMed, Inc., Northridge, CA, USA). Retinal oximeter Oxymap T1 (Oxymap ehf., Reykjavik, Iceland) was used to assess retinal oxygen saturation.

Results: Wilcoxon signed-rank test showed no $SatO_2$ difference between eyes and visits. A significant correlation between arterial $SatO_2$ and PG variability in T2D, a positive correlation of venous $SatO_2$ with HbA_{1c} and with finger pulse oximetry was found. No correlation of retinal oxygen saturation with acid-base balance, carboxyhaemoglobin, current PG, mean PG over the 72 hrs, age, diabetes duration, BMI, lipoproteinaemia, body temperature, systolic and diastolic blood pressure, heart rate, central retinal thickness and retinal nerve fibre layer thickness was shown.

Conclusion: This study confirmed the association of venous retinal oxygen saturation with long-term but not with short-term diabetes control and not with acid-base balance or other conditions. The increased oxygen saturation and questionable impact of PG variability should be clarified further on.

6. Conclusions

This chapter summarises the authors´experience along with outcomes of respected trials and inventions from the insulin era. It became clear that the intensive management of T1D comprising insulin, diet, exercise and control of therapeutic effectiveness may recover the balance between energy intake and expenditure. Active approach to the diagnosis of diabetes and to prevention of retinopathy, nephropathy, diabetic foot and other cardiovascular complications may reduce their potential risks. Adequate education focused on knowledge, skills, attitudes and communication has created a

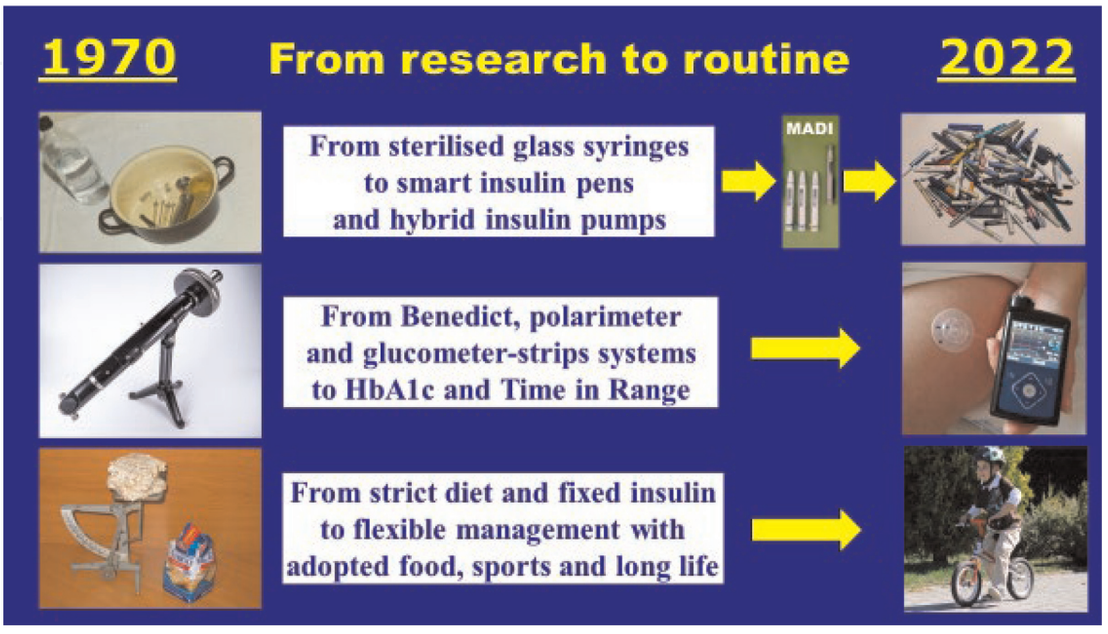


Figure 31.
Journey from the known past to perspectives of unknown future.

reliable base for effective approach. Recent technologies including smart insulin pens, hybrid insulin pumps, CGM, FGM and glucometer-strips systems as well as new insulin analogues, and transplantation of Langerhans islets and stem cells are offerring great perspectives (**Figure 31**).

Shall we always be strong enough to transfer the practice-related research outcomes to our daily routine?

7. Dedication

This chapter is dedicated to the memory of *Leslie James Park Dun*can (*Sumatra, 1922 – + Scotland 2005), unforgetable diabetologist who created a centre of excellence at the Royal Infirmary of Edinburgh [42, 136–140], for his empathy with patients, students and colleagues, as it was recognized by one of the authors of this Chapter in the course of his postgraduate training in Edinburgh in 1980.

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