Chapter

Pathophysiologic Approach to Type 2 Diabetes Management: One Centre Experience 1980–2020

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Abstract

This overview summarizes the evolution of pathophysiologic treatment of diabetes type 2 (T2D) in the period of the last 40 years. Randomized Controlled Trials (RCT) and Real World Evidence (RWE) studies resulted in recent Statements of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in the year 2020. Case reports and studies of a single-centre in Czech Republic are reported. The authors demonstrate the impact of (1) multiple doses of rapid insulin, (2) multiple doses of rapid or ultrarapid insulin analogs (3) continuous subcutaneous insulin infusion (CSII) (4) incretin receptor agonists, (5) fixed combination of insulin degludec with liraglutide (IDegLira) and (6) SGLT2 inhibitor dapagliflozin, on plasma glucose concentration, HbA1c, body mass and patient satisfaction. The importance of therapeutic patients' education and technology (personal glucometers, continuous/flash glucose monitors, insulin pens/pumps) is emphasized. Most of the observations were already published. Hence, individually adopted education, lifstyle, technical equipment, incretin receptor agonists and/or metformin and/or gliflozins and/or insulin analogs appear to be the core of an effective pathophysiologic approach. Scientific conclusions from RCTs, RWE trials and own clinical case reports may prevail over clinical inertia and induce early implementation of effective methods into routine T2D treatment.

Keywords: insulin analogs, incretins, gliflozins, insulin pen, CSII, glucose monitoring, education, case report, randomized control trial, real world evidence

1. Introduction

Type 2 diabetes mellitus (T2D) is a syndrome of disturbed metabolic pathways of sacharides (carbohydrates), proteins and fat due to various influence of eight pathophysiologic mechanisms described as ominous octet: disturbed dynamics of insulin secretion, reduced production of incretins in gut, hyperglucagonaemia, increased production of glucose from liver, disturbed endocrine function of adipose tissue, insulin resistance, increased activity of sodium glucose transporter 2 (SGLT2) resulting in increased reabsorption of glucose from renal tubules and malfunction of hypothalamic centers for satiety and hunger. [1] These mechanisms are induced by different genetic and environmental factors. [2, 3]

In previous centuries, clinical symptoms of T2D lead to therapeutic attempts based on lifestyle, diet and on oral antidiabetic drugs, mostly sulfonylureas.

The discovery of insulin by Paulesco in 1921 [4] and its final introduction to human medicine by Banting, Collip, Best and Macleod in 1922 [5] saved many lives of people with T1D. However, in T2D insulin was mostly used as an ultimate therapeutic alternative.

In 1957, the discovery of metformin resulted in reduction of hyperglycaemia without hypoglycaemias. In the course of several decades, metformin proved to be a relatively effective mean to reduce body mass and cardiovascular complications. In addition, in persons on metformin the frequency of neoplasms appears to be lower. Today, metformin undoubtedly remains the drug worthy of choice for the majority persons with T2D. [6]

At the end of the 20th century, a new concept of pathophysiologic approach to T2D was suggested by Bruns [7] under the descriptive term „complementary therapy", and, independently by Berger [8, 9] as „supplementary therapy".

Important role in the intensification of insulin regimens played insulin pens which were produced since the year 1983. [10] At the beginning of the 21st century, insulin pumps (first implemented by John Pickup in 1978 [11]) and intensive self-monitoring were also applied in people with T2D. [12–14] Despite of pumps many persons with T2D were unable to reach the expected metabolic improvement until incretin receptor agonists and gliflozins have been made available. [15, 16]

In 1974, the first glucometer (Ames) was introduced into clinical practice, followed by tenths of other glucometers [17–19], Continuous Glucose Monitors (CGM) [20] and/or Flash Glucose Monitors (FGM) [21]. Today, these devices have become mandatory means (together with HbA1c analysers [22]) to assess the metabolic control. Scientific inventions from the last 100 years were applied in official statements and guidelines. [23–25]

This overview introduces promoting insights and better understanding of pathophysiologic approach to various treatments of T2D. Purpose of the presented case reports and single-centre „real world trials "is to motivate to education and to implementation of incretins and/or gliflozins and/or insulin analogs and/or insulin pumps in daily routine of diabetes care.

2. Prerequisites for a pathophysiologic approach to T2D management

2.1 Therapeutic education

Lifestyle and education of people with chronic disorders have been recognised as an essential part of treatment. Many anonymous dedicated enthusiasts have created a solid platform for effective therapy. Some of them became famous educators, however, most of them remained unnoticed in everyday practice.

The Diabetes Education Study Group (DESG) of the European Association for the Study of Diabetes (EASD), was founded in 1977 [26] and the Therapeutic Patient Education (TPE) became a goal of many respected bodies in the world.

The DESG aimed to improve the quality of life through educational programmes designed to foster independence for the patient, to improve the quality of metabolic control, to emphasise the prevention and to encourage research. The DESG organised activities all over the Europe, published more than 30 Teaching letters and Series of the 5-min education basics. In eastern countries, the DESG workshops (Bucharest, 1982, Balatonfuered, 1985, Warsaw, 1987, Weimar, 1989, Olomouc, 1991) supported the cooperation between health care providers (physicians, teachers, psychologists, nurses, dietitians, social workers) and patients. (**Figure 1**) Therefore, the adopted 5- day scheduled teaching programs created by Assal, Berger and Jörgens in Genf and Düsseldorf [27] could be spread throughout Europe. Workshops at Grimentz,

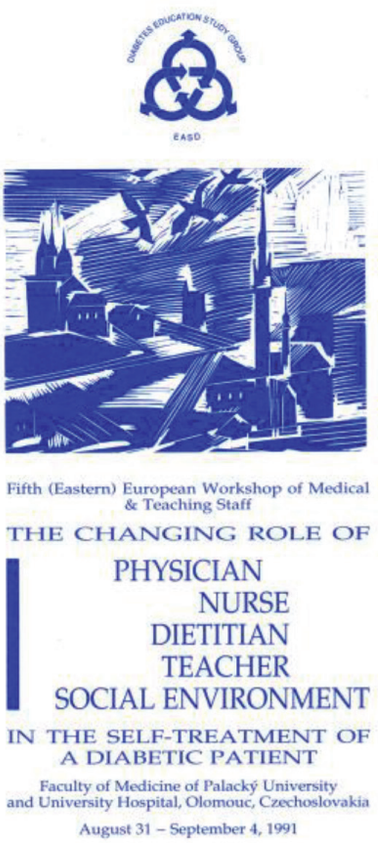

Figure 1.
Abstract Book from the last workshop of the Eastern DESG in Olomouc (1991).

Capri, Celano, Assisi, Chillworth, Cambridge, Winchester, Windsor, Sesimbra, etc., motivated to look at issues from various angels.

Process of TPE consists of three parts: teaching knowledge, training skills and formating attitudes. These principles have also been considered in our pathophysiologic approach to treatment of T2D in daily routine. [28, 29]

2.2 Technical support

2.2.1 Development and clinical implementation of insulin pens

Insulin pens opened the door to comfortable insulin administration thereby making the intensive regimens acceptable at work, at school, at leisure, during travels, etc.

In 1983, the first models of a MAnual Device for Insulin (MADI) proved to be a useful aid to injection of U-40 insulin either as a needle pen or as a catheter pen. [10] Within a few years other injectors appeared. [30, 31] Six models of a new type of MADI for insulin U-40, U-80 and U-100 were developed. [32] (**Figure 2**) In the needle pen (**Figure 3**) a sliding cover prevents the contamination of the needle which remains invisible in the course of injection and might be reused without sterilization. [33] In the catheter pen (**Figure 4**) the catheter remained inserted in subcutaneous tissue for 3 days. A syringe-like interchangeable plastic reservoir (3 ml) was refilled from insulin vials with any kind of soluble insulin. Actual insulin administration occurred by twisting the cap after subcutaneous insertion of needle or catheter.

To date, about one hundred of various types of insulin or incretin needle-pens have been distributed all over the world. (**Figure 5**) Most of them are disposable

pens [34] (prefilled with insulin, to be discarded after emptying), some of them are constructed for cartridged insulin produced by the respective company.

Despite initial enthusiasm, the preference of catheter pens [35] (**Figure 6**) was low over time.

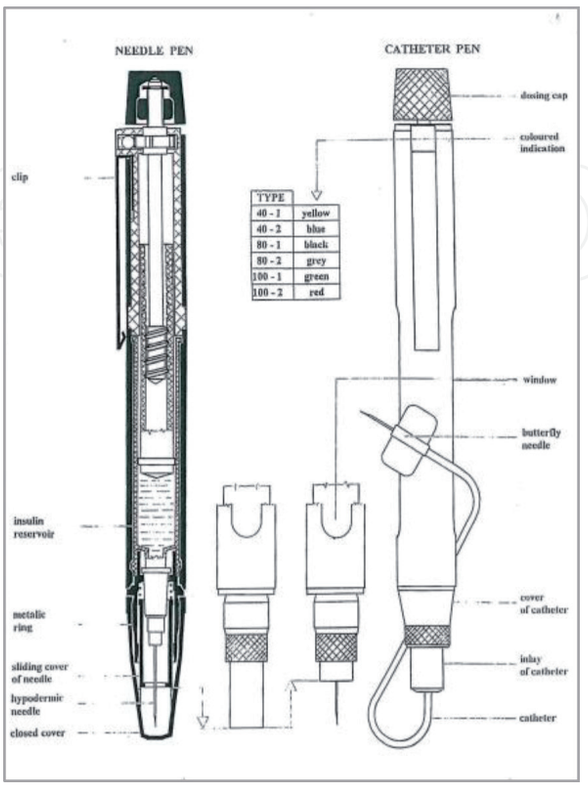

Figure 2.
Scheme of MADI: needle pen with telescopic sliding cover (left) and catheter pen [32] (1991).

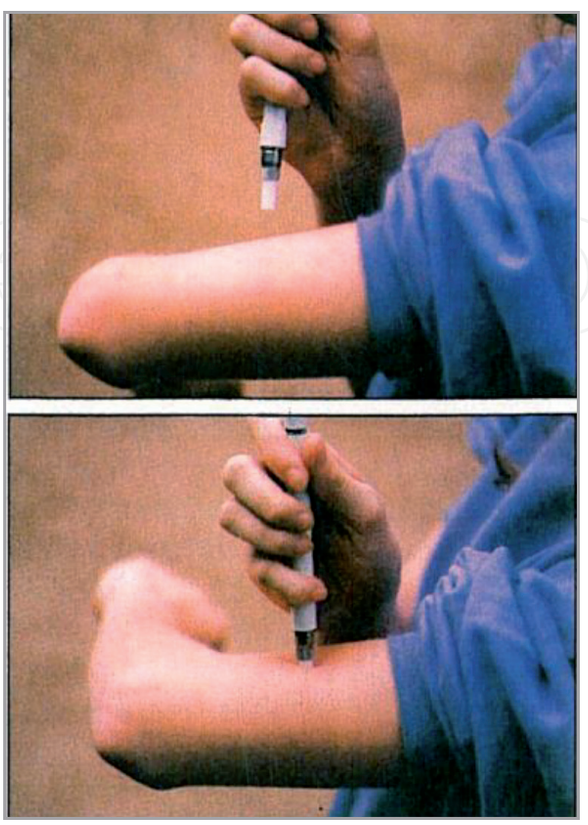

Figure 3.
MADI – needle pen in the course of injection (1994).

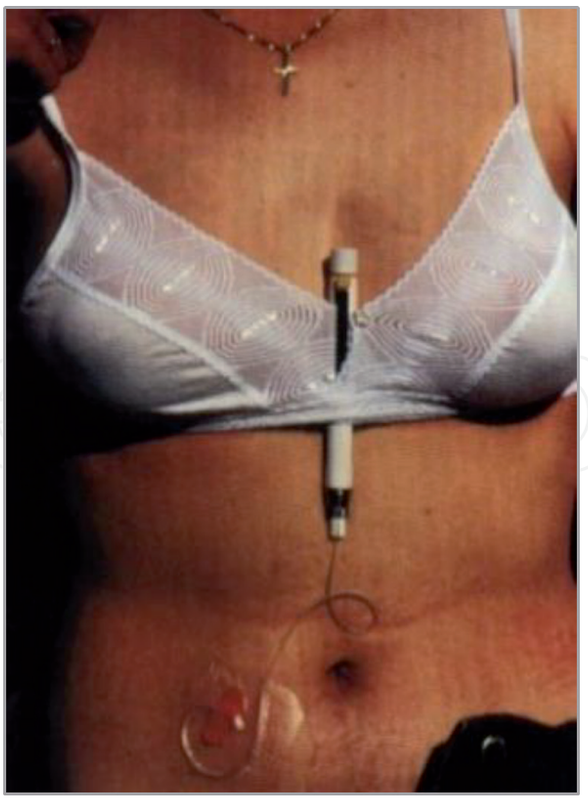

Figure 4.
MADI – catheter pen [35] (1994).

Figure 5.
Heaps of insulin or incretin pens produced by different companies all over the world since 1983. Photo V. Kupčik, Diabetes Museum, Háj ve Slezsku, CR. (2019).

2.2.2 Trials for testing accuracy and precision of glucometer-strips systems

Within the course of 25 years, we have tested the accuracy and precision of glucometer-strips systems Card (Medisense), OPTIUM (Abbott), ADVANCE (Hypoguard, GB) [17] and LINUS (Agamatrix, USA). [18] to support the reliability of our therapeutic recommendations.

The purpose of our last experimental and clinical trial (2010–2013) [19] was (1) to assess the electrochemistry-based glucometers CONTOURLINK (Bayer, Germany) using glucose dehydrogenase strips, CALLA, (Wellion, Austria) and

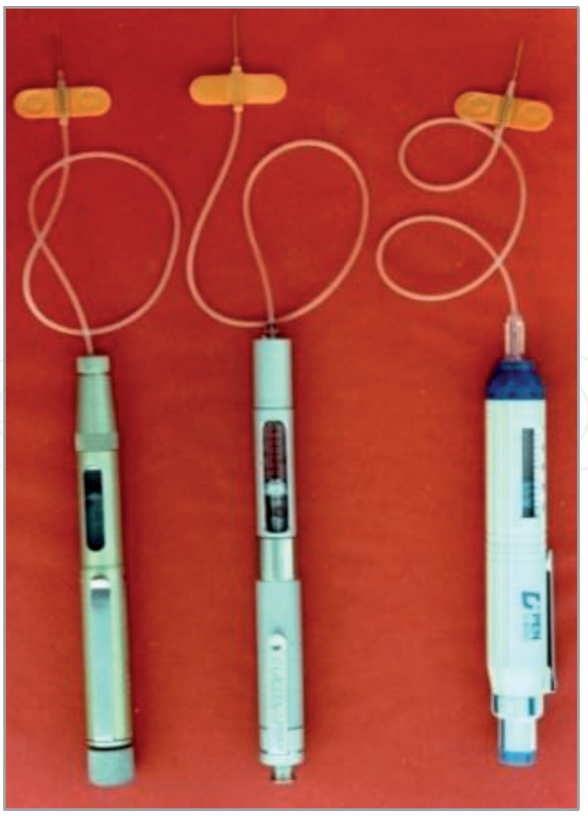

Figure 6.
Various catheter pens: MADI (CR), MD2 (GDR), D pen (CH) (1989).

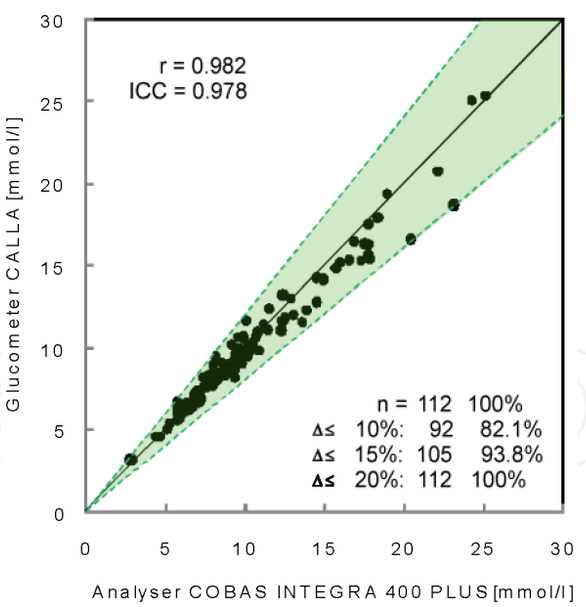

Figure 7.
Correlations (Spearman) between PG estimations on INTEGRA vs. CALLA [19] (2013).

LINUS (Agamatrix, USA) both using glucose oxidase strips; (2) to evaluate diabetes control using Ambulatory Glycaemic Profiles (AGP) and comparing the results with those of the COBAS INTEGRA 400 Plus analyser. There were 112 sets (each from one person) analysed. Means of 3 PG estimations on glucometers and on INTEGRA analyser were calculated.

Strong correlations between PG values estimated on COBAS INTEGRA analyser vs. individual glucometers (CONTOURLINK, CALLA, LINUS) were shown (**Figure 7**).

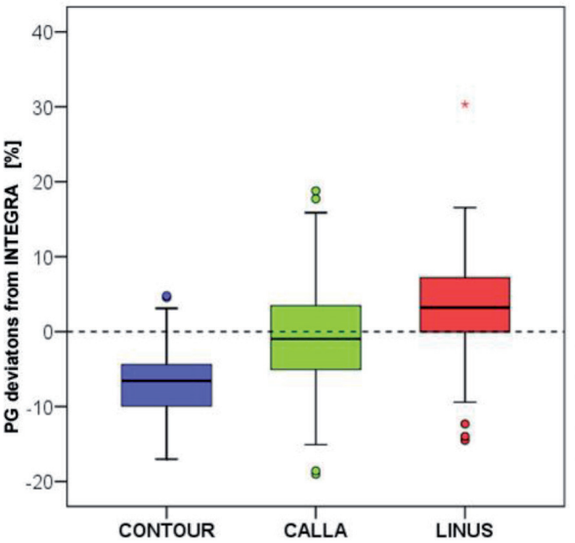

Figure 8.
Relative deviations of glucometer estimations from estimations on analyser Cobas Integra. PG deviations of respective glucometers from INTEGRA PG were within the range ± 15% (i.e. in 94.6%, 93.8%, 97.3% of 112 pairs, resp.) [19] (2013).

Deviations from INTEGRA were within the range ± 15%. (**Figure 8**) PG variability was measured by SD: SD INTEGRA = 0.061 mmol/l, SD CONTOURLINK = 0.256 mmol/l, SD CALLA = 0.290 mmol/l, SD LINUS = 0.286 mmol/l. The mean INTEGRA PG values ranged from 2.7 to 25.3 mmol/l.

All persons with T2D performed 10-point PG profiles to optimise balance between meals, physical exercise, and insulin boluses. PG differences between the respective glucometer-strips system and COBAS INTEGRA laboratory values were in borderline of ISO 15197. [25]. So, the practical acceptability of all tested glucometer-strips systems was demonstrated. Nevertheless, due to different (even though acceptable) accuracy of individual systems, it is advisable to use one type of glucometer-strips system in each diabetes centre. Since 2013 all our patients are trained in SMPG on glucometer CALLA. If insulin pump MINIMED 640 G is used, glucometer CONTOUR PLUS is sometimes preferred due to wireless signal transmission.

2.2.3 Trials for the efficiency of continuous glucose monitoring (CGM)

In 2005–2013 we tested benefits of CGM in three independent studies. Two of them were performed in people with T2D and T1D treated by insulin pumps PARADIGM (Medtronic MiniMed, Nordthridge, CA, USA). One study aimed to patients without insulin pump in perioperative care.

The pump PARADIGM 722 communicates with CGM and enables daily reading of 288 PG values determined by a SENsor inserted into subcutaneous tissue (PARASEN study). Real-time PG values are helpful to adapt further treatment.

2.2.3.1 Single center trial for benefits of CGM vs SMPG (2005–2009)

Aim of this clinical study [36] was to compare the evolution of HbA1c over the 3- month period with CGM vs. a period with conventional SMPG by glucometers.

Two cohorts of T1D + T2D on insulin pumps PARADIGM were investigated.

Cohort 1 comprised 17 persons using CGM sensors for continuous glucose monitoring (CGM group). Cohort 2 comprised 25 people performing self-monitoring as before (3 to 6 times/d) on glucometer LINUS, Wellion, Agamatrix (SMPG group).

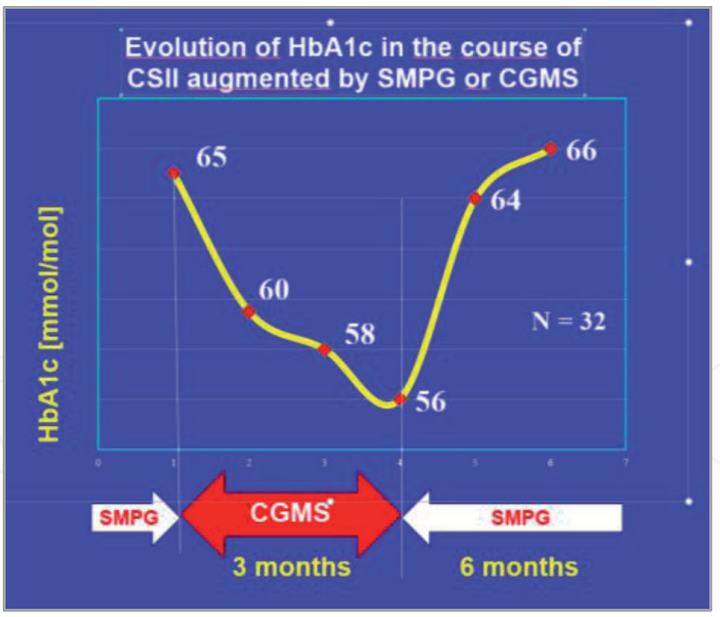

Figure 9.
Benefits of CGM in individuals on insulin pump [36] (2013).

In the CGM group (but not in the SMPG group) HbA1c significantly dropped within one month and remained reduced as long as the CGM was applied, i.e., until the switch back to SMPG. (**Figure 9**).

Hence, continuous glucose monitoring with transcutaneous sensors appeared to be an important measure for improving metabolic compensation in people with diabetes. With CGM, the evolution of HbA1c showed metabolic improvement. The PARASEN study demonstrated that continuous self-monitoring should become a regular part of treatment in educated persons on insulin pumps.

Several years later, the COMISAIR study [37] demonstrated that also a conventional intensive multiple dose insulin regimen (MDI), if supported by CGM, can be a suitable alternative to CGM augmented insulin pump therapy.

2.2.3.2 Multicenter trial on CGM-augmented insulin pump therapy in T1D (2005–2009)

The multicenter CGM study (2005–2009) [38] aimed to the assessment of benefits of CGM-augmented insulin pump therapy for persons with T1D.

Community or academic practices in six Central and Eastern European/Mediterranean countries established a registry of people with T1D starting CGM-augmented insulin pump therapy with the pump PARADIGM® X22 under everyday conditions. We compared HbA1c values before and after 3 months of CGM and assessed relationships between insulin therapy and glycaemia-related variables.

Sensor data and HbA1c data were evaluated in 85 of 102 enrolled persons with longstanding T1D, mean age 33.2 ± 16.9 years. Mean HbA1c declined after 3 months of CGM from 59.0 ± 8.9 mmol/mol at baseline to 50.9 ± 11.7 mmol/mol ($P < 0.001$).

Hence, CGM-augmented insulin pump therapy appeared to improve glycaemic control in T1D in everyday practice settings.

2.2.3.3 The trial for CGM benefits in perioperative care (2009–2013)

Our third CGM study (2009–2013) [39] payed attention to the assessment of implementation of CGM in perioperative care of T2D.

PG monitoring was performed by means of GUARDIAN REAL-Time CGMS (Medtronic, Northridge, USA) in perioperative periods of 20 persons with T2D. Sensor was inserted on the day before surgery and continued for 3 days.

This approach was successful in the intensive care unit setting only. Neither electromagnetic interference nor other side effects appeared. No significant difference between sensor and laboratory analyser values was found. Pearson's correlation coefficients between PG by sensor and by Wellion Linus glucometer during the whole perioperative period were significantly strong (0.9). Hypoglycaemia was registered in 4 of 20 persons.

So, transcutaneous CGM appears to be a safe approach offering a detailed insight into perioperative PG homeostasis. However, confirmation of sensor data by an approved method remains necessary.

3. Clinical trials on effectiveness of preprandial complementary (= supplementary) insulin boluses in T2D

Disturbed dynamics of insulin secretion in T2D (**Figure 10**) makes the need of small complementary preprandial boluses of rapid insulin understandable.

In the years 1991–2019 we carried out three single centre trials to this topic.

3.1 Trial on effectiveness of rapid insulin

In 1991–1994, a nonrandomized uncontrolled study with 251 T2D assessed the effectiveness of supplementary insulin regimen [40, 41]
The complementary insulin therapy using insulin pen MADI started in hospital following the baseline PG profile on day 2. The final ten-point PG profile was performed on day 4. (**Figures 11** and **12**) At a check-up 8–10 weeks later a decrease of HbA1c, BMI and improved lipoprotein-spectrum was found (**Figures 13** and **14**).

We concluded that in T2D better metabolic control can be achieved with complementary insulin therapy than with oral antidiabetic drugs or long-acting insulin 1–2 times daily. Our "surprising" results were based on pathophysiologic concept of Bruns, Berger and Kalfhaus. [7–9] To date, intensive insulin therapy in people with T2D appears to be more accepted in daily routine. [6, 23]

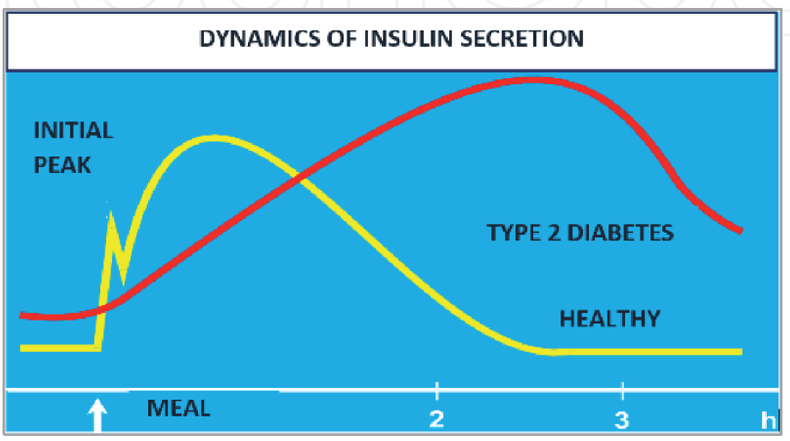

Figure 10.
Dynamics of insulin secretion in blood in healthy people (initial postprandial peak is present, insulin concentration returns to baseline within 3 h); in T2D (missing Initial peak, maximum is delayed and hyperinsulinaemia remains over 3 h) [7] (1995).

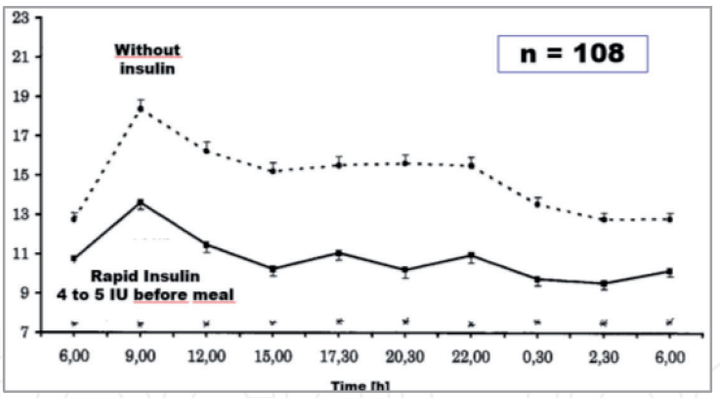

Figure 11.
*Ten- point BG profiles (mean ± SE) in insulin-naïve-T2D treated on baseline with oral antidiabetic drugs and/or diet (upper curve) and then with complementary boluses (4 to 6 U each = 26 U/d) of rapid insulin (lower curve) *P < 0,05. [40] (1997).*

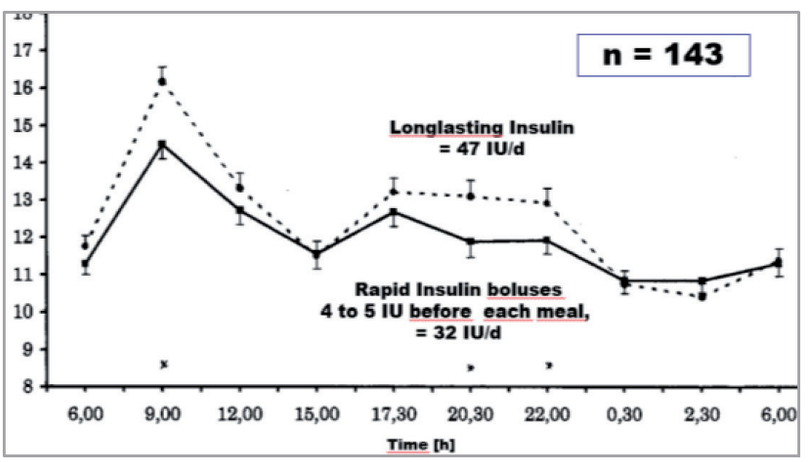

Figure 12.
*Ten- point BG profiles (mmol/l, mean ± SE) in T2D treated on baseline with long-acting insulin (1 to 2 boluses/d = 47 U/d) and/or diet and then with complementary boluses (4 to 6 U each = 32 U/d) of rapid insulin (lower curve) *P < 0,05. [40] (1997).*

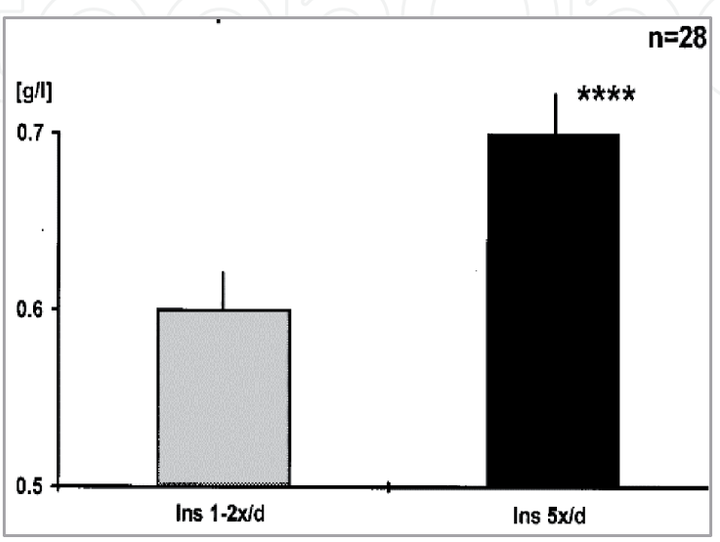

Figure 13.
Lipoprotein apoLpA1 at baseline and after 8–10 weeks of complementary insulin therapy [41] (1997).

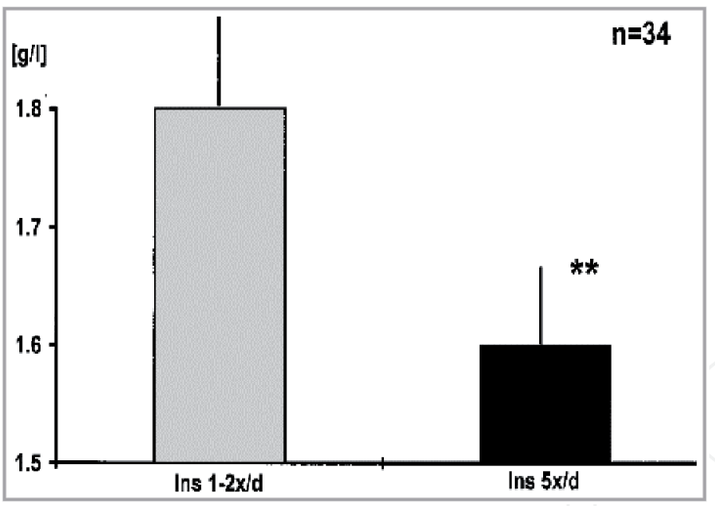

Figure 14.
Lipoprotein apo LpB at baseline and after 8–10 weeks of complementary insulin therapy [41] (1997).

3.2 Trial on effectiveness of complementary boluses of rapid insulin analog

The rapid acting insulin anologs (aspart, lispro and glulisin) are available since the end of the 20th century. Their absorption rates prevail over that of regular human insulin. [42, 43]

The aim of our prospective observational open-label controlled study (2004–2007) [44] was to compare the effects of insulin analog aspart and human regular insulin resulting from their routine administration in small preprandial boluses according to identical algorithms.

Fifty-seven persons with T2D aged 64.0 ± 1.29 (mean ± SE) years, diabetes duration of 12.4 ± 1.06 years, C-peptide positive, were enrolled into the study. Their treatment with human regular insulin lasted 5.2 ± 0.44 years. Human regular insulin was replaced with insulin analog aspart. Two check-ups in the course of 330 ± 11.1- day sequential period were carried out. The control group consisted of 17 persons of equivalent age, duration of diabetes and insulin dosing.

Following the switch from human regular insulin to insulin analog aspart, HbA1c concentration in blood decreased **Figure 15**, while plasma glucose

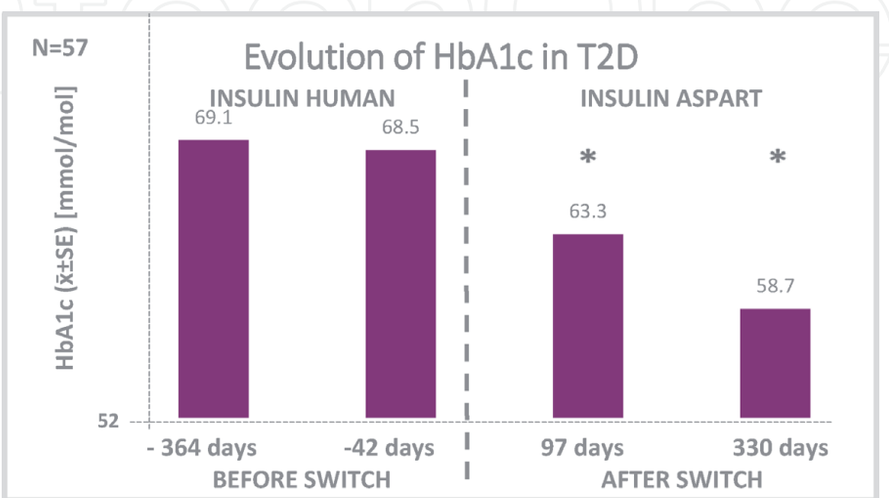

Figure 15.
Impact of insulin aspart (given according the same algorhithms as human insulin) on HbA1c in 57 persons with T2D (P < 0,05) [44] (2007).*

concentrations in 10-point profiles, daily insulin dose, BMI, and frequency of hypo−/hyperglycemic episodes did not change.

No significant influence of insulin aspart on serum concentrations of triacylglycerols, total cholesterol, and LDL-cholesterol was found. Patients' satisfaction was good. No adverse events were recorded. In the control group, no significant changes of baseline HbA1c, insulin dose and BMI were found.

Hence, insulin analog aspart appears to be more effective than human regular insulin in intensive (complementary) treatment in individuals with T2D.

3.3 Trial on effectiveness of Faster (ultrarapid) Insulin ASPart (FIASP)

The benefits of faster insulin aspart (insulin aspart + nicotinamid) were described and discussed. [45, 46]

Aim of our prospective monocentric uncontrolled Real World Evidence study (2017–2019) [47] was to compare the efficacy of FIASP with the efficacy of previous therapy with insulin aspart in people with T1D and T2D on MDI or on insulin pump.

No adverse events appeared in any group. In T2D groups (N < 24) an unsignificant tendency to reduction of PG, MPG, HbA1c, body mass and total daily dose of insulin in the course of FIASP therapy was shown.

So, only the evidence of noninferiority of FIASP versus insulin aspart was demonstrated. Introduction of improved algorithms together with intensive patients´ education appears necessary to improve the expected outcomes of FIASP therapeutic regimen.

4. Trial on effectiveness of Continuous Subcutaneous Insulin infusion (CSII) vs. multiple boluses of rapid insulin analog plus once daily basal insulin in T2D

The effectiveness of CSII in T2D was sought for in many previous studies [48–52]. Our (Medtronic supported) prospective single-centre randomized study (2011–2014) [53–55] recruited 36 insulin-resistant, C-peptide-positive, glutamic acid decarboxylase antibodies (GAD Ab)-negative, and CSII-naive patients with T2D (eight screen failures). Insulin treatment was optimized with insulin analogs and metformin. Following the run-in period, patients were randomized into two arms: a CSII arm (n = 11) and an MDI continuation arm (n = 12). HbA1c ≥ 64 mmol/mol, (mean ± standard deviation), age of 57.2 ± 8.0 years, BMI of 36.2 ± 7.0 kg/m^2, BM of 106.9 ± 18.3 kg, diabetes duration of 13.3 ± 4.7 years, and HbA1c of 80 mmol/mol). In both arms, at the CSII start the daily insulin dose was reduced by 10% –50% in order not to exceed 80 U/day. After 6 months, persons receiving MDI crossed over to insulin pump and both arms were followed up during consequent 6 months. A total of 10 scheduled visits were carried out in each arm. The final Visit 10 occurred at 12 months. The mean frequency of self-monitoring varied between 3.4 and 5.4 measurements per day.

Patients assigned to the CSII arm (N = 11) achieved a significant HbA1c reduction of 10–12 mmol/mol while reducing their daily insulin dose by 33% of baseline; BMI reduction was 0.86% of baseline. No significant changes were revealed in patients on MDI **Figure 16**.

So, the use of insulin pump (supported with SMBG) in T2D is safe and effective for improving glucose control and reducing daily dose of insulin. Treatment adherence and satisfaction were excellent. All subjects decided to continue using their insulin pumps. On the other hand, an optimum metabolic balance and sustainable reduction in body mass, blood pressure or lipid profile in most of the patients could not be reached.

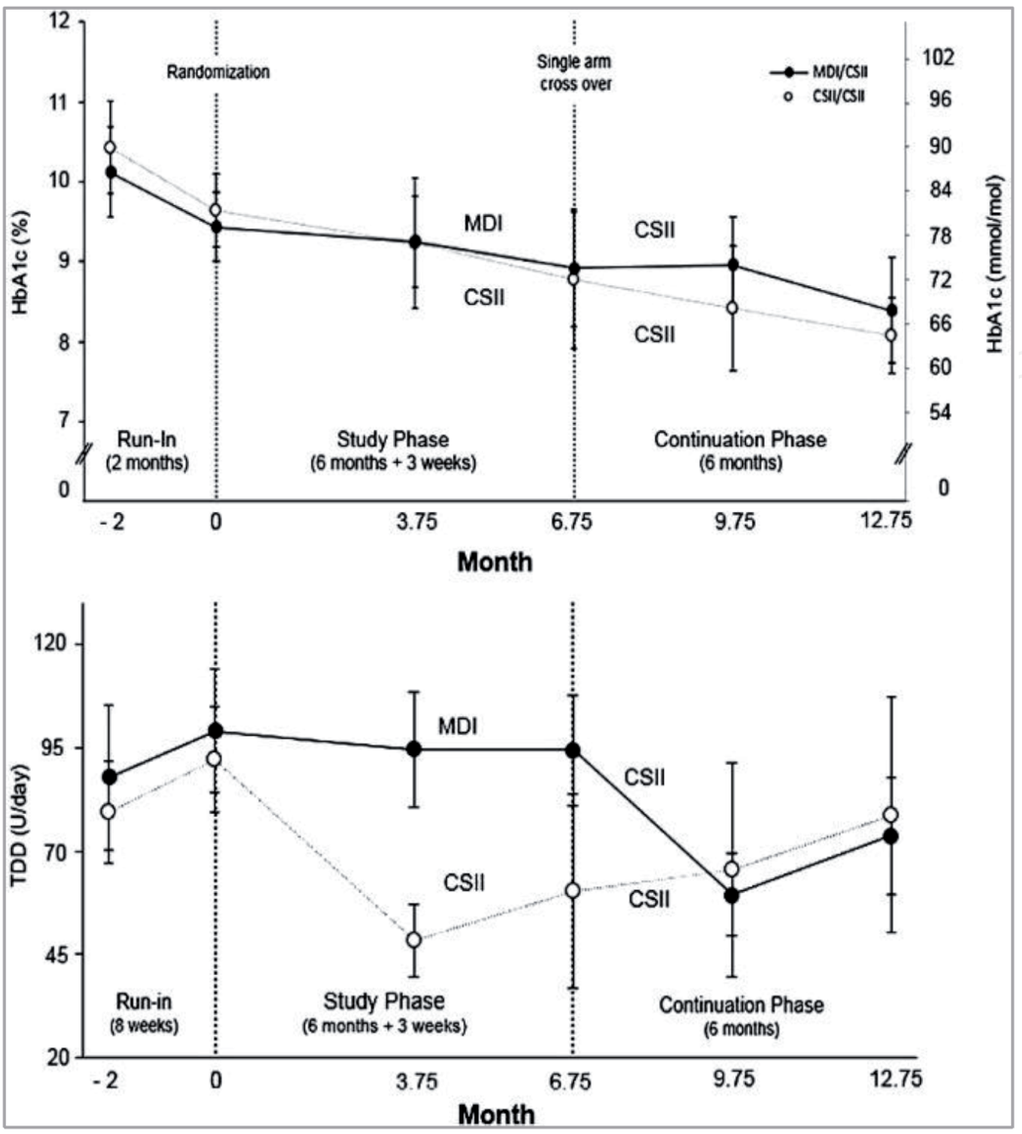

Figure 16.
HbA1c (top) and total daily insulin dose (bottom) in the MDI/CSII arm (N = 11, closed symbols) and in the CSII/CSII arm (N = 11, open symbols). Symbols and bars - mean and 95% CI (confidence interval); CSII - continuous subcutaneous insulin infusion; MDI - multiple daily injections [55] (2017).

5. Case reports targeting incretin analogs/GLP-1 receptor agonists

The first incretin analogs exenatid [56], lixisenatid, liraglutide were used in persons with T2D to improve metabolic control and to reduce body mass - mostly when HbA1c exceeded 60 mmol/mol, BMI was over 35 kg/m2 and oral antidiabetic drugs failed. Their beneficial metabolic and cardiovascular effects were described recently in RCTs LEAD 1 – LEAD 6 [57–62] and LEADER. [63] We had the option to confirm their benefits in several persons.

5.1 Effects of liraglutide on body mass and HbA1c

Our case report from the year 2010 [64] demonstrates the benefits of treatment with liraglutide in a 57-year old obese woman (adequately treated for hypothyreosis) with recent evolution of metabolic syndrome. Four-month metformin (M) and liraglutide (L) therapy reduced both body mass index (**Figure 17**), and glycated haemoglobin (**Figure 18**) Even though the previous diabetes control was acceptable, the treatment with high doses oť metformin and sitagliptin (S) failed to reach sufficient reduction of body mass and HbA1c.

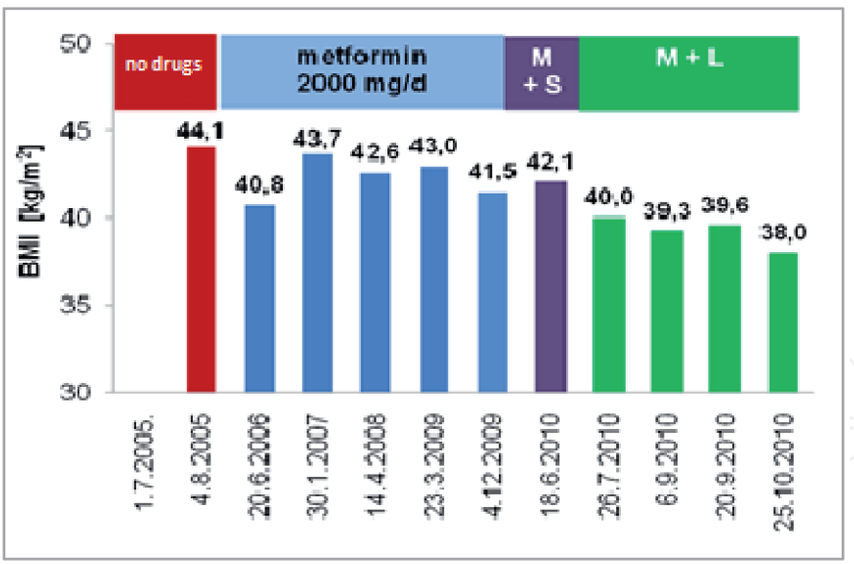

Figure 17.
Lady, age 57. Therapy and evolution of BMI since the detection of T2D in 2006. M-metformin, S-sitagliptin, L-liraglutide (L-start 18.8.2010) [64].

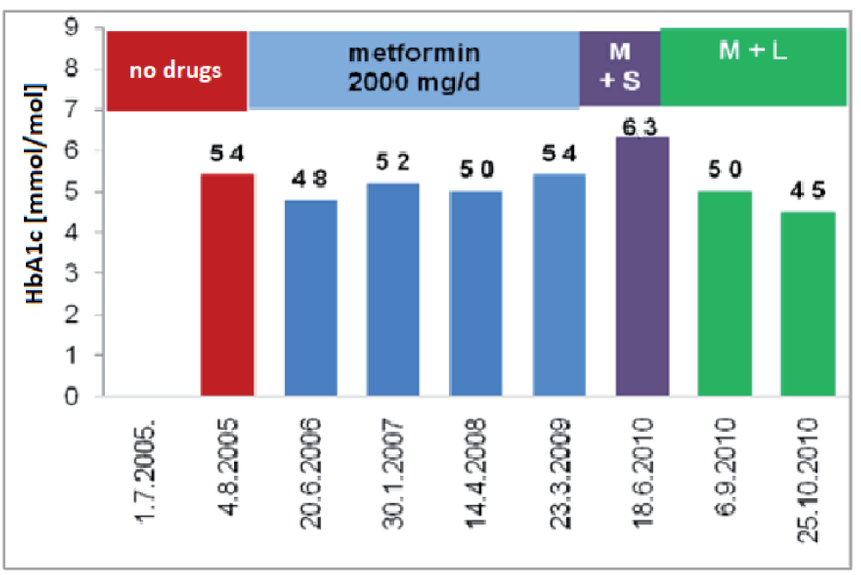

Figure 18.
Lady, age 57. Therapy and evolution of HbA1c since the detection of T2D in 2006. M-metformin, S-sitagliptin, L-liraglutide (L-start 18.8.2010) [64].

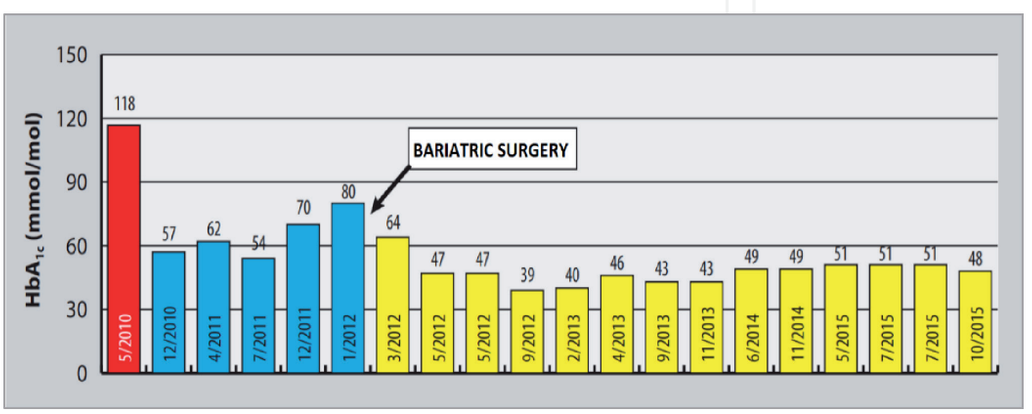

Figure 19.
Man, age 57 y, T2D duration 13 y. Evolution of HbA1c with liraglutide and metformin before (2010–2012, blue) and after (2012–2015) bariatric surgery [65] (2015).

5.2 Effects of liraglutide and bariatric surgery

Our second case report (2010–2016) [65] deals with a temporal positive influence of a 5-year liraglutide therapy on HbA1c (**Figure 19**), BMI and 10-point glyceamic profile in a man with 13-year history of uncontrolled T2D. After one year on liraglutide 1,2 mg/d + metformin 2000–3000 mg/d, the initial decrease of BMI and HbA1c was followed by their slow increase. Following bariatric surgery, the continuing liraglutide and metformin treatment resulted in near-normal HbA1c concentrations not exceeding 51 mmol/mol. The BMI decreased from 39 to 32 kg/m^2.

5.3 Effects of liraglutide in T2D prevention

The purpose of this case report (2011) [66] is to demonstrate the effects of 5-month off label administration of L and metformin (M) in a 60y old woman with impaired fasting plasma glucose (IFG), BMI 36.4 kg/m^2, HbA1c 41 mmol/mol and in excellent physical condition. Since 2005 her body mass increased by 10 kg. Recently diagnosed hypertension was successfully treated by metoprolol and losartan (BP 140/80 mmHg, HF 64/min). She was treated by simvastatin since 2008 (LDL cholesterol 3,4 mmol/l). Proinsulin, C-peptide, TSH. T3, T4 and routine laboratory parameters were found within normal limits. Results of SMPG using glucometer Linus, Agamatrix, USA were slightly abnormal. In August 2010 the therapy with L and M started. First evaluation was made in January 2011 (**Figures 20** and **21**). In 2012 – 2014, L 1.2 mg/d was given only during a 3- month period each year. Then, M 2 g/d continued without L. Food intake was reduced due to lasting satiety. The final check up in February 2021 revealed excellent clinical condition, BM 66.1 kg, BMI 29.4 kg/m^2 and HbA1c 39 mmol/mol.

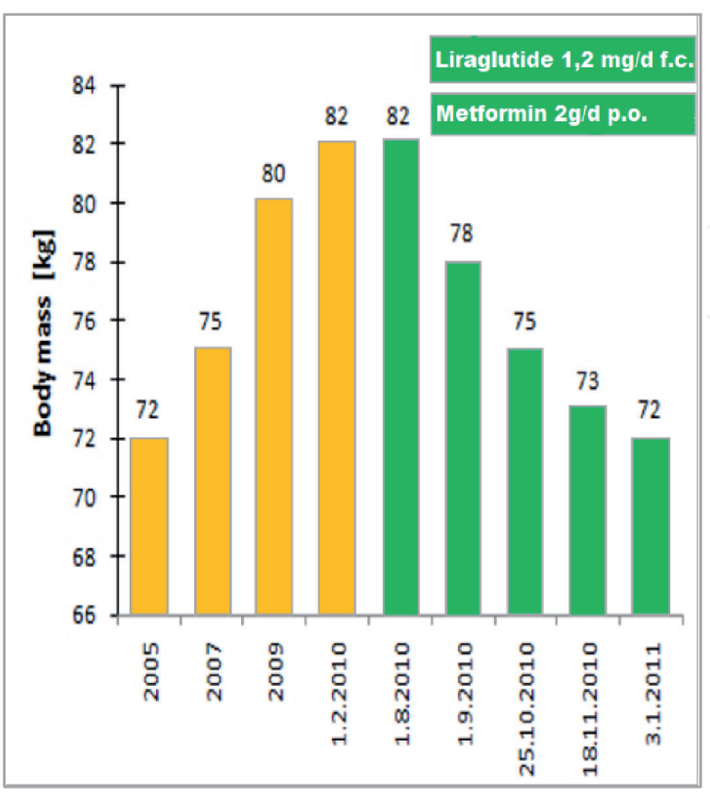

Figure 20.
Lady, age 60 y, prediabetes. Evolution of body mass before and with L + M [66] (2011).

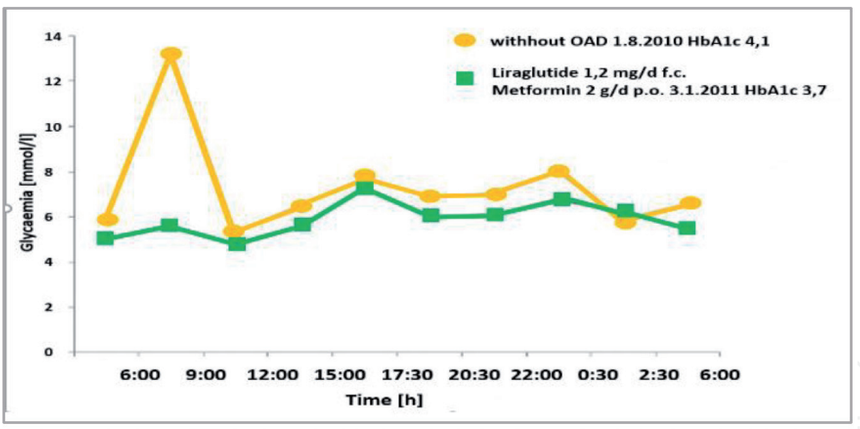

Figure 21.
Lady, age 60 y, prediabetes. 10-point PG profile before and with L + M [66] (2011).

Independently, 4 of other 6 obese persons with IFG/IGT reduced body mass during L supplementation. So, L therapy appears to be a potentially effective approach to prediabetes conditions and its administration should start rather at an early stage.

5.4 Effects of once weekly semaglutide on HbA1c, body mass and well-being

Effects of long-acting incretin analogs (exenatid QW, dulaglutid [67] and semaglutide [68–77] on metabolism, cardiovascular and renal protection were described in clinical studies REWIND and SUSTAIN 1–10, resp.

Our case report (2019–2020) [78] brings insight on benefits of semaglutide in a 79-year-old lady with long-lasting T2D. She has been suffering from both metformin intolerance and insulinofobia. In the course of a long- lasting period of gliptin therapy, the patient's HbA_{1c} concentration increased to 61 mmol/mol. During the following 4-month period with semaglutide, the patient's mean PG concentration

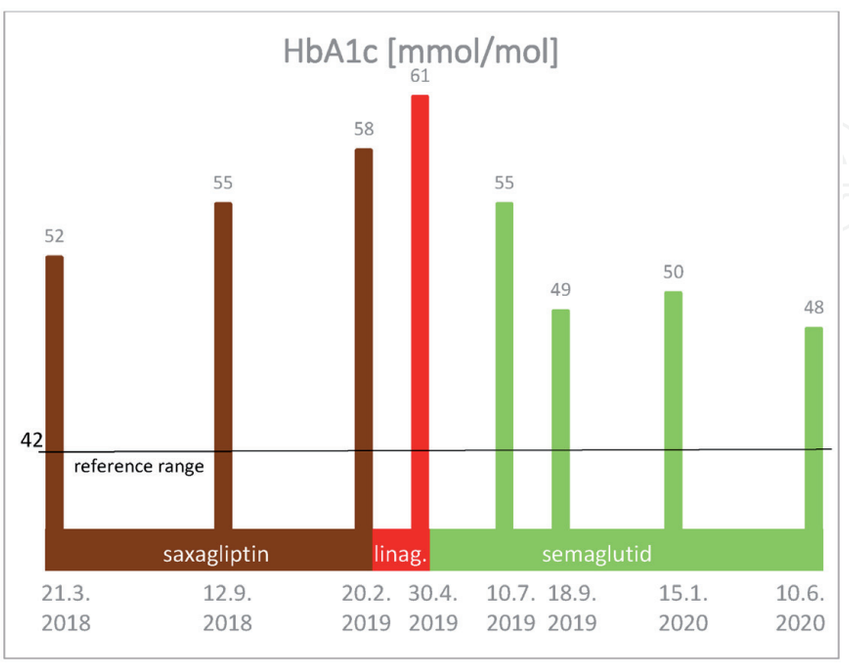

Figure 22.
Lady, age 79 y. Evolution of HbA1c in the course of treatment with saxagliptin, linagliptin and semaglutide, resp., 2018 to 2020 [78].

of a 10-point daily profile (MPG) decreased from 7.4 mmol/l to 7.0 mmol/l, and her body mass from 80,9 kg to 77,7 kg. One year later, the HbA1c reached 48 mmol/mol (**Figure 22**). No adverse events appeared. We can conclude, the early indication of once-a-week subcutaneously administered semaglutide resulted in improvement of all investigated parameters of saccharide metabolism.

5.5 Effects of fixed combination of insulin degludec and incretin liraglutide (IDegLira)

Metabolic and cardiovascular benefits of the fixed combination IdegLira were evaluated in studies DUAL and others. [79–87]

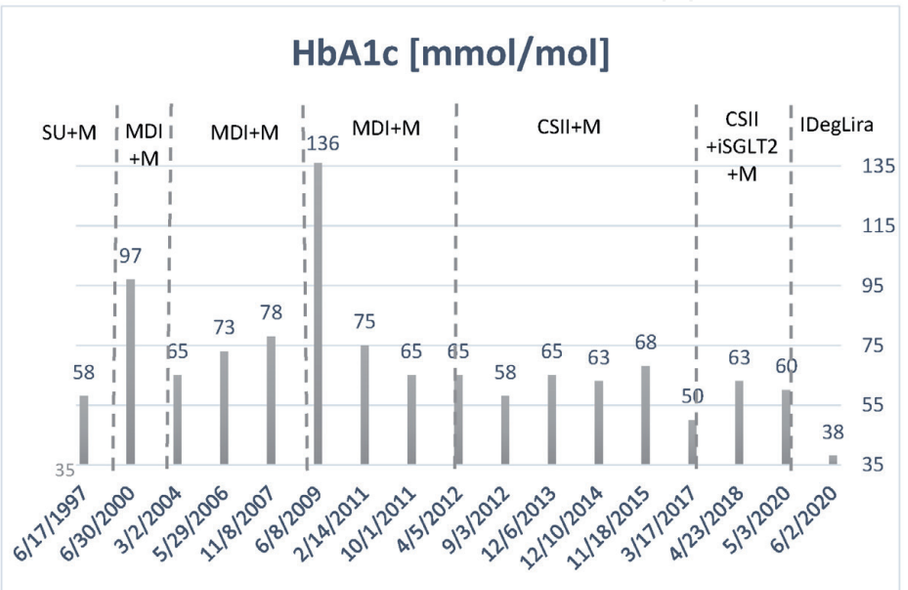

Figure 23.
Lady, age 77 y, T2D since 1985, cast away syndrome. Evolution of HbA1c in the course of different therapy (MDI-CSII-CSII with iSGLT2-IDegLira only) (1997–2020) [88].

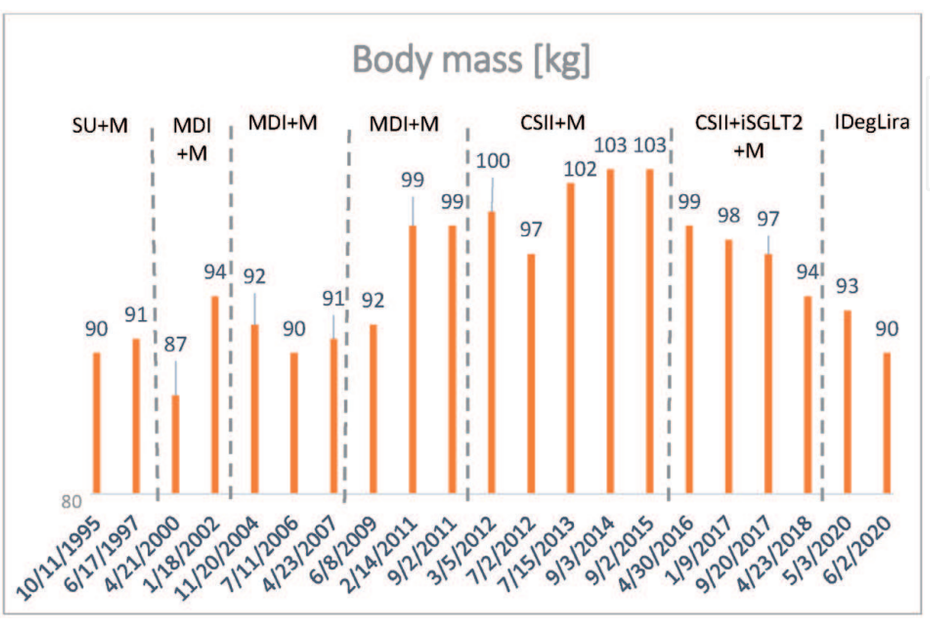

Figure 24.
Lady, age 77 y, T2D since 1985, cast away syndrome. Evolution of BM in the course of different therapy (MDI-CSII-CSII with iSGLT2-IDegLira only) (1995–2020) [88].

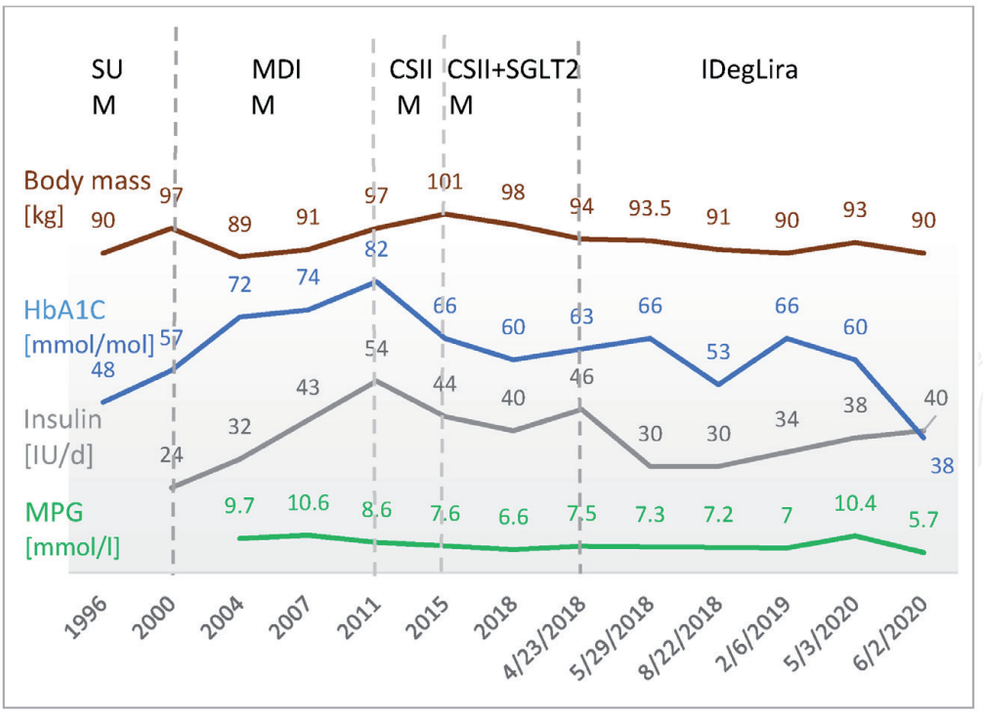

Figure 25.
Lady, age 77 y, T2D since 1985, cast away syndrome. Overview of all parameters (HbA1c, BM, insulin/day, MPG) in the course of different therapeutic regimens (MDI-CSII-CSII with iSGLT2-IDegLira only) (1996–2020) [88].

We deemed IDegLira could be an option for T2D suffering from impaired cognitive functions. We described this condition as "cast away syndrome".

Our case report (1995–2020) [88] pays attention to IDegLira in a 77-year-old woman with T2D. Her diabetes was treated for 33 years (since 1985) including the last seven- year period of effective insulin pump therapy, finally combined with dapagliflozin. Recently, signs of cognitive deterioration ("cast away syndrome") appeared and the patient was unable to operate her insulin pump. Adding IDegLira to previous metformin and dapagliflozin therapy alongside with support of educated family lead to improvement of patient's condition. The final in-patient period (30. 4. - 1. 7. 2020]) with IDegLira 40 IU/d (no CSII, no metformin, no gliflozin) and specialized diabetes care of nursing staff resulted in reduction of HbA1c to 38 mmol/mol (reference range 20–42 mmol/mol) (**Figures 23–25**).

6. Trial on effectiveness of dapagliflozin in uncontrolled T2D using insulin pumps

Gliflozins are inhibitors of sodium glucose co-transporter 2 (SGLT2) in proximal part of renal tubules. Their influence results in lowering of the renal thresholds for glucose and lowering of hyperglycaemia (due to urine excretion of about 70 g glucose per 24 h). Impact of gliflozins (dapagliflozin [89–91], empagliflozin [92] canagliflozin [93–95] and ertugliflozin) on metabolic control and cardiovascular and renal outcomes in T2D was demonstrated in trials EMPAREG, EMPEROR, CANVAS, CREDENCE, DECLARE HF, DECLARE Timi 58 and VERTIS. Benefits were observed in simultaneous therapy with insulin/incretin and gliflozin. [96]

Our pilot prospective trial (2015–2017) [97] aimed to the assessment of effectiveness of dapagliflozin added to people with T2D treated by CSII and metformin (M). A group of 13 T2D on CSII, without serious complications, aged 44.6–70.4 y, diabetes duration 5–26 y, BMI 24.9–57.6 kg/m2, were monitored at 4 visits (before

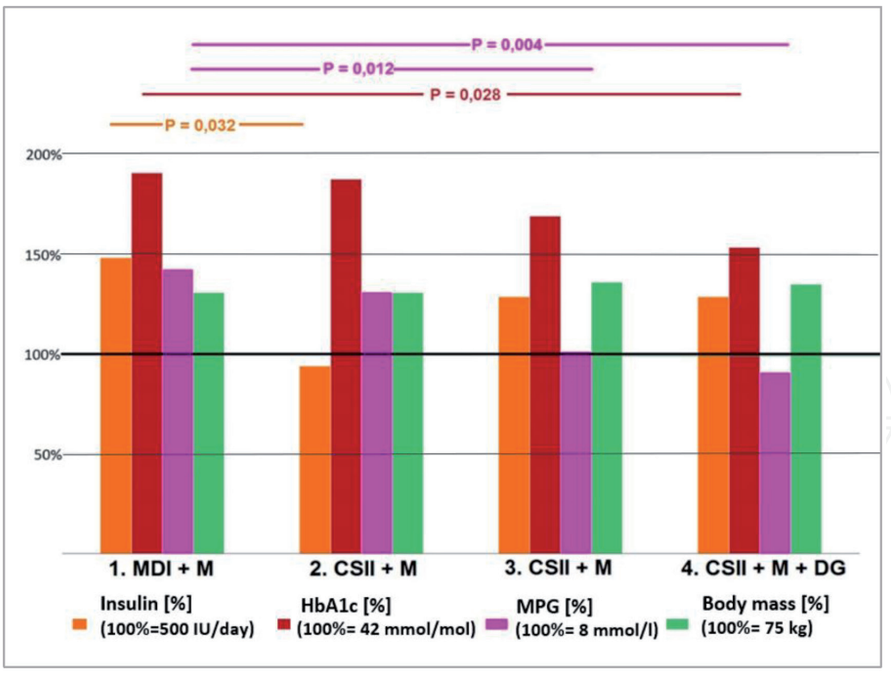

Figure 26.
A group of T2D (N = 13) treated with 3 consequent regimens: 1. MDI + M, 2. CSII+M, 3. CSII+M + DG. Evolution of relative values of INS/d, HbA1c, MPG, BM. Upper border of the reference range of respective parameter was defined as 100% of its value (2015–2017) [97].

CSII, on CSII + M, on CSII + M shortly before dapagliflozin and finaly on CSII + M after 2.5–11.0 months with dapagliflozin.

CSII appeared to enable reduction of total daily insulin dose with no consequent change of HbA1c and glycaemia. Adding dapagliflozin to CSII resulted in significant reduction of HbA1c. (**Figure 26**) Even though the change in BM was not significant, Spearman analysis revealed correlations between the change of daily insulin dose and change of BM at visit 3 and 4 vs. visit 1.

No side effects appeared. So, dapagliflozin may be considered as a rational therapeutic addition to CSII + M treated people with T2D.

7. Conclusions

This chapter summarizes the authors' experience along with outcomes of respected randomized control trials and real world evidence studies. It became clear that the pathophysiologic approach comprising insulin, incretins and gliflozins has created a reliable base to effective treatment of type 2 diabetes. Reduced morbidity and mortality along with other breaking reports [98–101] are offerring some great perspectives.

On the other hand, in everyday practice, hidden clinical inertia, resulting from outdated treatment approach, customs, imbalance between powerty and affluency, should be considered as a dangerous rival.

So, which direction do we take from here?

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performance of therapeutic protocols including HbA1c and 10-point glycaemic profiles, H.Z. was responsible for medical reports, files and IT operations, B.D. took care of laboratory investigations. There is no conflict of interests.

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Dedication

Taking into account the dawning observations of Paul Langerhans (1847–1888) [102], Oskar Minkowski (1858–1931) [103], George Ludwig Zülzer (1870–1949) [104], Ernest Lyman Scott (1877–1966) [105] and others in [106, 107], this paper was written in the memory of Nicolae Constantin Paulescu (1869–1931), James Bertram Collip (1892–1965), Frederick Grant Banting (1891–1941), Charles Herbert Best (1899–1978) and John James Rickard Macleod (1876–1935) on the occasion of the 100-year anniversary of insulin (pancrein) discovery (Bucharest, May 1921) [4], and its purification and implementation to human medicine (Toronto, January 1922) [5].

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