Gravicentric approach to Type 2 Diabetes therapy. The success prediction. A proof-of-concept

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This study is the proof-of-concept of our "Gravicentric" theory. This concept is based on several fundamental points: obesity as the main foe; rapid reversibility of the disease; as well as a new perspective on the roles different pharmacological classes play in general, and the role of insulin and GLP-1 analogs, in particular. The paper presents and discusses our experience of the implementation of insulin and GLP-1 analogs. The possibility of "insulin weaning", the therapeutic approach for over-treated patients, and physiological dosing of insulin are all discussed therein.

OBJECTIVES
Primary To evaluate the long-term efficacy of GLP-1 analogs in insulin-treated Type 2 Diabetes Mellitus (T2DM) patients.
Secondary To analyze which patient would most likely benefit from this combined treatment.
METHODS
In 54 T2DM patients with a mean disease duration of 17.5 years and a mean extent of insulin therapy of 4.5 years, additional GLP-1 analogs therapy was prescribed. Mean duration of GLP-1 treatment was 25.8 months (2.15 years).

During the intervention, clinical, biochemical, and anthropometric parameters were analyzed. Compliance, Hypoglycemia and Metabolic Index (MI) assessments were implemented.

ABBREVIATIONS:

GLP-1 – Glucagon-like peptide-1
T2DM – Type 2 Diabetes Mellitus;
MI – Metabolic Index;
BMI – Body Mass Index;
TDI – Total Daily dose of Insulin;
IBT – Incretin-Based Therapies;
CGMS – Continuous Glucose Monitoring Systems;
SU – Sulfonylurea;
OAD – Oral Antidiabetic Drug;
BG – Blood Glucose;
SMBG – Self-monitoring of Blood Glucose;
CVD – Cardiovascular Disease

RESULTS

Mean Glycated hemoglobin (HbA1C) decreased from 9.28 ± 1.43 to 8.54 ± 1.4% on GLP-1 analogs, p < 0.01. Total Daily dose of Insulin (TDI) showed considerable reduction: 80.6 ± 42.7 U/day before starting GLP-1 vs.41.0 ± 30.7 U/day on GLP-1, p< 0.01. These changes were directly linked to weight loss: BMI has dropped from 35.1 ± 4.8 kg/cm^2 before, to 32.8 ± 5.0 kg/cm^2 on GLP-1 analogs, with patients losing 6.7 kg on average. Moreover, 13 (24%) participants discontinued at least one kind of insulin, while 7 (13%) stopped taking insulin completely, with simultaneous improvement in diabetes control. No clinically significant hypoglycemia was observed.

Post-hoc, the participants were categorized according to each patient's ability to reduce TDI by more than 20 U/day, and then split into two groups. Group A – 34 patients (64.2%) who successfully reduced TDI; Group B – 19 patients (35.8%) who failed to do so. The comparison of the two groups showed the following:

1. Significantly larger – virtually twice as large – baseline TDI in Group A (97.4±40.4 U/day vs. 52.2±31.0 U/day), p< 0.001.

2. Very effective BMI reduction (ΔBMI 3.3 ± 2.4 kg/cm^2 vs. 0.9 ± 1.2 kg/cm^{2,} p< 0.001) and much better compliance (1.4 ± 1.1 vs. 2.2 ± 1.0, p< 0.02) in Group A.

3. A considerable decline of insulin requirements in group A, on GLP-1 therapy (ΔTDI on GLP-1 was -62.4 ± 31.9 U/day) with no TDI reduction in Group "B" (ΔTDI on GLP-1 was +0.03 ± 14.1 U/day, p< 0.001).

Thus, in spite of the fact that on GLP1 therapy HbA1C has declined to the same levels in both groups, patients from group A became much leaner and metabolically healthier.

We suggest overtreatment as the critical factor of obesity in Group A.

CONCLUSIONS

Adding GLP-1 analogs to insulin in poorly controlled, insulin-treated T2DM patients resulted in an impressive weight (BMI) reduction with significant improvements in glucose control. This provided for a further decline in insulin resistance and insulin requirements. We suggest that the best candidate for successful GLP-1 analogs therapy is an obese, overtreated and compliant T2DM patient. Changes in Metabolic Index (MI) rather than surrogate glycemic parameters (HbA1C) are better predictors of a successful T2DM therapy. Neither the duration of diabetes nor the length of insulin therapy in the past is likely to have a critical role in predicting success. These findings are proof-of-concept of our Gravicentric theory in T2DM.

INTRODUCTION

We live in a fascinating era, where a real revolution in the treatment of Type 2 Diabetes Mellitus (T2DM) is being observed. This revolution involves three new players. Namely, these are Incretin-Based Therapies (IBT), latest modifications of Bariatric Surgery techniques and finally, extensive use of CGMS (Continuous Glucose Monitoring Systems) in a wide clinical practice [1]. These three events provided us with entirely new insights into the T2DM pathogenesis, therapeutic approaches and curability of the disease.

Thus, in the light of the great success of Bariatric Surgery, rapid reversibility of T2DM became a routine [2–7].

Although different theories attempt to explain this success, most investigators lack a complete understanding of the underlying pathophysiological processes active in T2DM reversibility. Instead, they try to clarify this phenomenon in other ways, such as accentuating some known and unknown insulin-stimulating factors, like incretins, and even changes in intestinal microbiota which are presumed to occur after Bariatric Surgeries.

However, the problem lies in the fact that T2DM remission is frequently observed at the very early stages of intervention, usually even before the patient has lost his first 10 pounds, and very often at the point of preparation to the surgical procedure, when a very low-calorie diet is commonly prescribed. The fact that such dramatic changes occur in such a narrow time frame, contradicts the theories about the "magic touch" of the surgeon, microbial changes, and other intriguing explanations [8–10].

We have recently proposed an energetic (Gravicentric) concept of T2DM pathogenesis and therapy [11, 12]. This concept is key to a better understanding of the underlying processes in T2DM and allows us to revise the traditional (Glucocentric) approach to the perception and therapy of the disease. The fundamental points of this concept are: obesity as the primary foe; rapid reversibility of the disease; energy surplus as the main player and trigger of insulin resistance, which in turn, is rapidly reversible with energy balance restoration; preference for anti-energetic drugs implementation (such as Metformin, Incretin- based therapies (IBT) etc.); avoidance of pro-energetic medications such as Sulfonylurea (SU), Glinides, TZD's and supra-pharmacological doses of insulin, whereas reversal of overnutrition, lessening adipose tissue mass, and healing the β cells become our treatment priorities. Moreover, we view insulin resistance as a defensive mechanism against rapid body destruction by chronic energy surplus [13, 14].

IBT and specifically, GLP-1 agonists, appear as an almost ideal solution to the problem. Indeed, GLP-1 agonists affect main pathogenetic mechanisms of T2DM in several ways which include: decreasing calorie intake and promoting weight loss; slowing down the gastric emptying; while assisting in Glucagon suppression; reversing insulin resistance; stimulating insulin secretion; and even β- cell recovery. The beneficial cardiovascular effect of these drugs is well established today [15–17].

We, therefore, asked: if our concept is true, can we revert T2DM without any surgical intervention? Moreover, if true, can we do it in patients who were unambiguously defined as "failures" due to their long-standing uncontrolled T2DM and extended (years) insulin therapy?

MATERIALS AND METHODS

Study design and methods

The study involved all 54 T2DM patients from Diabetes Institute, Maccabi health fund, Petah-Tiqwa, Israel, suffering from long-standing (mean duration of 17.1 years) and uncontrolled diabetes (mean HbA1C, before new therapies were added, was 9.28 ± 1.43%) whose therapy included the concomitant application of insulin and GLP-1 analogs. The study was conducted during 2007-2014. In August 2014, the study was closed, and patient's files were analyzed.

All these patients were previously treated according to the standard "Treat to failure" Glucocentric schemes [18] and reached a "failure" state where multiple and combined therapies were unable to control their long-lasting disease. Afterwards, all of them were on insulin, receiving one to several injections per day, combined with other oral antidiabetic drugs (OADs).

Most of these diabetic persons were previously informed by medical staff that their pancreas had stopped working and could no longer produce sufficient insulin. This "β-cell atrophy and destruction" was presented by diabetes educators as "irreversible". Thus, patients were treated for years (mean duration of insulin therapy was 4.7 years) with different types of insulin.

With such an intensive therapy background, patients were severely obese (mean BMI = 35.1 ± 4.8), while most of them have continued gaining weight.

Objectives

Primary: To evaluate the long-term efficacy of GLP-1 in insulin-treated T2DM patients.

Secondary: To analyze which patient would most likely benefit from this combined treatment.

Methods

Fifty-four T2DM patients who already were on insulin therapy, were prescribed an additional treatment with GLP-1 analog – Liraglutide. Patients continued their follow-up in Diabetes Institute, Maccabi health fund, Petah–Tiqwa, Israel. Therapeutic changes, in accordance to our Gravicentric algorithm [11, 12], included not only a simple addition of GLP-1 but also stopping all pro-energetic (hypoglycemic) oral drugs and TZDs. Insulin was combined with Metformin in all participants, while most of them were also treated at baseline with other Oral Anti-Diabetes therapies (OADs), such as Sulfonylurea (SU), Glinides, Acarbose (Alpha-Glycosidase Inhibitors), TZDs, and DPP-4 inhibitors. Metformin therapy remained at the maximal allowed doses (usually 2500mg/day) until contraindicated. In parallel, energy-sparing medications (SU, TZDs, and Glinides) were stopped immediately after GLP-1 administration. Voluntary insulin dose elevation and "titration" was strictly prohibited.

Insulin doses were adjusted to reduce the probability of hypoglycemia. This provided the patients with the unique opportunity of "Hypoglycemia-free" life, facilitating their ability to lose weight, all the while they were allowed to eat only when they felt hungry (see "Dietary and lifestyle recommendations" below).

As long as the patient had a very low probability of hypoglycemia due to insulin dose adjustments, the absence of "titrations" and avoidance of concomitant energy-sparing medications, some unique diet and lifestyle guidelines were implemented.

The patients were permitted to skip meal while not hungry.

All participants received an explanation regarding their disease from an energetic point of view, strongly emphasizing the goal of overcoming obesity. The theoretical possibility of diabetes remission and "insulin weaning" was discussed, albeit no promises were given.

The follow-up included regular (about once in three months) visits to the doctor, a diabetes nurse, and a dietitian. Once switched to combined therapy (GLP-1 and insulin), patients were asked to strive towards reducing their weight. This included patients weighing themselves regularly at home while adhering to a low carbohydrate (CHO) diet.

As for the investigated measures, in each parameter, the mean value of the three last measurements just before switching to GLP-1 was compared to the mean value of the three last measurements on GLP-1 therapy.

Dietary and lifestyle recommendations

All patients were explained that their body mass (and not specific glucose levels) – is the primary target. So as to avoid old habits of defensive eating, all instructions were made under the motto: "There is only one reason to eat: the feeling of hunger". The main principles of this approach are summarized as follows:

1. Personalized instructions. During each patient's first visit, the dietitian performed a thorough personal data collection, including a psychological portrait, detailed eating anamnesis, and habits, as well as the patient's lifestyle and the nature of his/her occupation.

2. Preference for a low CHO menu. As opposed to regular low CHO diets, which count vegetables as CHO, our guidelines did not do so. In fact, one of the instructions specifically said: "the more vegetables – the better!". Patients were guided to

have vegetables of five different colors on their plate at each meal – three times per day on average.

3. In cases where the patient's habits at baseline had a CHO ingestion of almost 100%: gradual changes were made to minimize CHO ingestion, while simultaneously preventing a patient's failure to adhere to a strict menu.

4. Patients were advised to prefer the CHO in specific foods, such as lentils, whole grains, whole grain bread, and foods containing a high amount of dietary fibers.

5. No calorie counting. Instead, patients were instructed according to the average gastric volume of a healthy person, which is 500cc. We chose to work with food volumes, which in turn were gradually decreased during the follow-ups.

6. Meal schedule. The timing of meals was selected on an Individual basis, by the maximal activity periods of each patient.

7. The time gap between meals. The minimal gap between meals was 3 hours. No maximal limit of fasting duration was indicated.

8. Obligatory physical activity. Aerobic activity was preferable, and so it was the most recommended activity, with some additional minimal anaerobic (muscle strength) exercises. Consulting with a sports trainer was strongly recommended, albeit we do not provide this service at our Diabetes Institute. Patients were required to walk 3–4 hours per week as part of their required aerobic activity.

Definition of remission

Normalization of glycemia (HbA1C ≤ 7%) together with complete insulin discontinuation ("insulin weaning") was defined as a remission of diabetes. Normalization of glycemic status (HbA1C ≤ 7%) with a significant reduction of insulin dose (more than 25% of basal TDI) and substitution of Multiple Daily Injections (MDI's) by one insulin injection only was defined as a partial remission of diabetes. Our compliance Score and Hypoglycemia Assessment were successfully used in our previous works: [19, 20].

Compliance assessment

When at least two of the four following parameters were met, the patient was considered as incompliant:
- Patient has missed two or more appointments at the diabetes clinic during the last year.
- Patient has not provided self-monitoring of blood glucose (SMBG) results at least twice during the last year.
- Low compliance with diet and physical activity.
- Patient has not measured postprandial blood glucose (BG) during the last year.

Table 1.
Hypoglycemia assessment score

Табл. 1.
Система градации тяжести гипогликемии по оценочным баллам

Score	Hypoglycemia frequency
0	No hypoglycemia episodes
1	Less than 1 episode/month
2	1-3 episodes/month
3	1 episode/week
4	2-4 episode/week
5	5 or more episodes per week

Hypoglycemia assessment

All hypoglycemia events were divided into severe (patient required assistance) and non-severe. Non-Severe hypoglycemia was assessed according to the following score (Table 1).

Metabolic Index (MI)

A new parameter of metabolic health in T2DM

While Hemoglobin A1C (HbA1C) is associated with increased risk of cardiovascular events, its use in the prediction of cardiovascular disease (CVD) events in combination with conventional risk factors has not been well defined [21].

Deciding on including novel risk markers in risk assessment remains a topic of intense debate and research [22– 24].

The focus of health systems worldwide on glycemic indicators, i.e., HbA1C levels – the therapeutic approach is known as "Glucocentrism" – has improved glycemic levels in the population during the last decade, mainly via therapeutic intensification. Indeed, more patients reach the target HbA1C level, which is less than 7%, but without any apparent benefits regarding cardiovascular (CV) complications [25–28].

Meanwhile, growing evidence indicates that cardio-metabolic risk factors – obesity, hypertension, and dyslipidemia – rather than hyperglycemia per se, are the principal culprits for CV complications among type 2 diabetes mellitus patients, particularly in young adults [29].

There is currently a strong need for a new way to measure T2DM treatment quality, which would help predict CV risk and prevent possible patients' overtreatment [30–32].

On the other hand, energy surplus, which results in obesity and high BMI, strongly correlates with the main components of metabolic syndrome – adiposity, hyperlipidemia, hypertension, proteinuria, glucose intolerance – well known as major CV risk factors. Other anthropometric measures (e.g., waist circumference, waist-to-hip ratio) could well add extra information to BMI. However, BMI is in itself a strong predictor of overall mortality, while progressive excess mortality above 25 kg/m² is mainly due to vascular disease and is probably mostly causal [33–36].

Knowing that every additional 5 kg/m² of BMI would elevate the hazard ratio of major CV events up to 1.39 [35] while every reduced unit of HbA1C would reduce the risk of those events by approximately 16% [37], we developed and mathematically substantiated a new parameter which is based not only on a surrogate glycemic parameter (HbA1C) but takes into account a patient's anthropometrical and energy status (BMI).

We named this new parameter "MI" – Metabolic Index. The metabolic index (MI) fluctuations are a result of changes in both body mass index (BMI) and HbA1C values.

Assuming the range of the potential impact HbA1C and BMI may have on CV risk, a simplified formula for MI can be issued as follows:

$$MI=(BMI)^{1.5} \times (HbA1C)$$

It is clear that we may reduce MI by a lowering both HbA1C and BMI. On the other hand, a reduction in HbA1C at the price of an elevated BMI (with hypoglycemic and energy-sparing therapies) will result in an increased MI, and therefore should be deemed unacceptable. This is in complete accordance with our Gravicentric theory. Thus, implementation of the MI parameter, as opposed to HbA1C levels alone, can help predict CV risk and protect T2DM patients from possible overtreatment. For a more detailed mathematical assessment, please see the Appendix.

Statistical analysis

Pre and on GLP-1 measures were compared using a paired samples t-test. Due to the small sample size, the Wilcoxon signed-rank test was applied to analyze measures that resulted in small values and noticeably deviated from normality. Pearson correlation coefficient was performed to estimate the strength of correlation between several measures.

RESULTS & DISCUSSION

Basal patient's characteristics

As shown, adding GLP1 to poorly controlled, severely obese insulin-treated patients with T2DM – in accordance with our

Gravicentric theory – leads to significant improvement in body mass (BMI reduction from 35.1 ± 4.8 to 32.8 ± 5.0, p < 0.001), concomitant decrease in insulin requirements (by 50% from baseline), and impressive improvement in glycemia (HbA1C reduction from 9.3 ± 1.4 to 8.5 ± 1.4 %, p < 0.001).

One of the exciting findings of our investigation was the phenomenon of reversibility of T2DM, which includes "insulin weaning". The metabolic improvement can be easily seen through a reduction in insulin requirements.

Thus, 64.2% of the patients have reduced their TDI by more than 20 u/day, while 20 patients (37% of total cohort) reduced their insulin requirements dramatically: with 13 of
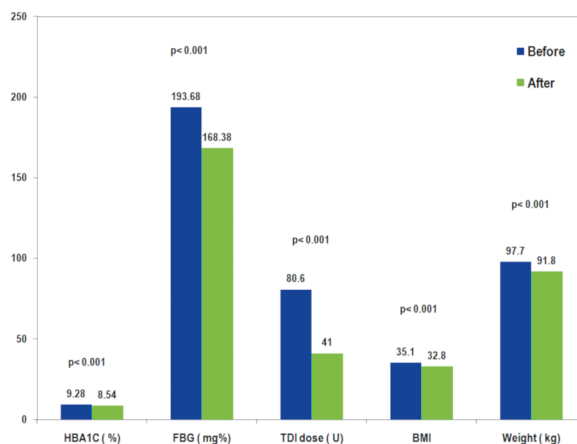

Fig.1. Dynamics of main parameters on GLP-1 added to insulin therapy in total cohort
Рис. 1. Динамика основных показателей на фоне ГПП-1, добавленного к инсулинотерапии. Все пациенты

them (24%) switching from MDI to only one insulin injection per day, and with 7 patients (13%) stopping any insulin therapy, see Table 4.

Post Hoc, we performed a more detailed analysis to find out which kind of patient is the most likely to succeed on this type of intervention. As previously noted, the vast majority of participants, 34 patients (64.2%), had reduced the Total Daily Insulin (TDI) dose by 20 U/day at the very least, along with improved diabetes control - **Group A** , while 19 (35.8%) - **Group B** – did not succeed to do so.

Table 2.
Табл. 2.

Basal characteristic of patients
Исходные характеристики пациентов

Total N of patients	54
Male	24
Female	30
Mean age (years)	59.9
Mean age of T2DM beginning (years)	43.6
Mean DM Duration (Months)	205 ± 80
Mean duration of Insulin therapy before GLP-1 was added (Months)	56.1
Mean Duration of GLP-1 therapy (Months)	25.75 ± 18.79

Table 3.
Табл. 3.

The main results of the study. A total cohort.
Основные результаты исследования. Все пациенты

Parameter	Before GLP-1	On GLP-1	P value
HbA1C (%)	9.3 ± 1.4	8.5 ± 1.4 %	p < 0.01
FBG (mg %)	193.7 ± 72.1	168.4 ± 64.8	p < 0.001
TDI dose (U)	80.6 ± 42.7	41.0 ± 30.7	p < 0.01
BMI (kg/cm2)	35.1 ± 4.8	32.8 ± 5.0	p < 0.001
Weight (kg)	97.7 ± 11.7	91.8 ± 11.8	p < 0.01
Severe Hypoglycemia	0	0	NS
Non-severe Hypoglycemia Frequency Score	0.21 ± 0.7	0.53 ± 1.6	P=0.17
Metabolic index (MI)	1960.7 ± 561.4	1599.6 ± 501.5	p < 0.001

Remission rate on Gravicentric approach with GLP-1 added to insulin therapy

Частота ремиссий в результате применения Гравицентрического метода с помощью ГПП-1, добавленного к инсулинотерапии

Metabolic improvement as demonstrated by insulin requirements reduction	N (%)
Stopped one kind of insulin, while Multiple injections (MDI) were substituted by one injection only (partial remission)	13 (24.0 %)
Complete Insulin discontinuation (Insulin weaning and full remission)	7 (13.0%)
Total number of patients with partial or full remission	20 (37%)

Table 5 offers a comparison of the main clinical and laboratory parameters, as well as patients' compliance in the two groups. It should be noted that although any differences in body weight and BMI at baseline were absent, Group A showed an impressive weight reduction with GLP-1 added to insulin therapy, while Group B showed minimal BMI reduction, p≤ 0.001. This led to an improvement in insulin resistance (IR), which in turn led to the notable reduction in insulin requirements in group A (ΔTDI on GLP-1 was -62.4 ± 31.9 U/day) with no TDI reduction in Group B (ΔTDI on GLP-1 was +0.03 ± 14.1 U/day). However, both groups improved their HbA1C levels to the same range (Group A: 8.7±1.4%, Group B: 8.8±1.4%, p =NS). An intriguing notion which could explain the differences between the groups is our Compliance Score. The higher the score, the more incompliant the patient. Thus, the Compliance Score in Group A was 1.4 ± 1.1, while in Group B it was 2.2 ± 1.0, p<0.02.

Discussion

In our study, the Gravicentric therapeutic approach with a gradual de-intensification of treatment was applied to all 54 patients, according to our previously published algorithm [11]. Most participants have tried all possible therapeutic options before and have reached the "failure-stage" of therapy intensification according to standard treatment schemes, with no other available therapeutic options besides further insulin dose elevation. Before the study, the patients' long-lasting diabetes combined with a long-term insulin therapy has led the attending medical staff to frustration and disappointment with their inability to control the disease. Unfortunately, this is a typical situation in this category of diabetic patients. Most patients previously underwent additional intensification by switching from one insulin injection per day to MDI, together with insulin dose titration. All this – with virtually no effect on diabetes control.

Shifting treatment objectives from glycemic parameters (HbA1C) to the restoration of energy balance (BMI reduction) leads to impressive and often fast improvement of diabetes control. As can be seen in the study, only those who significantly reduced their body weight were able to decrease the insulin dose by more than 20 units per day, with concomitant improvement of glycemia. The ΔBMI was -3.3±2.4 in the successful Group A and only -0.9±1.2 in Group

A comparison of the main clinical and Laboratory parameters in the two groups.

Сравнение основных клинических и лабораторных показателей в обеих группах

	Group A (TDI reduction by ≥ 20 U/day)	Group B (TDI reduction by ≤ 20 U/day)	p
N (%)	34 (64.2%)	19 (35.8%)	NS
Male	18 (53%)	6	NS
Female	16 (47%)	13	NS
BMI before GLP-1 kg/cm2	35.5 ± 4.8	33.6±3.9	NS
BMI on GLP-1 kg/cm2	32.3 ± 5.3	32.7 ± 3.7	NS
Δ BMI on GLP-1 kg/cm2	3.3 ± 2.4	0.9 ± 1.2	< 0.001
HbA1C before GLP-1 (%)	9.5±1.5	9.3±1.5	NS
HbA1C on GLP-1 (%)	8.7 ± 1.4	8.8 ± 1.4	NS
TDI Before GLP-1 (U/day)	97.4±40.4	52.2±31.0	< 0.001
TDI on GLP-1 (U/day)	29.0 ± 33.2	52.4 ± 31.1	< 0.001
Δ TDI on GLP-1 (U/day)	- 62.4 ± 31.9	+ 0.03 ± 14.1	< 0.001
IWR before GLP-1(U/kg)	1.0 ± 0.4	0.55±0.32	< 0.001
IWR On GLP-1 (U/kg) on GLP-1	0.4 ± 0.31	0.55 ± 0.32	NS
Tot. Compliance Before GLP-1	2.6 ± 1.0	2.8 ± 0.73	NS
Tot. Compliance on GLP-1	1.4 ± 1.1	2.2 ± 1.0	P < 0.02
MI Before GLP-1	2043.9 ± 638.2	1803.6 ± 375.4	NS
MI on GLP-1	1557.2 ± 557.2	1643.7 ± 382.0	NS
Δ MI on GLP-1	- 486.6 ± 436.7	-159.9 ± 83.2	p=0.005

B, p<0.001. It is noteworthy that there was no difference in BMI levels at baseline between the two groups.

This weight-losing paradigm has been recently presented in a position statement by the American Association of Clinical Endocrinologists (AACE), under the motto "Treat obesity first." [38]. We have been recommending this approach for years [1]. As for our Gravicentric algorithm, it has been created in line with an almost 20-year-old proposal [39] to divide patients according to their BMI: *"Patients must also be separated for therapeutic purposes into obese and nonobese groups, inasmuch as beta-cell function and sensitivity can be improved in the former by weight reduction. Pima Indians with obese type II NIDDM experienced improvement in beta-cell function and glucose intolerance after 3 wk of caloric restriction and improved sensitivity of target tissues after 18 wk. Such remissions occurred only in patients with fasting glucose levels below 14 mmol/L (250 mg/dL) and diabetes of less than 5 y duration. Unfortunately, in the United States dietary adherence and weight reduction are seldom achieved in the obese patient with NIDDM".* Unfortunately, this recommendation was disregarded and remained forgotten for many years.

In the current study, we only prescribed weight-lowering, anti-energetic (energy wasting) medications, and simultaneously stopped all pro-energetic (energy sparing) medications. In our experience, when a doctor provides a clear explanation regarding the role of energy in the treatment of the disease and then prescribes the patient with the anti-energetic medications, most patients (more than 64%) begin effectively losing weight, insulin resistance subsides, and insulin requirements decrease dramatically.

All in all, we had two groups in this study:
- The biggest group (Group A, success) is characterized by significantly (virtually, twice) larger TDI at baseline; very impressive weight reduction and much better compliance as compared to Group B.
- The smaller group, (Group B) is characterized by physiological TDI, minimal weight reduction, and no insulin dose reduction (no improvement in IR).

As a result of the therapy, patients in Group A have significantly improved their metabolic health, with impressive TDI reduction (reflecting the disappearance of IR), and in some cases, even up to insulin weaning. This metabolic improvement is best represented by our new index (MI - Metabolic Index). Indeed, ΔMI was maximal in group A (-486.6 ± 436.7) as compared to Group B (-159.9 ± 83.2), p=0.005.

Thus, even though both groups had similar MI levels at baseline and had achieved the same HbA1C levels on GLP1 therapy, evidently, patients of group A became leaner and metabolically healthier.

Why did that occur? It is well known that obesity is primarily a positive energy balance, and as such, it is an expression of many concomitant factors: eating and social habits, low physical activity, psychological disturbances, genetics, etc. [40].

We suggest overtreatment as the key factor in obesity and the inability for weight reduction in Group A. Essentially, at baseline, these patients got insulin (TDI) in doses that were almost double the doses patients in Group B had received. Surprisingly, patients of Group A achieved success in their weight loss and metabolic recovery. In these patients, the sequence of events looks as follows:

De-intensification by reducing the supraphysiological doses of insulin to physiological ones > **Remarkable alleviation of weight loss** due to avoidance of energy retention, absence of hypoglycemia and no further need for defensive eating > **A "miracle effect,"** when the patient himself sees that in spite of noticeable insulin dose reduction, not only did diabetes control not deteriorate but in fact, it drastically improved. This event makes our patients feel as if they are experiencing a miracle, which leads to > **Dramatic improvement in patients' motivation and compliance >**

As a result, there is **more weight loss**, less insulin resistance, and an **additional reduction of insulin doses**, sometimes up to total insulin withdrawal. Hence, it is not surprising that patients' compliance became significantly better in Group A as opposed to Group B.

Unlike Group A patients, the impact of overtreatment on obesity in Group B patients was minimal (most were treated with physiological doses of insulin at baseline). This fact made their weight reduction much more complicated. As a result, patients from Group B had minimal weight reduction and no decrease in insulin doses. Thus, in spite of the fact HbA1C dropped to the same levels in both groups, patients in group A became much leaner and metabolically healthier than diabetic patients in group B (see ΔMI).

CONCLUSIONS

Adding GLP-1 analogs to insulin in poorly controlled, insulin-treated T2DM patients resulted in impressive weight (BMI) reduction with significant improvement of glucose control. This provided a further decline in insulin resistance and insulin requirements.

This approach would allow up to 37% of patients to attain partial or full remission of T2DM, while 64% of diabetic patients would significantly improve their metabolic status. Changes in Metabolic Index (MI) rather than surrogate glycemic parameters (HbA1C) are better reflectors of successful T2DM therapy. Hence it may be advised to substitute HbA1C in extensive clinical practice.

We suggest that the best candidate for successful GLP-1 therapy is an obese, overtreated, and compliant T2DM patient. It is likely that neither the duration of diabetes nor the length of insulin therapy plays a critical role in success prediction. All in all, these findings are proof of concept of our Gravicentric theory in T2DM.

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APPENDIX 1.
MI (METABOLIC INDEX) CALCULATION

The metabolic index (MI) change is resulting of changes both body mass index (BMI) and glycosylated hemoglobin (HBA1C) value. This dependence can be expressed by the following:

$$MI = f(BMI) \times f(HBA_{1c});$$

Where "f" means some function dependence of independent variables.

The nominal value of BMI is 25, while the nominal value of HBA1C is 5.8.

It is known, that independent increasing of BMI by index 1 (4%), increases value of MI by 6%, while increasing of HBA1C by index 1 (17.2%), increases the value of MI by 16%.

These relationships lead us to the simple following expression for MI:

$$MI = (BMI)^{m} \times (HBA_{1c})^{n}$$

Let's estimate values of "m" and "n" according to above limitations.

The derivative of MI leads to the following expression of MI deviation (increase/decrease):

$$\Delta MI = m \cdot BMI^{m-1} \cdot \Delta BMI + n \cdot BMI^{m} \cdot (HBA_{1C})^{n-1} \cdot \Delta(HBA_{1C})$$

Let's check independent impacts of ΔBMI and Δ(HBA1C) on relative (in percentage) change of MI.

First, assume the partial impact of ΔBMI. In this case Δ(HBA1C) = 0 and

$$\frac{\Delta MI}{MI} = \frac{m \cdot BMI^{m-1} \cdot (HBA_{1C})^{n}}{MI}\Delta BMI = \frac{m \cdot BMI^{m-1} \cdot (HBA_{1C})^{n}}{BMI^{m} \cdot (HBA_{1C})^{n}}\Delta BMI =$$

$$= \frac{m \cdot BMI^{m-1} \cdot (HBA_{1C})^{n}}{BMI^{m-1} \cdot (HBA_{1C})^{n}}\Delta BMI = m\frac{\Delta BMI}{BMI}$$

Taking in account, that the relative increase of BMI by 0.04 (4%) leads to relative increase of MI by 0.06 (6%), one can find m=1.5.

Repeating the same manipulation in the case of partial impact of Δ(HBA1C) and ΔBMI=0, we get the following relationship:

$$\frac{\Delta MI}{MI} = \frac{\Delta(HBA_{1C})}{HBA_{1C}}$$

And n=0.16/0.172=0.93.

Finally, the formula for calculation of Metabolic Index look like the following:

$$MI = (BMI)^{1.5} \cdot (HBA_{1C})^{0.93}$$

Assuming the range of possible impact of HBA1C on MI, the simplified formula for MI can be issued:

$$MI = (BMI)^{1.5} \cdot (HBA_{1C})$$

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Авторы заявляют, что у них нет конфликта интересов

Гравицентрический подход к лечению диабета второго типа. Прогнозирование успеха. Подтверждение концепции

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Аннотация

Это исследование является подтверждением нашей Гравицентрической концепции. Данная концепция основана на нескольких основных моментах: ожирение как главный враг; быстрая обратимость заболевания; новый взгляд на роль, которую играют в лечении СД2 различные фармакологические классы препаратов вообще, и роль инсулина и аналогов ГПП-1 в частности. В статье представлены и обсуждаются: наш опыт сочетания инсулина и аналогов ГПП-1, возможность отхода от инсулинотерапии; терапевтический подход для пациентов, подвергшихся чрезмерному лечению, физиологическое дозирование инсулина.

Цели

Первичная: оценить долгосрочную эффективность аналогов ГПП-1 у пациентов с сахарным диабетом 2-го типа (СД2), получавших инсулин.

Вторичная: проанализировать, какой пациент наиболее вероятно выиграет от этого комбинированного лечения.

Методы

У 54 пациентов с СД2 со средней продолжительностью заболевания 17,5 лет и средней степенью инсулиновой терапии 4,5 года была назначена дополнительная терапия аналогами ГПП-1. Средняя продолжительность лечения ГПП-1 составила 25,8 месяца (2,15 года).

В ходе вмешательства были проанализированы клинические, биохимические и антропометрические параметры. Были произведены оценки комплаэнтности, гипогликемии и метаболического индекса (МИ).

Полученные результаты

Среднее содержание гликированного гемоглобина (HbA1C) снизилось с $9,28 \pm 1,43\%$ – до подключения ГПП-1 до $8,54 \pm 1,4\%$ – на фоне ГПП-1, $p < 0,01$. Общая суточная доза инсулина (TDI) показала значительное снижение: $80,6 \pm 42,7$ ед/день до начала ГПП-1 против $41,0 \pm 30,7$ ед/день на ГПП-1, $p < 0,01$. Эти изменения были напрямую связаны с потерей веса. ИМТ снизился с $35,1 \pm 4,8$ кг/см^2, до $32,8 \pm 5,0$ кг/см^2 на фоне аналогов ГПП-1. При этом пациенты в среднем потеряли 6,7 кг массы тела. Более того, 13 (24%) участников прекратили принимать хотя бы один вид инсулина, в то время как 7 (13%) прекратили прием инсулина полностью с одновременным улучшением контроля диабета. Клинически значимой гипогликемии не наблюдалось.

После этого участники были распределены по группам в соответствии со способностью каждого пациента снижать TDI более чем на 20 ед/день. Группа А – 34 пациента (64,2%), которые успешно снизили TDI. Группа В – 19 пациентов (35,8%), которым это не удалось.

Сравнение двух групп показало следующее:

1. На момент начала исследования общая суточная доза инсулина в группе А была вдвое больше (97,4 ± 40,4 ед/день против 52,2 ± 31,0 ед/день в группе В), p <0,001.

2. Очень эффективное снижение ИМТ (ΔИМТ 3,3 ± 2,4 кг/см^2 против 0,9 ± 1,2 кг/см^2, p <0,001) и намного лучшая комплаэнтность (1,4 ± 1,1 против 2,2 ± 1,0 баллов, p <0,02) в группе А.

3. Значительное снижение потребности в инсулине в группе А при терапии ГПП-1 (ΔTDI на ГПП-1 была-62,4 ± 31,9 ед/день) без снижения TDI в группе «В» (ΔTDI на GLP-1 была +0,03 ± 14,1 ед/сут, p <0,001).

Таким образом, несмотря на то, что при терапии ГПП-1 показатели HbA1C снизились до одинакового уровня в обеих группах, пациенты из группы А стали значительно более худыми и метаболически более здоровыми.

Мы полагаем, что критическим фактором ожирения в группе А послужила «перелеченность» этих пациентов.

Выводы

Добавление аналогов ГПП-1 к инсулину у плохо контролируемых пациентов с СД2, получавших инсулин, привело к значительному снижению веса (ИМТ) со значительным улучшением контроля глюкозы. Это обеспечило дальнейшее снижение инсулинорезистентности и потребности в инсулине. Мы полагаем, что лучшим кандидатом для успешной терапии аналогами ГПП-1 является страдающий ожирением, подвергнутый чрезмерному лечению и комплаэнтный больной СД2. Изменения метаболического индекса (МИ), а не суррогатных гликемических параметров (HbA1C) являются лучшими предикторами успешной терапии СД2. Ни длительность диабета, ни длительность инсулиновой терапии в прошлом, скорее всего, не играют решающей роли в прогнозировании успеха. Эти результаты являются подтверждением нашей Гравицентрической концепции в СД2.

КЛЮЧЕВЫЕ СЛОВА: аналоги ГПП-1; инсулин; СД2; метаболический индекс; Гравицентрическая концепция; ремиссия диабета