REVIEW

Стратегии лечения сахарного диабета 2 типа: почему мы не видим «слона в посудной лавке»?

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В течение двух последних десятилетий ранняя интенсификация лечения пациентов с сахарным диабетом 2 типа (СД2), в том числе путем перевода их на инсулинотерапию, рассматривается как единственно верная терапевтическая стратегия. Несмотря на всеобщую популярность, такой подход не имеет однозначных и безоговорочных доказательств в отношении эффективности и безопасности с позиций доказательной медицины. Более того, с точки зрения патогенеза нарушений углеводного обмена, многие положения такого подхода оказываются даже не спорными, а парадоксально неверными. Так, «глюкозоцентризм» и «интенсификация», являясь краеугольным камнем стратегии современной сахароснижающей терапии СД2, имеют настолько очевидные отрицательные стороны, что не заметить их столь же сложно, как «слона в посудной лавке». Многочисленные исследования последних лет убедительно свидетельствуют о наличии серьезных побочных эффектов «слепой» интенсификации сахароснижающей терапии и необоснованной или избыточной инсулинотерапии (с применением высоких доз) при СД2. Эти исследования вызывают серьезную озабоченность и требуют пересмотра традиционного подхода к лечению СД2. Роль инсулинотерапии, которую большинство специалистов считают неотъемлемой частью стратегии интенсификации лечения СД2, может быть в значительной степени пересмотрена. В настоящей статье не только представлен обзор исследований, результаты которых могут лечь в основу критики современной стратегии интенсификации лечения СД2, но и кратко обсуждаются альтернативные взгляды на выбор сахароснижающей терапии при СД2, в том числе – «гравицентрическая» концепция. Подробно разбирается «энергетический» потенциал сахароснижающих препаратов и его значение при лечении СД2 в рамках «гравицентрической» концепции, рассматривающей СД2 как болезнь нарушения энергетического баланса и позволяющей врачам рассматривать это заболевание не только и не столько «медленно прогрессирующим», сколько «быстро обратимым» состоянием.

Ключевые слова: *сахарный диабет 2 типа; гравицентрическая концепция; энергетический баланс; калории; инсулин; интенсификация; де-интенсификация; алгоритм; рак; ИМТ; сердечно-сосудистые осложнения*

Type 2 diabetes therapeutic strategies: why don't we see the «ELEPHANT» in the room?

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During the past two decades, the unequivocally recommended treatment method of Type 2 diabetes mellitus was insulin administration and intensification in the earliest possible stage of the diagnosis. This approach is not only unfounded but was never scientifically proven. Yet, it has been zealously advocated to medical professionals. In fact, a sound body of evidence disproves this long-standing treatment approach. This method is a cornerstone of, what we now know to be two great illusions of past century, namely, glucocentrism and intensification. Numerous recently published studies provide alarming data regarding serious side effects of blind intensification and insulin overdosing in T2DM. They raise major concerns and call for revision of the traditional approach. Since insulin is an integral and deeply rooted part of the intensification agenda of treating T2DM, it has now suffered a serious drawback. Alternatively, in this review authors present the novel Gravicentric (Energy) concept of T2DM acceptance and therapy. They offer a new classification of anti-diabetes drugs based on their energy effect and present their Gravicentric Algorithm for wide practical utilization. For that reason, the "ELEPHANT" abbreviation was found as a helpful reminder. Viewing T2DM as disease of energy balance together with anti – energy drugs implementation provide medical doctors an unique opportunity to transform T2DM from "slowly – progressive" disease to rapidly reversible condition, which it actually is.

Keywords: *diabetes type 2; gravicentric; energy-wasting; energy-sparing; calorie; insulin; intensification; de-intensification; algorithm; cardiovascular; cancer; body mass index*

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Introduction

The role and place of insulin in Type 2 diabetes (T2DM) is highly debated and controversial. Some authors insist on intensification of therapy while others do not share this approach (1;2).The problem became even more complicated in recent years with the appearance plentiful evidence raising our concern regarding insulin safety and efficacy in T2DM. In a recently published study (3) authors have concluded that among patients with T2DM on metformin therapy, the addition of insulin vs. sulfonylurea (SU) was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality. These findings surprised the authors. Their working assumption was that insulin, as the most potent glucose-lowering agent, would reduce mortality rates. Moreover, when specific causes of death among a propensity-matched cohort were compared, the following results were found:

- 21% increase in cardiovascular mortality
- 85% increase in cancer mortality (of note: cancer mortality was the most common reason for all-cause mortality)
- 36% increase in all-cause mortality.

Are these findings really surprising? In our opinion, they were quite predictable.

The "ELEPHANT"

We suggest an alternative view on diabetes therapies and insulin's place in T2DM. We termed it «**ELEPHANT**», which also serves as an acronym.

E (Evidence). *Current Evidence debunks the myth of insulin intensification*

During the past two decades , insulin administration and intensification in the earliest possible stage of the diagnosis was the unequivocally recommended treatment method. This approach is not only unfounded but was never scientifically proven. And yet, it has been zealously advocated to medical professionals.

In fact, a sound body of evidence disproves this long standing treatment approach:

T2DM intensification does not provide any benefit in terms of cardiovascular mortality and

morbidity. Hemmingsen et al. (2) analyzed 20 studies which included over 30,000 patients and concluded that intensification has absolutely no advantages over conventional treatments of T2DM when it comes to cardiovascular or all-cause mortality.

They did find intensive treatment lowered the occurrence of microvascular complications, yet with increased incidence of hypoglycemia.

According to John Yudkin, who calculated the Number Needed to Treat (NNT) index for intensive insulin therapy, no impact on hard endpoints was shown. Namely, in order to prevent one non-fatal myocardial infarction by intensified control, 143 people need to be treated for 5 years and 627 need to be treated to prevent one case of end stage renal failure (4).

L (Life). *The real-Life studies: alarming properties and side effects of insulin*

In fact, even in UKPDS study, insulin and SU were not superior to metformin in terms of cardiovascular outcomes (5).

In 2013, Craig Currie et al. published a study on 85,000 T2DM patients of the UK Registry. These patients were followed for over 10 years (between 2000-2010). The results were quite shocking.

Insulin-treated patients exhibited a 40% increase in cancer morbidity and a significant increase of major adverse cardiovascular events (MACE):

- patients administered with insulin as monotherapy exhibited a 74% increase in MACE;
- patients administered with insulin + metformin exhibited 22% increase in MACE.

These trends persisted even after adjustments for the HbA1C levels and categorizing the patients by severity of disease (low morbidity vs. high morbidity) (6).

A review of a large Canadian cohort study found that insulin significantly increases mortality, and that this phenomenon is dose dependent, i.e., the higher the dosage, the greater the

mortality rate (7).

Insulin and its carcinogenic effects

Gerstein et al. in 2012 (8) followed 12,537 T2DM and pre-diabetes patients treated with insulin Glargine (Lantus) for six years. They concluded that Glargine provides no benefits over controls in terms of morbidity or cardiovascular mortality.

It should be noted that the average insulin dosage administered to those patients was relatively low and could certainly be labeled “physiological”, i.e. between 0.31u/kg to 0.4u/kg. No statistical difference was found between the groups regarding the incidence of malignancies nor were there differences in incidence of diverse types of cancer (lungs, breast, colon, prostate, etc.).

However, this paper was peer-reviewed and criticized. For instance, Craig Currie noted that the prevalence of malignancy found in this paper is 3-4 times lower than that of the general population. "I think they've just been screened out at baseline," he said. He also noted that patients were not divided into 'high' and 'low' dose of insulin subgroups in order to find the association with malignancy. This is despite the fact that authors did it for Metformin. "They don't want to find an association, trust me" - Craig Currie replied (9).

So, why was this all so predictable?

In the discussion of his paper, Craig Currie writes: "There are multiple potential mechanisms that could link exogenous insulin with adverse outcomes such as cardiovascular endpoints and cancer in people with T2DM. Insulin initiation and titration result in weight gain in the region of 2 kg per 1% reduction achieved in HbA1c, an effect that may exacerbate both cancer and cardiovascular risk. Insulin is a growth factor known to have atherogenic and mitogenic effects, which may provide an adaptive advantage for malignant foci and potentiate the development of atherosclerotic vascular disease" (6).

Although this is all true, it is not a comprehensive explanation, nor is it the only one provided.

E (Energy). *Energetic (Gravicentric) concept in T2DM. Energy-sparing (pro-energetic) vs. Energy-wasting (anti-energetic) therapies*

In 2013 we published a new concept of T2DM understanding and management in which we look upon the disease from an energetic point of view (10). In other words, we consider T2DM is nothing but a pathophysiological (defensive) reaction of human body to chronic energetic intoxication. From this point of view it is easier to perceive why T2DM is rapidly reversible even at advanced stages of disease history (11). The direct correlation between calorie intoxication and metabolic syndrome (with high glucose levels as a marker), is a well-known fact (12). So is the correlation between the calorie intoxication and cancer morbidity (13). Consequently, we propose that all anti-diabetic medications in use today should be classified as pro-energetic (mostly hypoglycemic agents) or anti-energetic (mostly anti-hyperglycemic agents). That is to say, if a patient gains weight as a result of using a medication (i.e., has an energy surplus) it is considered pro-energetic. On the other hand, if a patient loses weight or at least does not gain weight while taking a medication we would classify it as anti-energetic. Given a progressive weight gain as a "natural history" of T2DM (5) it becomes clear that so-called "weight-neutral" medications are actually weight-lowering.

All in all, it seems that calorie poisoning kills a diabetes patient through two main pathways: by increasing cardiovascular morbidity and mortality and by inducing cancer morbidity and mortality. These mechanisms may affect patient's health directly (oxidative stress, inflammation and immunological disturbances) (14) and through adiposity pathway (toxic effects of adipokines and Glp-1 degradation by DPP-IV) (15).

The table below (Table 1) shows that virtually all the pro-energetic drugs cause weight gain, resulting in increased risk of cardiovascular complications and cancer. In contrast, all anti-energetic drugs cause weight loss or at least no weight-gain. Consequently, they reduce carcinogenesis and cardiovascular morbidity and mortality rates.

The classic anti-energetic drug is metformin which directs energy generation to an alternative ineffective pathway (16). That is, from aerobic glycolysis to anaerobic glycolysis. As a result, metformin dramatically reduces energy production, promotes weight loss, leading to reduction of cardiovascular and cancer morbidity and mortality.

In accordance with our gravicentric concept, a new medication class – sodium-glucose co-transporters (SGLT2) inhibitors – could also be expected to reduce the cardiovascular morbidity and mortality as latest studies clearly confirmed (17).

Regarding insulin, there are growing concerns about its negative cardiovascular and carcinogenic effects (18;19). It is also very interesting that recent data once again decisively confirms the ability of pioglitazone to induce carcinoma of bladder (20;21).

New data suggest that SGLT2 inhibitors may be linked to significant benefits in patients with cancer (22). The cardiovascular safety of DPP4 inhibitor Sitagliptin was shown in TECOS study (23) and recently published data demonstrate the cardiovascular benefits of GLP-1 (Liraglutide) (24). All of the above supports our energetic theory in T2DM.

P (Physiological dosing). *Insulin should be prescribed only in Physiological doses*

Our 2011 paper has proved that when administered in physiological doses (no more than 0.6 units per 1 kg of current body mass), even premixed insulin, does not cause weight gain or an increase of the incidence of hypoglycemia and actually lowers cardiovascular risks markers such as serum lipids levels and HBA1C (25). This has also been confirmed in our recent study regarding the place of insulin pumps in T2DM (26). Similarly, one probable explanation for the relatively low levels of cardiovascular and cancer mortality indicated by the ORIGIN study is that patients in this research were administered moderate insulin doses (up to 0.4 u/kg on average) (8).

H (Harm should be avoided). *High (supra-physiological) doses of insulin are pro-energetic and Harmful*

According to the gravicentric concept, high doses of pro-energetic potent glucose-lowering agent such as insulin will undoubtedly cause an increase in cardiovascular and cancer morbidity and mortality. Thus, insulin may become the strongest pro-energetic drug, if used in supra-physiological doses. Unfortunately, blind titration schemes without any upper limits as well as claims of certain opinion leaders that insulin may be administered in any dosage, may prompt medical professionals to prescribe it in supra-physiological doses. With this kind of intensification our patients enter the vicious cycle of overdosing syndrome.

Table 1

Effects of anti - diabetic medications on Cardiovascular and Cancer risk. (author's classification)

Medication class/Drug family	Effect on BMI	Cardiovascular Morbidity and/or mortality	Cancer Morbidity and/or mortality
Energy retaining/pro-energetic medications			
Sulfonylurea	↑	↑	↑
Insulin in supra-physiological doses	↑	↑	↑
Insulin in physiological doses	↕ Or even ↓ (our data)	↕ (origin STUDY) Additional studies are needed	↕ (origin STUDY) Additional studies are needed
Glinides	↑	No sufficient data	No sufficient data
TZD's	↑	↑ (mainly Rosiglitazone)	↑ (mainly Pioglitazone - Carcinoma of bladder)
Energy wasting/anti-energetic medications			
Metformin	↕ or even ↓	↓↓	↓↓
α-Glycosidase Inhibitors	↕ or even ↓	↓ "Stop NIDDM" - study	↕ No sufficient data
DPP 4 - I	↕ or even ↓	↓ Studies continue	↕ No sufficient data
GLP-1 Analogues	↓↓	↓ (LEADER study)	↕ No sufficient data
SGLT2 Inhibitors	↓	↓ (EMPA REG study)	↕ No sufficient data

↕ – no change ; ↓ – decrease; ↑ – increase ; SGLT2- Sodium–glucose co-transporter inhibitors; DPP 4–I – Decapeptil Peptidase 4 Inhibitors ; GLP-1 – Glucagon–like peptide–1.

We call it the Double "O" Syndrome: Over-treating and Overeating. When physiological doses are used insulin has a neutral influence on energy balance, thus making it safe to apply (25-27).

As anti-diabetic therapy intensification and over-treatment has become widespread, more and more experts recognize the danger and call physicians to avoid over-treating their patients. For example, Dr. Kasia Lipska from Yale's School of Medicine writes: "... submitting patients to treatment that is likely to cause more harm than good is unacceptable. Primum non nocere. First, do no harm...We are all committed to helping our patients do well, but I now wonder whether sometimes we've lost sight of what that means. Overdoing glucose control is one example" (28;29).

Why does insulin generate worse treatment results than SU?

According to the gravicentric concept, the SU family can clearly be labeled as pro-energetic. Consequently, these medications are expected to cause an increase in cardiovascular morbidity and mortality. In fact, numerous studies derived from large databases have demonstrated this in real life (6;30). Indeed, a detailed review published in 2014 stressed yet again that SU can cause serious complications to patients (31). Back to the article published in JAMA, claiming that insulin causes a higher increase in mortality than SU, despite the fact that SU is not an "innocent by-stander" either (3). Why is that? The answer is intensification and titration. These are the two factors which cause worse results with insulin treatment than SU, because at that point, doctors are encouraged to prescribe huge doses of insulin with all its side effects as a result.

A (Algorithm). *Algorithm of gravicentric approach in T2DM therapy*

In October of 2013 we published our own algorithm for T2DM management which allows clinicians to understand when to stop unnecessary treatment in general and over-titration of insulin in particular in order to avoid harming the patient (32). Insulin has its own place in this scheme, but it is repeatedly emphasized that it should be prescribed only in physiological doses, i.e., no more than - 0.6 units per kg of current body weight per day (Figure 1).

It is important to emphasize that patient's compliance to prescribed therapies is probably the second most important factor affecting this therapeutic approach after BMI.

Interestingly enough, computerized data of patient's medical records permit treating physicians around the world to evaluate patient's compliance, mainly through the amount of medications purchased during the requested time interval. Our unpublished data show that generally only 10% of all diabetes patients purchase more than 90% of their prescribed medications.

N ("No"). *The Five "No" Rule. Probably No major differences between various insulin types*

In our "position statement" paper (10) we also provide the main principles of choosing anti-diabetic therapy, named "Five "No" Rule":

- No cascade "add-on" therapies to obese (over-weight) patient with a positive weight;
- balance (progressive weight gain);
- No weight gain allowed regardless the type of treatment;
- No prescription of pro-energetic agents;
- No chronic insulin therapy for morbidly obese patient;
- No supra-physiological (more than 0.5–0.6 U/kg of current body weight) insulin.

Of note, our Five "No" Rule refers to "classic" T2DM patient and of course, does not include some rare forms of insulin resistant diabetes like secondary diabetes (for example, diabetes in Cushing's syndrome) or genetic

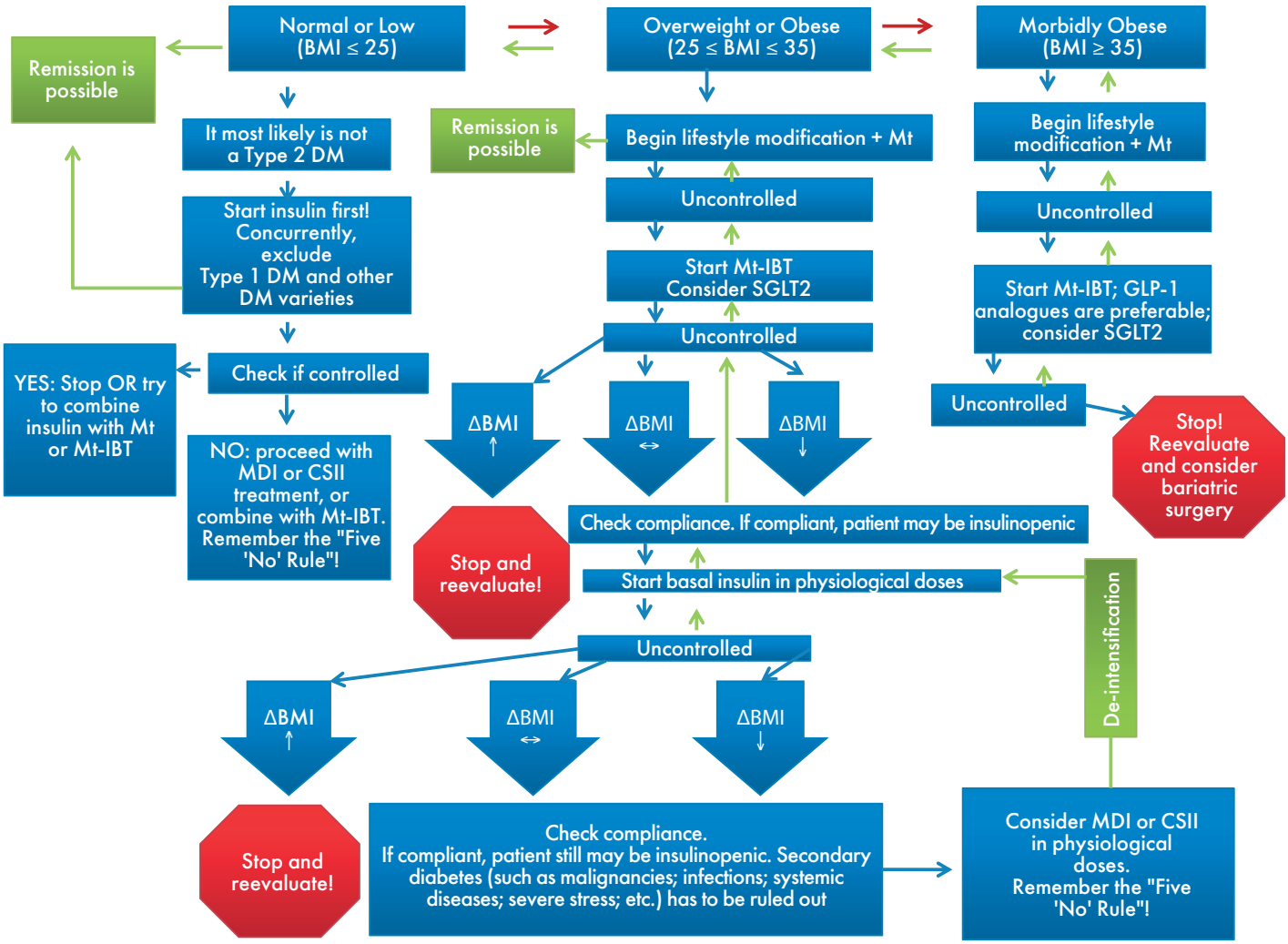


Figure 1. The Gravicentric Algorithm for Diabetes Treatment (updated and corrected). SGLT2 — Sodium–glucose co-transporter 2 inhibitors; GLP-1 — Glucagon –like peptide-1.
CSII – Continuous Subcutaneous Insulin Infusions (pump therapy); MDI – Multiple Daily Injections; Mt – Metformin; Mt-IBT – Metformin + Incretin-Based Therapy; OAD – Oral Antidiabetic Drugs; ΔDelta– Difference between basal and current measurement; Physiological doses of Basal Insulin ≤0.4 U/kg; Physiological doses of Total Daily Insulin ≤0.6 U/kg; ↑ Growing parameter; ↔ Stable parameter

(familial) diabetes with lipodystrophies.

As for routine investigation of C-peptide levels before insulin administration, we do not consider the C-peptide a reliable parameter, because in many patients endogenous insulin production can only be temporarily suppressed by large doses of exogenous insulin and/or by glucose-lipotoxicity and hyperglucagonemia.

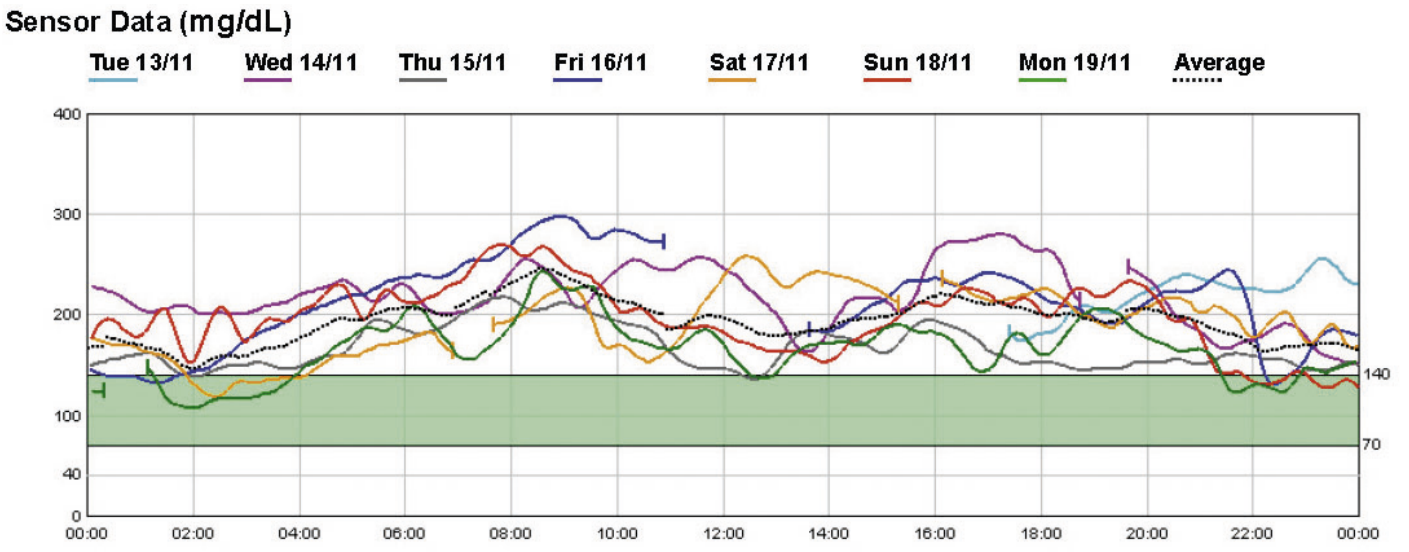
All this leads to erroneous interpretation of low or undetectable C-peptide as evidence of the absence of endogenous insulin. However, from the pathophysiological point, weight gain in obese patients is simply impossible without endogenous hyperinsulinemia. Therefore, in these patients, C-peptide is an unnecessary test. Again, it is BMI that determines endogenous insulin reserve and treatment strategies. We preserve the insulin/C-peptide investigation for unclear cases where T2DM cannot be easily differentiated from other forms of diabetes.

Is there a fundamental distinction between the different insulin types prescribed in T2DM?

The answer is probably "No", although the debate itself does not seem to be relevant. On

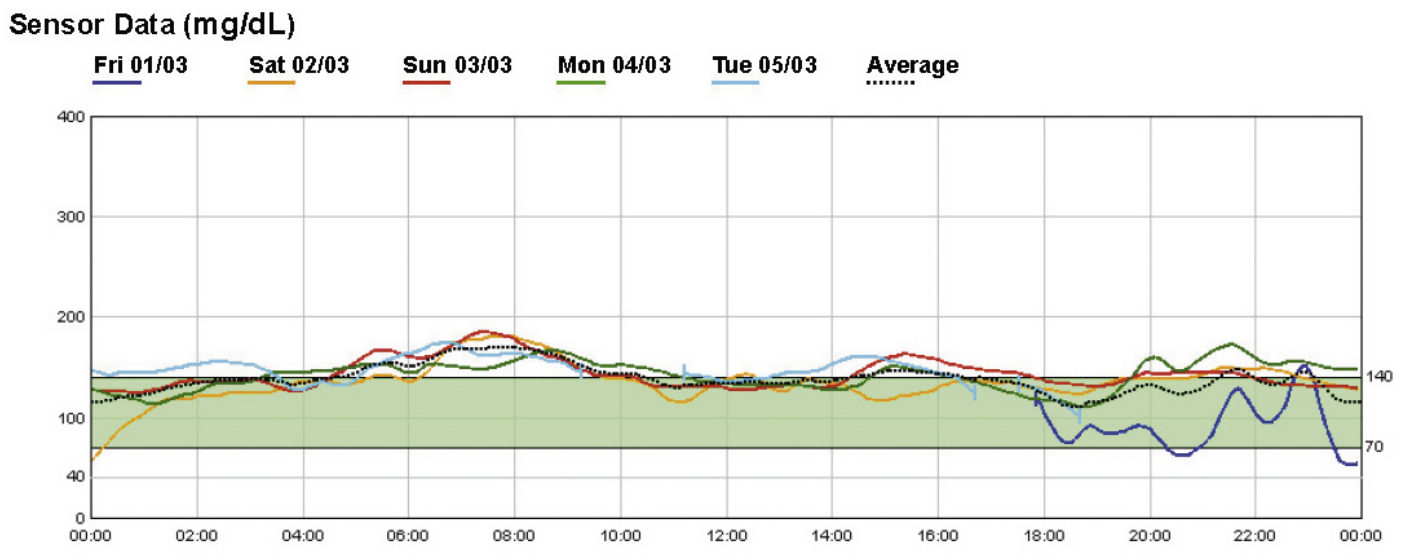
June 10th, 2014, JAMA published a study which analyzed the influence of insulin analogues on clinical outcomes (33). Despite a significant increase in administration of insulin analogues from 18.9% in 2000 to 91.5% in 2010 in the United States, and despite the substantial cost increase (prices per prescription almost doubled (34)), side effects did not decrease significantly (e.g. the rates of severe hypoglycemia were not reduced). Although patients are not expected to stop using insulin analogues, this paper raises serious concern regarding the efficacy and benefits of such treatment. Again, considering this argument from the perspective of the gravicentric concept, the whole debate seems to be irrelevant. Indeed, there is no point in debating which insulin is better when most patients probably do not need any insulin to begin with.

T (Therapy and cure). *A new Therapeutic approach, based on de-intensification*



	Tue 13/11	Wed 14/11	Thu 15/11	Fri 16/11	Sat 17/11	Sun 18/11	Mon 19/11	Average / Total
# Sensor Values	80	278	288	256	271	288	279	1,740
Highest	256	280	218	298	258	270	243	298
Lowest	175	151	136	131	119	127	107	107
Average	219	219	167	213	191	197	166	193
Standard Dev.	21	31	22	44	34	34	30	38
MAD %	1.7	7.4	9.8	4.7	9.3	2.2	3.6	6.1

Figure 2. CGM (Continuous Glucose Monitoring) chart prior to implementing of our treatment method: Estimated HbA1c = 8.4%. CV (Coefficient of Variability) = 19.7%.



	Fri 01/03	Sat 02/03	Sun 03/03	Mon 04/03	Tue 05/03	Average / Total
# Sensor Values	74	288	288	288	194	1,132
Highest	152	181	185	172	175	185
Lowest	53	57	125	111	101	53
Average	92	135	143	142	147	138
Standard Dev.	24	19	15	14	14	21
MAD %	7.6	3.5	3.1	4.3	3.9	4.0

Figure 3. The same patient's CGM chart after completing de-intensification and lowering insulin dose to 20 U/day: estimated HbA1c = 6.4%; CV (Coefficient of Variability) = 15.2%.

An integral part of the gravicentric concept is de-intensification of therapy. Once the treatment method is switched from pro-energetic to anti-energetic, patients will start losing weight and their resistance to insulin will subside. This will enable most patients to complete the de-intensification process, sometimes to a point of total insulin weaning and T2DM remission.

According to our recent data, applying gravicentric theory and algorithm in 54 T2DM patients with advanced disease (mean diabetes duration was 17 years with mean insulin treatment of 4.5 years before intervention) resulted in significant reversal of the disease, 50% reduction of

Table 2

Comparison of main parameters before and after de-intensification

Parameter	Before de-intensification	On de-intensification
Weight, kg	127	109.7
Laboratory HbA1c, %	9.3	6.7
Total daily insulin dose, U	170 (Glargine + Glulisin)	20 (Glargine only)
Other therapy	Metformin 1700 mg/day	Metformin 2550 mg/day
	Vildaglipin 100 mg/day	Liraglutide 1.8 mg/day
CV (Coefficient of variability), %	19.7	15.2

insulin dose and 20% rate of partial to complete remission. 13% of participants stopped their insulin injections completely (35);

Case report

The following is an example, illustrating typical de-intensification in a patient with long-lasting T2DM.

A 64-year-old male, married + 2. Background: was diagnosed with T2DM 15 years ago. His mother was also a diabetes patient and was treated with a combination of insulin and oral medications, died at the age of 92; his father died the age of 90 and did not have diabetes. Known comorbidities: Hypertension and Hyperlipidemia, treated with Enalapril 5 mg/day; Bezafibrate 400mg/day and Aspirin 100 mg/day. Patient receives insulin since 2005: Glargine 65 U/day at bedtime, Glulisin 35 U x 3/day with meals. His oral anti-diabetes therapies consisted of Vildagliptin/Metformin 50mg/850 mg x 2/day. His HBA1C at admission was 9.3%.

Summary

We live in a fascinating era. On the one hand, this is a huge crisis and a total failure of the traditional therapeutic approach to T2DM (otherwise, why do we keep losing the battle?). We're already "paying for the sins" of this erroneous approach which is based on, what we now know to be two great illusions of the past century, namely, glucocentrism and intensification. On the other hand, numerous recently published studies provide alarming data regarding serious side effects of blind intensification in T2DM. They raise major concerns and call for a revision of the traditional approach. Since insulin is an integral and deeply rooted part of the intensification agenda of treating T2DM, it has now suffered a serious drawback and there are more to come.

Therefore, we need to understand the true purpose of anti-diabetic medications in general and insulin in particular, in the realm of T2DM treatment plans in order to avoid "throwing the baby out with the bathwater". For that reason, we found the "ELEPHANT" acronym is a helpful reminder. After all, when correctly administered (i.e. correct indications and doses), insulin is an excellent medication.

But in the meantime, we can quote Craig Currie (9), who promised: “I can’t disclose too much but there will be contemporary data coming out that I think will potentially scare people a bit. The tide is turning. I think within 2 or 3 years, certainly 5 years, insulin is going to be a highly restricted drug in T2DM. The elephant in the room is insulin”.

Additional information

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