

Алгоритм лечения сахарного диабета 2 типа в свете «гравичесентрической концепции»

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Резюме. Эпидемический рост числа больных сахарным диабетом 2 типа (СД2) во всем мире продолжается, несмотря на все усилия, предпринимаемые международным врачебным сообществом. Появление новых лекарственных средств не способствует сдерживанию заболеваемости, ужесточение критериев диагностики обуславливает скачкообразный прирост численности больных, а пересмотр основных целей лечения (снижение целевых показателей гликемического контроля) часто становится аргументом в пользу излишне агрессивного подхода к фармакотерапии диабета. Используемые в мире алгоритмы ведения пациентов с СД2 [1] основной терапевтической целью ставят достижение и длительное поддержание показателей гликемического контроля, максимально близких к нормальным значениям, при этом практически не акцентируются на устранении факторов, патогенетически связанных с развитием и прогрессированием основного заболевания, таких как гиподинамия и избыток массы тела. Во имя достижения целевых показателей гликемии пациенты нередко получают лечение, которое заведомо способствует набору массы тела, прогрессированию инсулинорезистентности и усилению относительного дефицита инсулина, приводящему в итоге к потребности в экзогенном инсулине. В то же время, активное воздействие на патогенетические факторы развития СД2 — избыток массы тела и гиподинамию — может приводить к восстановлению регуляции углеводного обмена, снижая потребность в фармакотерапии вплоть до полной ее отмены, что было показано во многих крупных исследованиях [2]. «Гравичесентрическая концепция» лечения СД2 призвана пересмотреть основные терапевтические цели и изменить расстановку акцентов в схеме ведения пациентов. Ее задача состоит в том, чтобы создать у врачей и пациентов ясное представление о возможности деинтенсификации фармакотерапии при определенных условиях и сфокусировать максимум усилий на устранении факторов прогрессирования заболевания с надеждой на излечение или ремиссию.

The gravicentric Concept in type 2 Diabetes: practical implementation

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Resume. The epidemic rise of patients with type 2 diabetes mellitus (T2DM) worldwide continues, despite all efforts taken by the international medical community to curb it. It seems that the advent of new drugs does not contribute to a better control of the disease, the tightening up of diagnostic criteria causes an abrupt increase in the number of patients, while a revision of the main goals of treatment (a reduction of targets for glycemic control) often becomes an argument in favor of an overly aggressive approach to drug therapy in diabetes. The main therapeutic goal of existing algorithms for the management of T2DM patients is to achieve and maintain long-term indicators of glycemic control, as close to normal values as possible. However, almost none of these algorithms address the factors associated with the pathogenesis of development and progression of the underlying disease, such as lack of exercise and excessive adiposity. For the sake of achieving glycemic target values, patients often receive treatment that is known to be conducive to weight gain, insulin resistance and increased progression of relative insulin deficiency, eventually leading to the prescription of exogenous insulin. At the same time, an active modification of the pathogenetic factors of T2DM — excess body weight and physical inactivity — may lead to restoration of glucose tolerance, reducing the need of pharmacotherapy until its complete withdrawal, as has been shown in many major studies [2]. The "gravicentric concept" of treatment of T2DM is designed to redefine the basic therapeutic targets and change the emphasis in the of patients' management scheme. Its mission is to create a clear idea for both doctors and patients about the possibility of de-intensification of pharmacotherapy under certain conditions, and to focus maximum effort to address the factors of progression of the disease with the hope of a cure or remission. *Keywords:* type 2 diabetes; body weight; algorithm; therapy

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Abbreviations

CSII — Continuous Subcutaneous Insulin Infusions (pump therapy)

Double "O" Syndrome — the "Overeating-Overtreating" syndrome

MDI — Multiple Daily Injections

Mt — Metformin

Mt-IBT — Metformin + Incretin-Based Therapy

OAD- Oral Antidiabetic Drugs

T2DM — Type 2 Diabetes Mellitus

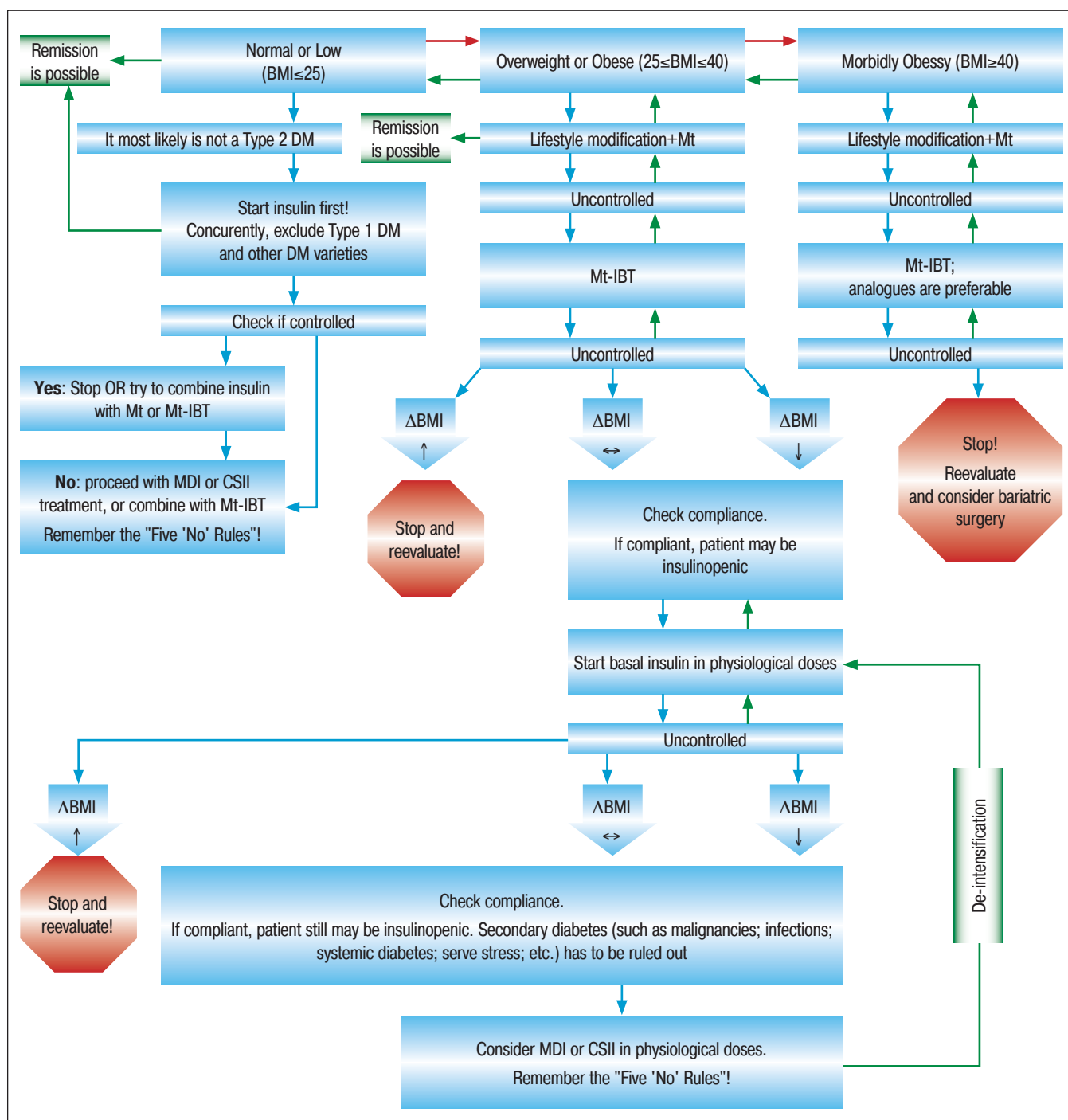


Fig. 1: Treatment algorithm for newly diagnosed Type 2 Diabetes patients in view of "Graventric Concept".

CSII – Continuous Subcutaneous Insulin Infusions (pump therapy); MDI – Multiple Daily Injections; Mt – Metformin; Mt-IBT – Metformin + Incretin-Based Therapy; OAD – Oral Antidiabetic Drugs; Δ Delta – 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; ↓ Declining parameter; ↔ Stable parameter

TZD – Thiozolidonediones

- Physiological doses of Basal Insulin: ≤ 0.4 U/kg
- Physiological doses of Total Daily Insulin: ≤ 0.6 U/kg

In modern-day medicine, obesity is widely recognized as "public enemy". Indeed, it is a grave threat to the health and wellbeing of millions. The American Heart Association has for many years considered it a disease and an independent risk factor for cardiovascular disease [3, 4]. Recently, the American Medical Association (AMA) has reinforced this opinion, declaring it too recognizes obesity as a "disease" which determines the prognosis of cardiovascular disease – the main cause of death of the adult population in western countries [5].

There is mounting evidence that weight loss is a key part of prevention and treatment not only for cardiovascular disease in individuals with obesity; weight reduction is also the base of successful treatment and cure of type 2 diabetes (a long-term remission) [2]. An approach to the treatment of T2DM, which places as its main therapeutic goal a decrease in body mass index (BMI) instead of emphasizing indicators of glycemic control, has been previously named "gravicentric theory" [6]. This approach is not consistent with most "glucocentric" algorithms recommended by the international medical community [7], the main focus of which is the achievement of glycemic target values (blood glucose; glycated hemoglobin). Unlike those therapeutic schemes,

our algorithm is aimed at the gradual de-intensification of glucose-lowering drug therapy through the elimination of one of the major pathogenetic mechanisms of development and progression of the disease: excessive body weight. It also distinguishes the "gravicentric concept" from the traditional approaches that imply a unidirectional, gradual intensification of pharmacotherapy in parallel with the impairment of the regulatory mechanisms of carbohydrate metabolism.

The presented algorithm for the treatment of patients with T2DM, based on the "gravicentric concept", is simple to use, taking the "Five 'No' Rules" of our new concept as a cornerstone [6]:

- No cascade "add-on" therapies for obese/overweight patients with a positive weight balance;
- No weight gain allowed regardless of the type of treatment;
- No use for all hypoglycemic agents and TZDs; Preference for antihyperglycemic medications;
- No chronic insulin for morbidly obese patient;
- No supraphysiological doses of insulin (more than 0.5–0.6 U/kg of current body weight) and no insulin/OAD dose-elevation for persons who gain weight.

Despite traditional guidelines, no cascade "add – on" schemes are implemented here; in the vast majority of insulin – treated patients it is recommended to use only the medium-duration insulin and genetically engineered long-acting insulin analogues, but not a "basal-bolus" regimen in multiple daily injections. Chronic insulin therapy is unequivocally not recommended for patients suffering from morbid obesity, with a focus on insulin administration in the "physiological" doses (less than 0.5–0.6 U / kg of current patient's weight), which is strongly emphasized [8].

The algorithm presented here assumes the possibility of de-intensification of pharmacotherapy during the course of any initial treatment scheme, alongside with the normalization of the patient's body weight. It offers a variety of approaches to the treatment of newly diagnosed T2DM persons as well as patients with long-standing diabetes. The following is a detailed description of the algorithm, which focuses on the treatment of newly diagnosed T2DM patients in terms of "gravicentric concept" (Fig. 1).

Algorithm description

All patients with newly diagnosed T2DM are split into groups according to three main BMI categories: normal or low ($BMI \leq 25$); overweight or obese ($25 \leq BMI < 40$); and morbidly obese ($BMI \geq 40$). This classification permits physicians to properly evaluate the intrinsic pancreatic function while deciding on the proper treatment scheme for the patient. Clearly, patients who are obese, gaining weight, and especially, morbidly obese persons, have a very low probability of being truly insulinopenic.

Normal or low ($BMI \leq 25$)

Unlike overtly obese/overweight persons, patients with normal or low BMI are much less likely to develop type 2 diabetes. Therefore, if patients with normal/low BMI or with severe weight loss during the onset of the disease show signs of T2DM, it is essential to rule out other forms of diabetes, such as: LADA; MODY; mitochondrial diabetes; and various types of secondary diabetes. However, in such instances, there is a likelihood of various degrees of insulinopenia and

so, it is preferable to start treatment with insulin first. Even a short-term insulin therapy should eliminate glucose toxicity, place the patient's β -cells on rest, and may result in a remission of type 2 diabetes or in a "honey moon" in type-1 diabetes [9].

If all other possible causes of impaired carbohydrate metabolism besides T2DM are excluded, it is possible to combine insulin therapy with Metformin (Mt) alone or with incretin-based therapy (Mt-IBT). If the diabetes still remains uncontrolled, physicians may implement treatment with MDI (multiple daily injections) or CSII (continuous subcutaneous insulin infusion). Prescribing insulin in physiological doses and in accordance to the "Five 'No' Rules" is of the highest priority.

Overweight or obese ($25 \leq BMI < 40$)

The vast majority of patients with type 2 diabetes fall into this category. Lifestyle changes and effective correction of eating and exercise habits are crucial to this group. Indeed, the results of the recently published "Look AHEAD" study convincingly show that thanks to lifestyle modification alone, diabetes remission may reach a rate of 11.5% per year. The benefit of an intensive lifestyle remained significant in the 4 year duration of the study, though with lesser remission rates during the following years [2].

The first conversation about diabetes is a critical educational moment in the life of a patient newly diagnosed with T2DM and it is vital that they should get proper information regarding the reversibility of their disease. All in all, the remission of type 2 diabetes is no longer a legend. Thus, the presentation of this valuable information to patients, especially at the beginning of diabetes, is crucial and can improve their motivation and compliance.

Adding Metformin to lifestyle modification is very effective. The most significant influences of this medication are the inhibition of aerobic glycolysis and reduced efficiency of energy production (instead of 38 molecules of ATP to only 2 molecules of ATP per glucose molecule in anaerobic glycolysis) [10; 12]. Given the understanding of type 2 diabetes as "energy intoxication", from the perspective of the "gravicentric concept", treatment with Mt can be considered as pathogenetic therapy. Equally important is the effect of Metformin on insulin resistance. Improvement in insulin sensitivity may lead to a decreased blood insulin concentration, while maintaining normal glucose concentration. Decreasing of insulin levels in the blood leads to a declining of its lipotrophic effect and significantly simplifies weight reduction in obese persons.

The use of weight-neutral or weight-lowering medications is crucial in these cases. Given the fact that progressive weight gain is a "natural history" of diabetes [6], it becomes evident that the so-called "weight-neutral drugs", such as Mt, α -glycosidase inhibitors and DPP4 inhibitors, are actually weight-lowering.

Providing a patient's diabetes cannot be controlled with lifestyle modifications and Mt, a combination of the above with Incretin Based Therapies (IBT) is recommended. This combination should be effective in the vast majority of type 2 diabetes persons. However, if the disease still remains uncontrolled, there are three main possibilities which are yet again, weight-dependent.

1. **T2DM remains uncontrolled while the patient gains weight.** This indicates bad eating habits, low exercise activity and probably poor adherence to medications. At this point, the physician must stop and thoroughly reevaluate the situation. It is important to consider and rule out secondary diabetes, such as Cushing's; acromegaly; hypothyroidism; thyrotoxicosis; etc., as well as reasons for weight gain other than adiposity, like heart or renal failure with fluid retention, severe stress, use of medications with an anabolic effect or appetite stimulants; etc.
2. **The disease remains uncontrolled while the patient's weight remains stable.** Poor medication adherence may be a plausible cause. However, if compliance is not an issue, the patient may be truly insulinopenic.
3. **The diabetes remains uncontrolled yet the patient loses weight.** In such cases insulinopenia is highly suspected and therapy with insulins of medium duration or with long-acting insulin analogues should be started.

Body weight dynamics should be re-evaluated every 3 to 6 months.

- If the patient exhibits elevated glycemic control values while gradually gaining weight and as long as compliance with medication and lifestyle modification is satisfactory, no additional therapy is needed. This situation indicates a strong likelihood of overtreatment (e.g., patients may consume many additional carbohydrates for the prevention of frequent hypoglycemic episodes) and thus, therapy must be carefully reassessed.
- If weight remains stable or continues to go down, MDI or CSII should be taken into account, but only after a reevaluation and the exclusion of comorbidities such as malignancies; infections (e.g., tuberculosis; HIV; etc.); systemic diseases; hormonal disturbances (e.g., Adrenal insufficiency), etc. .

Notwithstanding insulin therapy, even with MDI or CSII, there is often a possibility of de-intensification of pharmacotherapy until remission.

Morbidly obese (BMI \geq 40)

In general, morbidly obese type 2 diabetes patients have the poorest eating and exercise habits. Lifestyle modifications are of utmost importance in this group, but unfortunately, the majority of these patients have little motivation and sometimes their abilities are medically limited. The aim of glucose-lowering therapy in such patients should be phar-

macological support of weight loss or, at the very least, the preservation of current body weight. Therefore, Mt-IBT is the treatment of choice in patients whose diabetes remained uncontrolled in spite of lifestyle intervention. Mt +GLP-1 analogues are preferable because of a much more impressive effect on body weight. Given the recognition of bariatric surgery as an effective treatment for T2DM (American Diabetes Association), it is strongly recommended to consider surgical treatment of obesity. Chronic insulin therapy should be avoided, as it will invariably cause greater weight gain.

It should be kept in mind that since the "gravicentric concept" guidelines deal with anti-hyperglycemic therapy as opposed to hypoglycemic therapy, the target of glycemic control may be set at HbA_{1c} <7.0% or even <6.5%, regardless of patient's age, diabetes duration, co-morbidities and other secondary measurements. Thus the probability of hypoglycemia and latent hypoglycemia is extremely low even with such stringent treatment goals.

Summary

The algorithm for the treatment of type 2 diabetes introduced in this paper is a practical implementation of the "gravicentric concept" and may be a useful tool in the hands of physicians and endocrinologists. It gives a clear idea regarding the best treatment scheme in patients who are motivated to achieve remission and are able to follow the prescribed lifestyle and dietary modifications.

Unfortunately, not all patients with T2DM will be able to follow the path towards de-intensification of drug therapy. This may be caused not only by low motivation and non-compliance, but also by a wide variety of forms of diabetes, the presence of comorbidities that prevent weight loss or significantly limit physical activity, as well as by other conditions. The above approach has certain disadvantages that are particularly associated with the complexities of growth estimates and weight parameters in patients with non-standard constitution, such as athletes, children younger than 18, etc., as well as with the verification of the diagnosis of T2DM itself (it is a known fact that there are no pathognomonic features which distinguish T2DM from other types of diabetes with a probability of more than 95%).

Yet the presented algorithm is designed to be the basis of the pathogenetic treatment of T2DM and a powerful tool for motivating patients to modify lifestyle – the most important component of effective treatment of this non-infectious epidemic of our time.

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