Review

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The Concept of Development of Insulin Resistance in Type 2 Diabetes Mellitus: A Systematic Review

Kuat P. Oshakbayev [*,†] , Altay N. Nabiyev [†] , Aigul K. Durmanova , Gani M. Kuttymuratov , Timur S. Suleimenov , Nurzhan A. Bikhanov , Alisher S. Idrissov , Guldana Zh. Bazheneyeva , Kenzhekyz Manekenova , Ainur A. Akilzhanova , Bibazhar A. Dukenbayeva [*]

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Review

The Concept of Development of Insulin Resistance in Type 2 Diabetes Mellitus: A Systematic Review

Short Title: The Concept of Type 2 Diabetes Mellitus Development

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Abstract

Background: The impact of overweight and adipocyte size on the development of type 2 diabetes mellitus (T2DM) even remains unclear. **Aim:** To study: 1) the relationship between the state of adipocytes and/or overweight/obesity, the development of T2DM and its clinical and laboratory signs; 2) the effect of weight loss on glycemic level, hyperinsulinemia (HI), insulin resistance (IR), and T2DM status. **Methods.** Design: a systematic review. Settings: Web of Science, EBSCO, Scopus/ Science-Direct, Google Scholar, PubMed, Cochrane, и Wolter Kluwer were searched for articles published for 26 years (2000-2026). The study bases on a systematic review of 3853 articles published worldwide. **Results.** In total, 142 full-text articles were assessed for eligibility. With an increase in overweight, the size of adipose tissue increases, adipocytes increase, the cell radius increase. All it leads to an overload of intracellular transport and internal organs. Increase in cell size triggers intracellular mechanisms to limit further nutrient supply. When cell size increases excessively, conformational changes in cellular receptors are activated, resulting in the development of IR. The increase in cell size and the maximum accumulation of overweight, as parallel processes, lead to hyperglycemia and HI with gradual development of IR and T2DM. Any type of intentional weight loss leads to a decrease in IR, HI and the disappearance of T2DM. Targeted weight loss in patients with T2DM improves metabolic and cardiovascular health, reduces blood pressure and blood sugar, reduces doctor visits, normalization of HbA1c, HI, IR. **Conclusions.** IR is a protective reaction of the cells, preventing its oversaturation and overflow. Overweight is an independent risk factor for the development of T2DM and its clinical and laboratory manifestations. Targeted weight loss leads to disappearance of symptoms of HI, IR and T2DM.

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Keywords: type 2 diabetes mellitus; insulin resistance; hyperinsulinemia; HbA1c; "obesity paradox"; overweight (maximum); overweight (growing); weight loss

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global socio-clinical public health problem affecting more than 450 million people worldwide, [US Centers for Disease Control and Prevention. National diabetes statistics report. 2024. https://www.cdc.gov/diabetes/php/data-research/index.html] with high morbidity and mortality rates in both adults and children[1–3].

Over the past twenty years, an increasing number of clinical studies have been collected showing the disappearance of clinical and laboratory indicators of T2DM with a decrease in body fat mass[4,5]. This has led to a boom in the use of various methods of weight loss in patients with T2DM. Among these weight loss methods, three main areas with evidence-based medical basis have attracted particular attention: pharmacological therapy[6,7], bariatric surgery[8,9], and low-calorie diets with physical activity. [10]Each of these methods has its own advantages and disadvantages. [9,11]

Some authors suggest that "...we have misunderstood the cause of T2DM development, so we have been treating T2DM incorrectly...". [7,8,12]

Despite the increasing use of glucagon-like peptide-1 receptor agonists (GLP-1RA) and sodium-glucose transport protein 2 inhibitors (SGLT-2i), many people with T2DM often have glycated hemoglobin (HbA1c) levels that exceed the American Diabetes Association's recommended target values for long periods of time. [7,13]

The normal state of glucose in the blood is ensured by insulin under constantly changing conditions in accordance with the principle of the cybernetic feedback system through dynamic alignment. For example, long-term insulin therapy in T2DM sooner or later leads to a decrease in synthesis and suppression of pancreatic beta cells, which worsens insulin resistance (IR) and, consequently, leads to an increase in the dose of exogenous insulin[14,15].

Mechanistic ideas about the harmful effects of sugar are not supported by any research, as glucose does not accumulate in the body. Today, the pathogenesis of T2DM appears to be much more complex than simply depleted insulin stores or decreased activity of the islets of Langerhans. [5,14,16]

To date, there is no consensus regarding the underlying cause of metabolic disturbances in the pathogenesis of T2DM. Some authors believe that the development of T2DM occurs as a result of long-term essential hypertension, which leads to reduced peripheral blood flow and the development of IR. [12,17,18]Other researchers suggest that a hereditary predisposition to IR and obesity, combined with low physical activity and overnutrition, determines the development of tissue IR and, as a consequence, compensatory hyperinsulinemia (HI). [17,19–21]

There are also studies showing that central obesity is a cause of IR, HI and other metabolic disorders. Visceral adipose tissue adipocytes secrete free fatty acids directly into the hepatic portal vein, high concentrations of which suppress hepatic insulin uptake, leading to HI and relative IR. [7,8].

Another theory of the pathogenesis of IR in obesity has recently been discussed, according to which IR is caused by changes in the levels of hormones (leptin, ghrelin, adiponectin, etc.) in these people. [22]For example, leptin/ghrelin/adiponectin, etc. are hormones synthesized by adipocytes in adipose tissue; their levels closely correlate with body mass index (BMI) and regulate the feeling of satiety at the level of the subcortical nuclei of the brain. [23,24]

In patients with T2DM, dyslipidemia gradually causes atherosclerotic systemic changes in many arteries of organs and systems, leading to the development of renovascular hypertension, psoriasis, fatty liver/pancreatosis, and systemic inflammatory diseases. [22,25–27]

However, why does an overweight person eventually develop impaired glucose tolerance followed by the onset of T2DM?[22,28]. What is the reason that T2DM is almost always accompanied by overweight, which tends to decrease somewhat against the background of T2DM, which worsens the course of the disease itself? [29]Why is there an "obesity paradox," which suggests that gaining

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weight may actually be beneficial for the body, such that obesity in patients with chronic diseases may have protective effects, such as reducing mortality.[30,31]. How can we explain that targeted reduction of overweight leads to normalization of blood sugar, [32–35]and what pathophysiological mechanisms are involved? These and other questions concerning the mechanism of development of T2DM formed the basis for this systematic review, the purpose of which was to investigate: 1) the relationship between the state of adipocytes and/or overweight/obesity, the development of T2DM and its clinical and laboratory signs; 2) the effects of weight loss on glycemic level, HI, IR, and T2DM status.

2. Methods

2.1. Design and Registration

We conducted a literature systematic review. Details of the historical subject matter and clinical/research practice, detailed combined inductive and deductive analysis including results, authors' reflections, and lessons learned as applicable. This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[36].

2.2. Review Questions and Search Strategy

Two research questions of the systematic review: 1) the inductive question (cause): what is the affect of increasing adipocyte size and/or overweight/obesity on the development of IR and HI in T2DM? 2) the deductive question (effectiveness): what is the effect of weight loss on glycemia, GI, IR, and T2DM?

We searched seven electronic databases (Web of Science Core Collection/ pre-Prints/ EndNoteClick/ Kopernio/Medline, EBSCO/ Medline-Complete, Scopus/ EMBASE/ Science-Direct, Google Scholar, NCBI/PubMed, Cochrane/CENTRAL, и Ovid/Wolter Kluwer). We considered HbA1c, HI, and IR as parameters of T2DM.

The search results were recorded, analyzed, and the selection criteria were applied. Articles identified during the initial database review were assessed for inclusion/exclusion criteria if they represented original, peer-reviewed epidemiological and clinical studies conducted on humans or animals. There were no language restrictions. The search was repeated before the final analysis (qualitative/quantitative assessment), and eligible studies were selected for inclusion in this study. All articles considered eligible for this systematic review were required to contain data on adipocyte size, BMI, HbA1c, development of IR, HI, and T2DM.

Primary outcomes: increased adipocyte size; overweight/obesity, IR, T2DM. *Secondary endpoints:* HI, HbA1c, and lipids.

2.3. Inclusion and Exclusion Criteria

Study inclusion. For *the first question* of the systematic review, epidemiological, observational, cohort, cross-sectional, case-control studies and systematic reviews and meta-analyses were included. For *the second question* of the systematic review, randomized clinical trials, experimental studies, systematic reviews, and meta-analyses were included. The search for published studies was conducted between January 2000 and January 2026.

The search used a combination of MeSH terms and keywords, both together and individually: increased adipocyte size and number (both exposure and outcome); weight change, overweight/obesity (exposure and outcome); HbA1c (outcome); HI (outcome); IR (outcome); T2DM (outcome); dyslipidemia/hyperlipidemia (outcome); "obesity paradox"; body potential energy and capacity for weight gain (exposure and outcome); weight loss/gain (exposure and outcome). From the included studies, we selected full-text articles demonstrating the influence of adipocyte size, body weight, and/or overweight/obesity on the development of IR, HI, and T2DM. We briefly discussed

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the interactions between the exposures and outcomes, as well as the impact of targeted weight loss on these outcomes.

Exclusion criteria: articles not indexed by Web of Science/Scopus, or PubMed; articles assessing glycemic parameters in inherited diseases; conference abstracts; book chapters; thesis/dissertations; case reports; editorials; articles that did not report any of our pre-specified primary and secondary outcomes.

2.4. Quality Assessment of the Included Studies

Three researchers (O.K., D.B., and K.G.) independently assessed a paper report form for each article and then reached an agreement on the included studies and the extracted data, according to the study inclusion/exclusion, with the other three authors (D.A., N.A., and I.A.). The researchers considered the validity and rigor of the study, the reliability of the results, the generalizability or applicability of the results, and the usefulness and how useful and relevant the results included in the study were. Three researchers (O.K., D.B., and K.G.) conducted the data analysis, and other three researchers (B.N., S.T., and M.K.) reviewed, verified and validated the results.

Ethics approval. The Ethical Committee of the University Medical Center (phone: +7-7172-69-25-86; Web: https://umc.org.kz/en/?ethics-commission=post-2; Email: asanova.aruzhan@umc.org.kz) approved the study (approval protocol #8/2024/ПЭ of 28.08.2024; monitoring and re-approval protocol #1/2025/ПЭ of 12.02.2025. Board Affiliation: University Medical Center). The committee confirms that all methods were performed in accordance with the Declaration of Helsinki and guidelines of the Council for International Organizations of Medical Sciences (CIOMS). In this study, patients were not physically enrolled in the study.

Definition of the term "Dysfunction of overweight". Lipids in the body perform various functions, such as an energy source, a shock-absorbing cushion for organs, an insulating and structural function, a fat depot, and the adsorption of various substances. [37,38]Overweight is a part of lipids that represent a depot in the form of fat reserves. Overweight serves as a source of energy in the absence of available food. Consequently, overweight dysfunction occurs when the body does not demand excess body weight, which leads to the interference of adipose tissue in the body's metabolic processes. [39]

3. Results

3.1. Search Results

The initial search included 3853 relevant articles and 46 pre-printed articles. 1761 records were removed after duplicates. After the titles/abstracts/texts were evaluated, 1792 articles also were excluded. In total, 346 full-text articles were assessed for eligibility. From them, 204 articles were excluded for the following reasons: 52 articles did not measure adipocytes; 42 articles did not examine the relationship between excess BMI/obesity and adipocyte size; 29 articles did not provide sufficient data on glycemic parameters; 81 articles contained non-quantitative parameters. The final sample comprised 142 quantitative articles (77 were observational studies and 65 were clinical studies). Literature screening is summarized in Figure 1.

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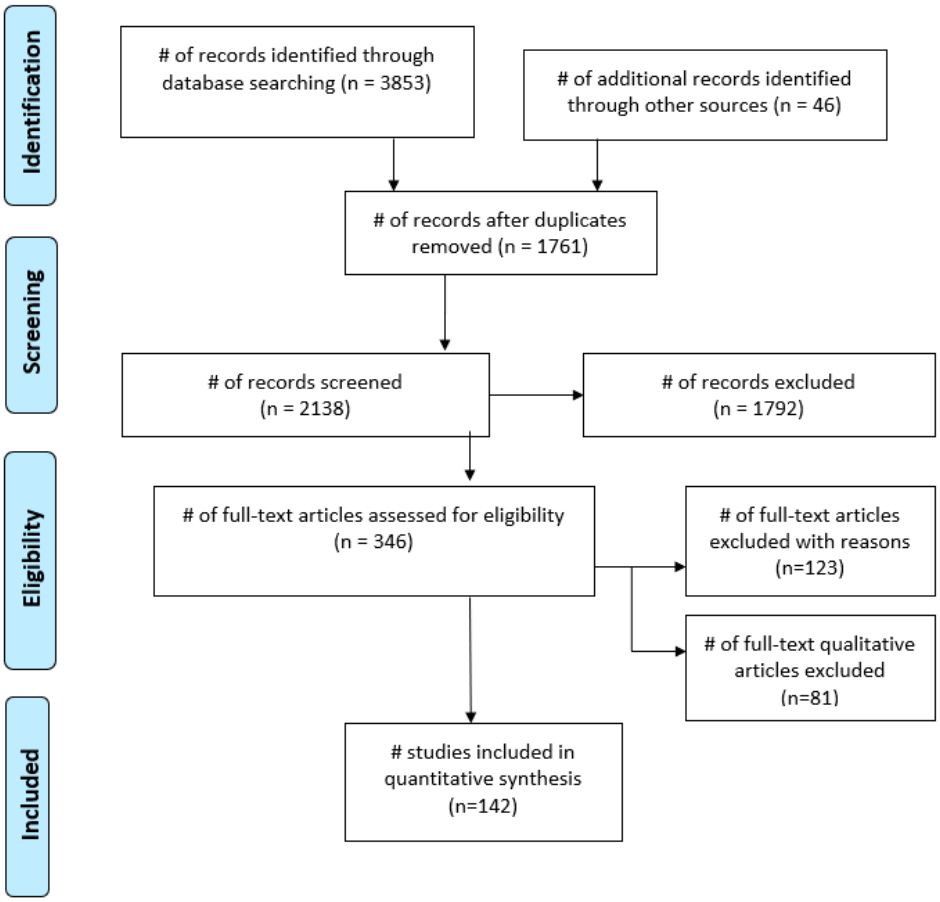

Figure 1. PRISMA Flow Diagram. Data collection process.

3.2. Characteristics of Included Studies

We included both animal and human studies because the study inclusion terms underlie the development of all biological organisms (including humans). All the studies were published between January 2000 and January 2026 (26 years). 113 human studies, 29 animal studies, including 56 systematic reviews/meta-analyses (a total of 142 articles) were included in the analysis. **Table 1** summarizes the results of the relationship between overweight/obesity and/or increased adipocyte size (exposure) and increased HbA1c, insulin, and the development of IR and T2DM (outcomes) based on data from 77 original epidemiological/observational studies, including systematic reviews and meta-analyses.

Table 1. The relationship between overweight/obesity and/or increased adipocyte size (exposure) and increased HbA1c, insulin, and the development of IR and T2DM (outcomes) based on data from original epidemiological/observational studies, including systematic reviews and meta-analyses.

Authors	Protocol	Overweight/obesity, increased adipocytes	HbA1c, HI, IR, T2DM
		Human studies	
Dundar et al., 2022 [2]	860 subjects	Overweight/obesity	Elevated HOMA-IR, developed T2DM

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Zhao et al., 2023[12]	12 studies	Overweight/obesity, increased adipocytes	Elevated HbA1c, HOMA-IR, lipotoxicity
Bakker et al., 1998[19]	1986 subjects	Overweight	Elevated HbA1c
Ricci et al., 2015[8]	22 studies, 4160 subjects	Overweight/obesity	Elevated HbA1c, HOMA-IR
Tahrani et al., 2022[9]	55 studies	Overweight/obesity	Elevated HbA1c, HOMA-IR
Papaetis et al., 2025[22]	14 studies	Overweight, increased adipocytes	Elevated HOMA-IR, lipotoxicity, developed T2DM
Verkest et al., 2011[23]	294 subjects	Overweight/obesity	HI, Elevated HOMA-IR
Villagrán-Silva et al., 2025[21]	24 studies	Overweight/obesity	Elevated HbA1c, HOMA-IR, and miRNA
Musilanga et al., 2024[3]	30 studies	Overweight/obesity	Elevated HbA1c, HOMA-IR, developed T2DM
McLaughlin et al., 2014[61]	148 subjects	Overweight/increased adipocytes	Elevated HOMA-IR
Nakamura et al., 2020[74]	32 studies	Overweight/increased adipocytes	Elevated HbA1c, HOMA-IR, lipotoxicity, developed T2DM, cardiomyopathy
Nakamura, 2024 [42]	47 studies	Overweight/increased adipocytes	Elevated HbA1c, HOMA-IR, lipotoxicity, developed T2DM
Szablewski et al., 2024[46]	14 studies	Overweight/increased adipocytes	Elevated HOMA-IR, lipotoxicity, developed T2DM
Ferrannini et al., 2004[163]	14 studies	Overweight/obesity	Increased β-cell mass, Elevated IR, developed T2DM
Berglund et al., 2016[164]	331 subjects	Overweight/obesity	Elevated HbA1c, developed HI
Cotillard at el., 2014 [75]	295 subjects	Overweight/increased adipocytes	Elevated HbA1c, developed HI, T2DM
Szukiewicz et al., 2023[50]	27 studies	Overweight/obesity	Developed IR, T2DM, Chronic diseases

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Castillo et al., 2023[53]	38 studies	Overweight/Intracellular lipid accumulation	Developed IR
Guria et al., 2023[48]	53 studies	Overweight/macrophage lipid infiltration	Developed IR, T2DM
Ye et al., 2022[72]	62 studies	Overweight/increased adipocytes/ectopic fat accumulation	Developed IR, T2DM
van Vliet et al., 2020[92]	24 subjects	Overweight/increased adipocytes/ectopic fat accumulation	Developed IR, HI, developed T2DM
Sarkar et al., 2019[93]	650 subjects	Overweight/weight gain	Developed IR, β-cell deficiency, developed T2DM
Vertemati et al., 2008 [95]	56 subjects	Overweight/increased adipocytes	Developed IR, T2DM
Human and animal studies			
Lipke et al., 2022[44]	35 studies	Overweight/increased adipocytes	Elevated HbA1c, HOMA-IR, lipotoxicity
Mota et al., 2016[45]	22 studies	Overweight/increased adipocytes	Developed IR, lipotoxicity
Longo et al., 2019[52]	19 studies	Overweight/increased adipocytes	Lipotoxicity, developed T2DM
Ahmed et al., 2021[47]	26 studies	Overweight/increased adipocytes	Elevated HbA1c, HOMA-IR, lipotoxicity
Dahik et al., 2020[56]	37 studies	Overweight/increased adipocytes	Elevated HbA1c, HOMA-IR, lipotoxicity
Armato et al., 2025 [57]	1860 subjects	No overweight	Elevated HbA1c, Developed IR
Animal studies			
Hu et al., 2001[24]	Animal study (104 dogs)	Overweight/obesity	Developed HI, developed HOMA-IR
Setayesh et al., 2019 [40]	Animal study (36 mice)	Overweight/obesity	Developed HI, DNA damage
Ozcan at el., 2014[70]	Animal study (90 mice)	Overweight/obesity	Developed IR, T2DM

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Peyot et al., 2010[91]	Animal study (Mice)	Obesity/ lipid deposition	Developed IR, beta-cell failure
Bozec et al., 2016 [96]	Animal study (Mice)	Overweight/increased adipocytes	Developed IR, hypoxia, adipocyte apoptosis
Sakaguchi et al., 2017[97]	Animal study (Mice)	Overweight/increased adipocytes	Developed IR, T2DM, metabolic syndrome

Abbreviations: HbA1c, glycated hemoglobin; DNA, deoxyribonucleic acid; HI, hyperinsulinemia; HOMA-IR, the Homeostasis Model Assessment of insulin resistance index; IR, insulin resistance; T2DM, type two diabetes mellitus; VLCD, very-low-calorie diet.

With an increase in overweight, the load on internal organs increases. [40,41]An increase in overweight is accompanied by an increase in the size of adipose tissue. [12,22]If the cell size increases due to fat accumulation, the increase in cell radius leads to an overload of intracellular transport mechanisms. The number of pathways for delivering nutrients from the membrane surface to the center of the cell increases, and, conversely, the removal of metabolic products from the cell to the surface increases.[42,43], lipotoxicity and glucose toxicity develop. [44,45]An increase in the volume of functioning cells (cytomegaly) occurs either as a result of cells hypertrophy or, as in T2DM, as a result of fat accumulation. This leads to a disruption of the cell's energy supply system. An increase in cell size/volume/number (hypertrophy and hyperplasia) triggers intracellular mechanisms to limit/stop further nutrient supply to the cell. One of such mechanisms may be conformational changes in cellular receptors, leading to a decrease in the sensitivity of cellular receptors to the anabolic effect of insulin, which, in turn, causes the development of the clinical IR. [46,47]The processes of forced infiltration of cells with fats, including macrophages, [48]can lead to either apoptosis or necrosis. [49,50]In clinical practice, this may manifest as progressive weight loss in patients with T2DM. [51,52]Weight loss in patients with chronic diseases is a compensatory and adaptive measure of the body. The mechanism of cellular IR development is a necessary measure to limit further nutrient penetration into the cell. [53,54]

In contrast, decompensated T2DM triggers lipolysis, characteristic of diabetes, as a result of false energy starvation and the "search" for additional energy sources caused by counter-insular hormones. IR manifests itself at the receptor level, meaning changes in the conformational properties of receptors lead to the inability to transport nutrient substrates into the cell. [55,56]

The reserves of the enlarged (cytomegulated) cell decrease in their dynamic properties and become less full-fledged for the following reasons (Figure 2):

1. In such an enlarged cell, the number of blood vessels per unit tissue surface area decreases. The additional blood supply, innervation, and trophism of the enlarged cell overload its transport functions.

2. As a result of enlarged cells, the specific surface area of cells increases relatively, and as a result, the intercellular space decreases, intercellular metabolism worsen, and a relative deficiency of oxygen, regulatory mediators, and hormones occurs.

3. In the enlarged cells, the relationships between intracellular structures are disrupted. Cell mass growth lags behind the growth of mitochondria, endoplasmic reticulum, ribosomes, and other components of intracellular organelles. The rate of oxidation-reduction reactions in the cytoplasm decreases, and energy supply functions deteriorate.

4. The tissue's nervous system and its conduction system suffer from excessive nervous regulation, and conditions for cell trophism worsen.

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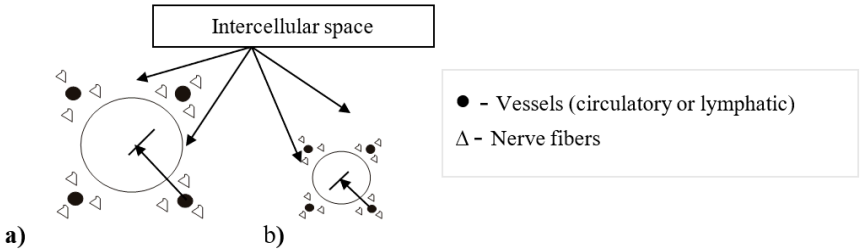

Figure 2. Schematic representation of a cell and the comparative relationship of its structural elements (vessels and nerves around the cell; cell radius, the distance from the center to the surface of the cell) with an increase in its size. Comparison of the structural elements of an enlarged cell (a) and a normal cell (b).

Over time, the cytomegulated cell loses its functional adaptive value and ceases to be useful for the body.

An enlarged cell is an unfavorable process for its normal functioning. The consequences of this include compression of blood vessels, impaired circulation, and impaired innervation. Increased cell size due to chronic nutrient consumption always occurs alongside the accumulation of overweight. Some studies suggest that up to 25% of the population, even those who are not overweight, may have elevated HbA1c and blood insulin, leading to the further development of T2DM. [57]In the literature, this is called the "obesity paradox," [30,58]which we will discuss in more detail in the Discussion section.

Table 2 presents the results of the impact of weight loss (intervention) on the regression of parameters (HbA1c, IR, T2DM (outcomes)) based on 65 original randomized clinical and experimental trials, including systematic reviews and meta-analysis.

Table 2. The relationship between weight loss (intervention) and such parameters as HbA1c, insulin resistance, and development of T2DM (outcomes) based on data from randomized clinical trials, animal studies, including systematic reviews and meta-analyses.

Authors	Protocol	Weight loss	Parameters of T2DM (HbA1c, IR)
Franz et al., 2015[4]	Human study (6754 patients) Diet therapy	Weight loss ≥5%	Decreased HbA1c
Ricci et al., 2015[8]	Human studies (22 studies, 4160 patients) Bariatric Surgery	Weight loss ≥10%	Decreased HbA1c, HOMA-IR, T2DM remission
Tahrani et al., 2022[9]	Human studies (12 studies) Bariatric	Weight loss ≥10-30%	Decreased HbA1c, HOMA-IR, T2DM remission
Tahrani et al., 2022[9]	Human studies (11 studies) Lifestyle	Weight loss ≥7.8%	Decreased HbA1c, HOMA-IR, T2DM remission
Tahrani et al., 2022[9]	Human studies (12 studies) Pharmacotherapy	Weight loss ≥10%	Decreased HbA1c, HOMA-IR, T2DM remission

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Lean et al., 2019 [165]	Human studies (149 patients) Lifestyle	Weight loss ≥10%	Decreased HbA1c, HOMA-IR, T2DM remission
Fonseca et al., 2019[6]	Human study (2432 patients) Semaglutide	Weight loss ≥7%	Decreased HbA1c, HOMA-IR
Kashyap et al., 2022[10]	Human studies (16 studies including 834 patients) VLCD	Weight loss ≥5%	Decreased HbA1c
Horn et al., 2022[11]	Human studies (45 studies) Lifestyle, Pharmacotherapy, Bariatric Surgery	Weight loss ≥5-15%	Decreased HbA1c, HOMA-IR
Zhao et al., 2023[12]	Human studies (26 studies) Diet therapy vs. Pharmacotherapy	Weight loss≥5-10%	Decreased HbA1c, HOMA-IR
Buse et al., 2020[32]	American Diabetes Association и European Association for the Study of Diabetes (2018) Pharmacotherapy	Weight loss≥5%	Decreased HbA1c, HOMA-IR
Oshakbayev et al., 2017[34]	Human study (272 patients) VLCD	Weight loss≥10%	Decreased HbA1c, HOMA-IR
Setayesh et al., 2019 [40]	Animal study (36 mice)	Weight loss	Decreased IR, inflammation and DNA damages in internal organs
Daniele et al., [41]	Human studies (26 studies) caloric restriction diet	Weight loss≥10%	Decreased HbA1c, HOMA-IR, SBP/DBP
Cotillard et al., 2014 [75]	Human study (74 patients) Bariatric Surgery	Weight loss≥10%	Decreased HbA1c, HOMA-IR
Reinehr et al., 2004 [81]	Human study (232 patients)	Weight loss≥5%	Decreased HOMA-IR
Oshakbayev et al., 2019[60]	Human study (80 patients)	Weight loss≥10%	Decreased HbA1c, HOMA-IR, NASH

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	VLCD		
Ferrannini et al., 2004[163]	Human studies (17 studies) Pharmacotherapy vs. Bariatric Surgery	Weight loss≥10%	Decreased HbA1c, HOMA-IR
Goni et al., 2017[166]	Human study (757 subjects) Low-fat diet vs. high-fat diet	Weight loss≥5%	Decreased HOMA-IR
van Vliet et al., 2020[92]	Human studies (24 studies)	Weight loss≥20%	Decreased HOMA-IR, basal/postprandial insulin secretion
Zhang et al., 2015[101]	Human studies (26 studies)	Weight loss/Autophagy	Decreased HbA1c, HOMA-IR
Murphy et al., 2017 [99]	Human studies (33 studies)	Weight loss ≥7-10%	Decreased IR, adipocyte size, cardiometabolic diseases
Oshakbayev et al., 2026[121]	Human study (130 patients)	Weight loss ≥10-20%	Decreased HbA1c, HOMA-IR cardiometabolic diseases, T2DM
Banji et al., 2025 [122]	Human studies (56 studies)	Weight loss ≥10-20%	Decreased HbA1c, HOMA-IR, T2DM
Albai et al., 2025[59]	Human study (256 patients)	Weight loss ≥10%	Decreased HbA1c, HOMA-IR, T2DM, MASLD
Delrue et al., 2025[123]	Human studies (25 studies)	Weight loss ≥10%	Decreased HbA1c, HOMA-IR, T2DM
Wei et al., 2025[124]	Human studies (39 studies)	Weight loss ≥10-20%	Decreased HbA1c, HOMA-IR, T2DM
Lingvay et al., 2020 [157]	Human study (995 patients)	Weight loss ≥5-10%	Decreased HbA1c, lipids, SBP/DBP, T2DM
Davies et al., 2022 [131]	Human studies (57 studies) Drug therapy, VLCD	Weight loss ≥5-10-20%	Decreased HbA1c, HOMA-IR, lipids, cardiorenal health, T2DM

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Jooste et al., 2023 [159]	Human studies (11 studies and 1519 patients) VLCD	Weight loss ≥5-10%	Decreased HbA1c, HOMA-IR, lipids, T2DM
Van den Burg et al., 2023 [133]	Human studies (9 studies) Different diets	Weight loss ≥5-10%	Decreased HbA1c, BMR, T2DM
Schauer et al., 2012 [140]	Human study (150 patients). Medical and bariatric surgery	Weight loss ≥10-25%	Decreased HbA1c, HOMA-IR, lipids, SBP/DBP, T2DM

Abbreviations: HbA1c, glycated hemoglobin; DNA, deoxyribonucleic acid; HI, hyperinsulinemia; HOMA-IR, the Homeostasis Model Assessment of insulin resistance index; IR, insulin resistance; NASH, Nonalcoholic Steatohepatitis; SBP/DBP, systolic/diastolic blood pressure; T2DM, type two diabetes mellitus; VLCD, very-low-calorie diet.

Weight loss interventions resulted in significant reductions in all glycemic parameters (fasting glucose, HbA1c, blood insulin), improvements in liver and kidney function, and normalization of lipids and blood pressure. [32,41,59,60]Regardless of methods of intentional weight loss, one way or another, there is always a reduction in HbA1c, HI, IR, and T2DM.

4. Discussion

From a pathophysiological point of view, T2DM literally represents sugar in the blood when a cell, saturated with fats (nutrients), is no longer able to store them. [61]Impaired glucose tolerance is an indirect indicator of excess fat in the body's cells, when lipid-saturated cells have a limited reserve for further utilization of glucose from the blood. Cells do not contain glucose, they contain fat, which is what glucose is converted into when its level in the blood rise. [62]The cell gradually increases in size as it becomes saturated with fats. [61,63]With an increase in radius (a cell as a fractal body has a radius calculated as the distance from the surface of the cell to its center), *the distance from the cell surface to its center increases, which, accordingly, increases the path of transport of trophic and metabolic products from the surface to the center of the cell.*

Chronic overeating coupled with overweight disrupts digestion and leads to metabolic intoxication and immune stress. [64,65]An increase in blood glucose leads to glycogenogenesis and lipogenesis, since when the saturation limit of cells with glycogen is reached, fat synthesis occurs. [62]The rationale for this sequence is that glycogen is a more hydrophilic and large-molecular compound than fats. In the context of an extremely continuous supply of nutrients, lipogenesis is a more energetically efficient process, since lipids are less reactive and take up less space; for example, the caloric value of 1 gram of fat is approximately equal to 3-4 grams of glucose. [62,63]Glucose, due to its relatively high hydrophilic properties, is high reactivity and occupies a relatively large space. [66,67]Fats/lipids are considered the most structurally diverse class of nutrients, with an estimated 20,000 to 40,000 unique discrete structures found in nature. Unlike proteins or carbohydrates, which are composed of a limited set of standard monomers (20 amino acids or a few sugars), lipids represent a huge variety of chemically distinct molecules.

Postprandial increase in blood carbohydrates and lipids (cholesterol, triglycerides) leads to the utilization of newly synthesized endogenous fats in depots (visceral, subcutaneous fats). If the fat depot becomes overloaded over time, then excess fat (interstitial, intercellular fat) begins to accumulate in the functionally active cells of the body, which leads to the development of metabolic disorders. Much attention is paid to the increase in blood postprandial glucose, which is of crucial metabolic importance for sustentation a constant HI.[68]. An increase in HbA1c level is one of

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indicators of the buffering properties of red blood cells. [69]The more functionally active cells are involved, the more pronounced the clinical manifestations of the disease. [70]The process of lipid infiltration of functionally active cells (also known as ectopic fat accumulation) is slowed down by the body's defense reactions, such as increased blood pressure, body temperature, free-radical oxidation, etc., which increases the rate of metabolism, [71–73], phagocytosis (the formation of foam cells, which then stick to the walls of blood vessels, forming atherosclerotic plaques), and IR. [74,75]

The natural "packaging" of nutrients in the body occurs in stages. The body has evolved the ability to store nutrients economically (using its space and energy). [76]There is a certain limit to the weight and volume of nutrient accumulation. Once glycogen has accumulated sufficiently, a transition to fat accumulation occurs, but if the body urgently needs glucose, glycogen can provide the body/cell with energy much faster (glycogen can, if necessary, act as an “emergency” energy source) than lipids. [77]

The more hydrophobic a molecule is, the easier it is for the body to retain energy – it takes up less space and is less reactive. Lipids are hydrophobic and chemically inert, but have a higher energy content. During the process of β-oxidation, one molecule of fatty acid (palmitic acid) releases 130 ATP molecules, whereas during the complete oxidation of one glucose molecule, only 36-38 ATP molecules are formed.[78]. Atherosclerotic plaques contain the most hydrophobic lipids, which is why they begin to accumulate in organisms that have not had the opportunity to reduce excess body mass. [79]

When target cells become overloaded with fat due to overweight, they use the resources of the body's organs and tissues to support their own vital functions. For example, with obesity, the levels of many hormones (insulin, ghrelin, prolactin, cortisol, etc.) increase in proportion to body weight. [80,81]Excess tissue requires vitamins, enzymes, hormones, and innervation to perform their vital functions. The body's internal organs have to perform additional work (nutrition, removal of toxins) on the enlarged cells. Overweight is in the growing stage. Over time, the body's compensatory resources become depleted. In the context of obesity, the islet system of the pancreas is depleted, and as the β-cells of the pancreas reduce adequate (in addition to overweight) insulin secretion, the symptoms of diabetes worsen. [72,82]Overweight leads to a relative insulin deficiency. Conversely, after weight loss, adipocyte insulin response returns to normal. [34,60,81]HI in overweight is not a primary but a secondary disorder.

Long-term non-use of fat reserves by the body leads to atheromatosis/atherosclerosis. [83]Since space in the body is limited, unsaturated fats are transformed into saturated fats, or HDL is converted into LDL/VLDL. [84]Overweight is under growing stage. Each subsequent stage of weight gain is characterized by a compaction of nutrients in the body. [85]Over time, the body reaches its individual “maximum overweight,” meaning that each person has their own terminal overweight. [86]

Nature has "invented" a way to store energy in the form of fat for use between meals, or during natural disasters when food availability decreased. The main source of energy reserves are lipids (adipose tissue). It is no coincidence that the ratio of nutrients in the body: fats, protein and carbohydrates is on average 2-8 (depending on the degree of obesity): 1: 0.25, respectively. [87]Fat accumulation is biologically and chemically preferable. The main factor controlling the rate of lipogenesis is the body's nutritional status. [88]

The need to gain additional fat reserves was one of the foundations of survival in conditions of food shortage, which has always accompanied humanity. In conditions of relatively high food availability, this ability leads to obesity. [89,90]We were not taught what eating behavior should be under conditions of relative nutrient excess.

Chronic overeating combined with overweight expends/consumes the body's potential energy on the processes of chemical digestion, absorption, transport, storage, and elimination of excess metabolites. [64,65]Increased insulin secretion by the pancreas is required to compensate for IR and maintain normal carbohydrate metabolism. In obese patients, the rate of insulin secretion is 3-4 times higher than in people with normal body weight, and HI is caused by both increased insulin secretion

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and decreased insulin clearance. [91,92]Gradually, the body's compensatory resources are depleted, and its additional synthetic and excretory functions are reduced. [93]

HI is a physiological response to each food consumption. [94]Chronic overeating against the background of constant postprandial hyperglycemia and hyperlipidemia leads to overweight. (Figure 3) Forced accumulation of fats in the body leads to an increase in cell size. [95]HI occurs as a compensation for the forced accumulation of fats by cells.[92] Hyperfunction of pancreatic β-cells leads to compensatory HI. An increase in HbA1c is a sign of both HI and a prolonged increase in postprandial blood glucose levels. [68,69]When cells have accumulated fat to the limit, its further increase can threaten their own destruction (death, apoptosis). [96]This happens in parallel when overweight is growing. HI induces conformational changes in cell membrane receptors leading to IR to limit further nutrient accumulation. [97]HI gradually loses its compensatory and adaptive value.

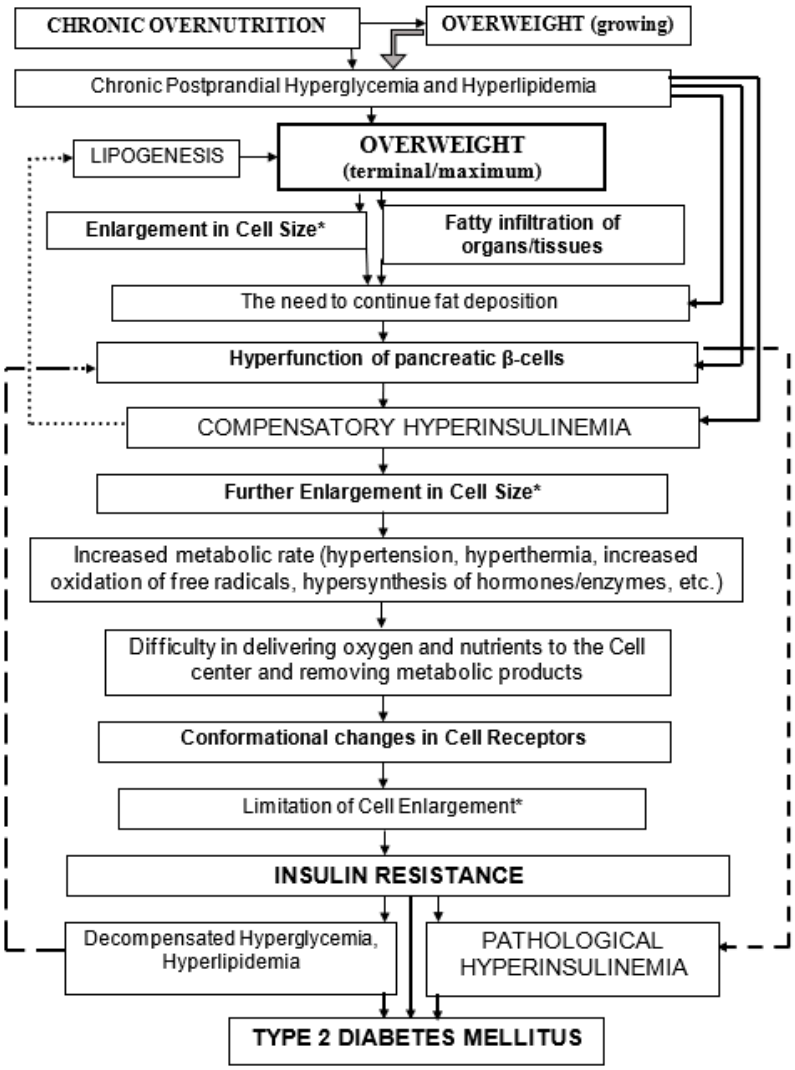

Figure 3. The concept of development of type 2 diabetes mellitus in the context of hyperinsulinemia and insulin resistance against the background of overweight. * Adipocytes and other cells of the body with lipid deposition.

IR is the body's pathophysiological reaction against the background of further entry of nutrients into the blood (hyperglycemia, hyperlipidemia). (Figure 3) IR is a rational response/process of the body that limits further flow of nutrients into the cells. IR occurs when overweight reaches terminal growth. Fat reserves stored in the body themselves require metabolic attention from the body, that is, they must be provided with blood circulation, thermoregulation, anabolic and catabolic

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metabolism. [97]IR is a protective mechanism of cells against dangerous fat deposition and superfluous energy expenditure. [96,98]In turn, IR triggers a cascade of protective mechanisms that increase the speed of oxidation-reduction processes, increase the pulse rate and respiration, etc. [97,99]This adaptive-compensatory mechanism is limited by the size of the cells. [73]Under IR conditions, the HI phenomenon suppresses lipolysis, which aggravates the progression of obesity and worsens IR itself. [100]Long-term HI, accompanied by overeating and overweight, depletes the secretory of pancreatic β-cells that develops cellular intolerance to glucose. IR development limits further accumulation of fat in cells.[101,102]: A doom loop is created in which it is sometimes difficult to understand what is primary and what is secondary. Hyperglycemia, HI, IR are different links of the same pathogenetic chain in the development of T2DM.

Dysfunction of overweight is a prerequisite for the development of IR. Terminal Overweight (maximum) depletes and limits the reserve capacity of the body's organs and tissues, including pancreatic β-cells. IR occurs when cellular spatial reserves are depleted and serves as a defense against excess fat deposition. IR is not a primary, but a secondary pathophysiological element in T2DM. We should cope with not the consequence (IR), but the cause is overweight.

Figure 3 presents the concept of development of T2DM and its symptoms/syndromes. The figure shows that the development of T2DM is associated with dynamic changes in overweight; the development of HI and IR are associated with the dynamics of overweight growth, and the final stage of IR is associated with reaching maximum values of overweight, which leads to the development of T2DM.

The effect of overweight *on basal metabolic rate (BMR).*

Overweight is the cause of the increase in overall energy costs[103]. Weight gain requires an increase in BMR and increased food intake. Most of the BMR is spent on the consuming and processing food. [104]The body expends about 50 kcal/day of its own potential energy for every 100 kcal/day of additional food intake. [105]BMR accounts for 75-80% of total energy expenditure, and only 20-25% of energy expenditure is spent on external work such as physical and mental activity.[106–108]. Daily excess food consumption increases the metabolic load on the body, as it increases both BMR and active metabolism. [109]Overweight speeds up BMR.[90,110,111]. Overweight people are more likely to complain of fatigue. [112]One kilogram of excess weight deprives the body of approximately 50 kcal/day of daily energy expenditure. [113]On average, increasing food consumption by 175 and 204 kcal/day results in 100 kcal of energy expended per day. [114]

The over-metabolism mode uses up the body's excess "vital energy". [115,116] Overweight is a useless cycle of consuming adenosine triphosphate[117]. The more active the metabolism, the higher the oxidative stress and the higher the oxidative function of the mitochondria.[115,116]. When consuming excess protein, the body expends more energy, which increases the thermogenic effect to 25% of total energy expenditure.[65]. A protein diet speeds up BMR. Overweight increases the total amount of metabolites.[118,119]. Restricting food intake can reduce your BMR by up to 45%. [120] Weight loss reduces BMR and increases lifespan.[106,119].

Therefore, there is a certain limit to the growth of cell volume. IR protects the cell from oversaturation, and limits the flow of nutrients into the cell to prevent its destruction. IR does not occur immediately; it is accompanied by hyperglycemia and HI, which are subsequent stages of a gradual process of metabolic disorder. In practice, any intentional weight loss leads to a decrease in IR, HI and the disappearance of T2DM. [59,121–124]Overweight correlates with the development of many chronic diseases such as T2DM, hypertension, allergic and inflammatory diseases, urolithiasis and cholelithiasis, fatty liver diseases and liver fibrosis, as well as tumors. [89,125]Overweight is a constant and chronic consumer of insulin, limiting the reserve capacity of pancreatic β-cells. Overweight is an independent risk factor for T2DM. We need to address the cause (overweight), not the symptom (IR). Treatment of T2DM requires proactive weight loss. Overweight shortens life expectancy, while weight loss increases it.[126]. Увеличение веса негативно сказывается на энергетическом балансе организма. Weight gain negatively impacts the body's energy balance.

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Intentional weight loss reduces cardiovascular risks, the need for medications and improves glycemic metabolism. [127,128]Weight loss in patients with T2DM results in cost savings through reduced doctor visits, medication tests, sick days, emergency department visits and hospitalizations, reduces the risk of developing of chronic diseases, and has long-term economic benefits. [129,130]

GLP-1 receptor agonists and GIP/GLP-1 agonists demonstrate significant weight loss, simultaneous improvements in blood pressure and blood sugar, and a reduction in cardiovascular events.[131,132]. The more weight lost, the better the fasting blood glucose, lipids, and blood pressure. [130,133–138]After bariatric surgery, the need for antidiabetic and antihypertensive medications is often gradually reduced (under strict medical supervision) due to improved metabolic and cardiovascular health. [124,139]Significant weight loss allows for discontinuation of symptomatic medications due to the need to reduce the dose or completely discontinue previously taken medications. [140,141]

The obesity paradox: Some people with T2DM are not obese; not all obese people develop diabetes. T2DM does not develop with a single fixed level of overweight; T2DM manifests with an individual level of overweight accumulation, namely its maximum value. [142,143]Thus, this is an indicator of the individual level of compensatory capabilities of each organism. One of the limits of the body's compensatory function can be considered the moment of stabilization of maximum overweight, when the body's weight does not increase even with further excessive food consumption. [57,109]The volume of feces produced increases. As compensatory reserves are depleted, sooner or later, a person with overweight will develop T2DM. [28,58]

Each person has own individual body weight and unique BMR, so the body's potential energy is the potential ability to gain weight – the more potential energy a person has, the more weight he can gain. [144,145]The body’s ability to gain weight is limited by its finite potential energy. [146,147]The limit of weight gain is the point at which the body weight cannot be increased further and the body weight stabilizes at its maximum point of overweight, which is called the "maximum overweight" or "maximum body weight", and it is different for each person. [118,144]Body weight is an aggregated and integral indicator of the body's energy reserve.

Individual body weight and individual limits to weight gain may explain the “obesity paradox,” where obesity in older patients with chronic diseases may be correlated with reduced mortality among them.[30,31].

A person capable of accumulating overweight is potentially strong, and the more excess body mass they can accumulate, the more individual potential energy they have. It's important to understand that this potential energy is expended on the biological maintenance of overweight. The more weight a weightlifter can lift, the more potential strength he has, but when he lifts the barbell to its maximum weight, all of his potential energy begins to be expended as kinetic energy to lift and hold the barbell. Health status of people should not be compared based on overall/average body weight, as body weight is an individual variable for each person. Each person has their own individual maximum weight limit and unique potential energy reserves. It is necessary to compare the health level of the same person with different dynamics of his weight, which may indicate the degree of his individual potential energy.

Weight loss creates "potential energy in the body," which enhances physical and mental performance and promotes recovery from illness or weight regain. Individual limits to weight gain may explain the "obesity paradox." [30,31,57,58]

It is necessary to distinguish three modes of body weight change in adults.

1. The body is in a state of excess body weight gain, which is when their potential energy begins to be expended on increasing/maintaining their weight (*Growing overweight mode*). The body can gain weight until it reaches the individual's maximum overweight point.

2. When the body is in the weight loss mode, there are two options: 1) intentional weight loss (restrictive diets, physical activity, etc.); 2) unintentional weight loss (chronic diseases, infections, stress and distress, other pathologies). Intentional (targeted) weight loss allows the body to increase potential energy, which promotes recovery and healing. [108,119,148]If there is an unintentional

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weight loss, then the body loses own potential energy, which is an unfavorable indicator for health. [30,58,143]Almost any illness leads to unintentional weight loss because BMR increases.[29] Perhaps the body copes better with the illness if weight loss occurs. Weight loss due to chronic and/or oncological diseases (unintentional weight loss) leads to depletion of BMR, while intentional weight loss (restrictive dieting) helps maintain BMR. [111,149,150]

3. When the body reaches its "maximum overweight", it gradually loses its own potential energy needed to maintain/provide for that overweight (biological, biochemical, mechanical, etc.). The development of pathology is a sign of a potential energy crisis. It is no coincidence that diseases are accompanied by unintentional weight loss. [128,151]Losing weight helps the body recover more quickly; simply restricting food intake reduces BMR by up to 45%. [120] A restricted diet improves intestinal microbiota and its function in vitamin synthesis in the intestine. [152,153]Intentional weight loss restores the body's "potential energy" (expended for metabolic maintenance of overweight), which increases physical and mental activity and promotes healing from chronic diseases. [34,128,154–156]

Almost any type of weight loss effort improves anabolic processes, increases hemoglobin levels, improves metabolism in tissues and organs involved in hematopoiesis, [32,131,157–159]increases HDL levels and bone mineral density, [133–136]has an anti-osteoporotic effect, improving bone metabolism. [130,137,138] We should use weight loss methods that allow the body to conserve/safe energy, but also burn accumulated fat at the same time. [129]During weight loss, old fat deposits cause metabolic intoxication, [160]which should be managed.[33,34]

The ability to accumulate fat mass is one of the foundations of survival, since food shortages have always accompanied humanity. This survival rule of “eat anytime, anywhere, at any opportunity” led to the accumulation of fat reserves. [161,162]This "rule of survival" is currently leading to an obesity epidemic. [89,90]“Whatsoever was the father of a disease, an ill diet was the mother” (Greek physician Hippocrates).

5. Conclusions

The results of a systematic review may suggest several distinct hypotheses:

(1) When cell size increases excessively, conformational changes in cellular receptors are activated, resulting in the development of IR, which limits the further flow of nutrients into the body. IR is a protective reaction of the cells, preventing its oversaturation and overflow.

(2) The increase in cell size and the maximum accumulation of overweight, as parallel processes, lead to hyperglycemia and HI with gradual development of IR and T2DM. Overweight is an independent risk factor for the development of T2DM and its clinical and laboratory manifestations.

(3) Intentional targeted weight loss leads to disappearance of symptoms of HI, IR and T2DM.

Strengths and limitations: The manuscript focuses on one biological aspect, such as the dynamics of overweight status, state of adipocytes size can influence the development of T2DM and its clinical and laboratory features in different ways; discussed the vision of the origin of the “obesity paradox”.

This study has several limitations. First, the study was not designed as a meta-analysis. Second, published studies about the influence of dynamics of overweight status is very limited in scope and number. Third, the study included systematic reviews, meta-analyses, animal and human randomized studies. There might be also publication/selection/analysis biases where valuable studies with negative results were not published or published in journals without indexing in main bibliographic sources.

Author Contributions: *KO and DB:* design and performance, narrative analysis and review, bibliography review, data collection, scientific analysis, qualitative analysis, scientific executor, writing, editing, and revision. *NA and DA:* study design, writing the methods and discussion, bibliography, qualitative analysis, paper review, and print. *KG:* study design, research executor, writing the methods, editing, and revision. *BN and ST:* preparation of e-version data collection, bibliography and paper review and re-review, scientific analysis. *IA and BG:*

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preparation of e-version data collection, bibliography, and paper review. *MK:* design and performance, scientific analysis, bibliography, and paper review. *AA:* data collection, writing discussion, and paper review. All authors have read and agreed to the published version of the manuscript. Our manuscript does not contain any individual person's data in any form. All authors of the manuscript affirm that they had access to the study data and reviewed and approved the final manuscript.

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Trial Registration: ClinicalTrials.gov NCT06410352 (05/08/2024): https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S000EG8K&selectaction=Edit&uid=U0006MBT&ts=56&cx=-vph5l9.

Declarations: The study was carried out in the Republic of Kazakhstan from January 5, 2025, through February 28, 2026. Participants were recruited gradually as they arrived in Center for Surgery, Clinical Academic Department of Internal Medicine, Center for Endocrinology at University Medical Center (Astana).

Declaration of Generative AI and AI-assisted technologies in the writing process: During the preparation of this work the authors did not use AI-assisted technologies.

Abbreviations

BMI – body mass index
BMR – basal metabolic rate
GLP-1RA – glucagon-like peptide-1 receptor agonists
HbA1c – glycated hemoglobin
HI – hyperinsulinemia
IR – insulin resistance
SGLT-2i – sodium-glucose transport protein 2 inhibitors
T2DM – type 2 diabetes mellitus

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