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DOES COMORBID OBESITY OR CHRONIC PANCREATITIS INFLUENCE THE CHOICE AND EFFECTIVENESS OF GLUCOSE-LOWERING THERAPY IN TYPE 2 DIABETIC PATIENTS?

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Abstract

Introduction. The complexity of the interaction between type 2 diabetes mellitus (T2DM), comorbidities, and emerging complications requires a clinical approach that manages risk while maintaining indicated therapeutic goals.
The objective of the study was to analyse the frequency and effectiveness of mono- and combined glucose-lowering therapy in T2DM patients with obesity and chronic pancreatitis (CP).
Material and methods. The retrospective study analysed 579 medical records of T2DM patients, who were divided in the following groups: group 1- patients with normal body weight and without CP (n=67); group 2 – patients with normal body weight and with CP (n=32); group 3- overweight patients without CP (n=126); group 4 – overweight patients with CP (n=33); group 5 – obese patients without CP (n=262); group 6 – obese patients with CP (n=59). When evaluating

Résumé

Obésité comorbide ou pancréatite chronique, influencent-t-elles le choix et l'efficacité de la thérapie de réduction du glucose chez les patients avec diabète de type 2 ?

Introduction. La complexité de l'interaction entre le diabète sucré de type 2 (DT2), les comorbidités et les complications émergentes nécessite une approche clinique qui gère le risque tout en maintenant les objectifs thérapeutiques indiqués.
L'objectif de l'étude. Le but de cette étude était d'analyser la fréquence et l'efficacité des traitements hypoglycémiants mono- et combinés chez les patients diabétiques de type 2 souffrant d'obésité et de pancréatite chronique (PC).
Matériel et méthodes. L'étude rétrospective a analysé 579 dossiers médicaux des patients atteints de DT2: groupe 1 – patients de poids corporel normal et sans

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the effectiveness of the received therapy, the target value of HbA1c less than 7% was considered.
Results. Most of the patients with T2DM+CP and T2DM with normal body weight received combined therapy. The presence of CP significantly influences the choice of treatment for T2DM, particularly, 81.5% of patients with T2DM and CP were prescribed combined therapy. There was no significant difference between serum glucose and HbA1c levels in patients with only T2DM and comorbid T2DM+CP+overweight/obesity regarding monotherapy vs combined glucose-lowering therapy. However, glucose and HbA1c levels in patients with only T2DM on monotherapy were significantly lower, respectively, by 41.72% and 25.64% vs patients with comorbid CP and overweight/obesity, who were also prescribed monotherapy.
Conclusion. The presence of CP significantly influences the choice of treatment for T2DM, while overweight/obesity is not a criterion for choosing mono- or combined glucose-lowering therapy. The use of metformin as monotherapy and the use of combined therapy in most of patients with only T2DM and comorbid T2DM do not achieve the target levels of glucose and HbA1c.

Keywords: type 2 diabetes mellitus, obesity, chronic pancreatitis, glucose-lowering therapy, effectiveness.

List of abbreviations:
CP – chronic pancreatitis
T2DM – type 2 diabetes mellitus
FFAs – free fatty acids
ApoB – apolipoprotein B
TG – triacylglyceroles
VLDL-C – very low-density lipoprotein cholesterol
HDL-C – high-density lipoprotein cholesterol
BMI – body mass index
ALT – alanine aminotransferase
AST – aspartate aminotransferase
ADA- American Diabetes Association

PC (n=67); groupe 2 – patients avec un poids corporel normal et avec PC (n=32); groupe 3 – patients en surpoids sans PC (n=126); groupe 4 – patients en surpoids atteints de PC (n=33); groupe 5 – patients obèses sans PC (n=262); groupe 6 – patients obèses avec PC (n=59). Lors de l'évaluation de l'efficacité du traitement reçu, la valeur cible d'HbA1c inférieure à 7% a été prise en compte.
Résultats. La grande majorité des patients atteints de DT2 + CP et de DT2 avec un poids corporel normal ont reçu un traitement combiné. La présence de CP affecte significativement le choix du traitement pour le DT2, en particulier, 81,5% des patients atteints de DT2 et de CP ont reçu une thérapie combinée. Il n'y avait pas de différence significative entre les taux de glucose et d'HbA1c chez les patients atteints uniquement de DT2 et de DT2 comorbide avec CP et de surpoids/ obésité en monothérapie par rapport à un traitement hypoglycémiant combiné. Cependant, les taux de glucose et d'HbA1c chez les patients atteints de DT2 uniquement en monothérapie étaient significativement inférieurs, respectivement, de 41,72% et 25,64% par rapport aux patients atteints de CP comorbide et de surpoids / obésité, qui ont également été prescrits en monothérapie.
Conclusion. La présence de CP affecte significativement le choix du traitement pour le DT2, tandis que le surpoids / obésité n'est pas un critère pour choisir un traitement hypoglycémiant mono- ou combiné. L'utilisation de la metformine en monothérapie et l'utilisation d'un traitement combiné chez la grande majorité des patients atteints uniquement de DT2 et de DT2 comorbide n'atteignent pas les taux cibles de glucose et d'HbA1c.

Mots-clés: diabète sucré de type 2, obésité, pancréatite chronique, traitement hypoglycémiant, efficacité.

Introduction

Diabetes mellitus (DM) has become a serious social problem because of its global spread[1]. According to the International Diabetes Federation data, in 2019 there were 463 million people in the world diagnosed with DM, 91% of whom suffered from type 2 diabetes mellitus (T2DM); it is assumed that the number of DM people will reach 700 million by 2045[2]. Healthcare outcomes associated with DM, related expenses and treatment options are complicated by its comorbidities[3]. The well-known comorbidities associated with DM are obesity and dyslipidemia[4,5]. Excessive abdominal fat, deregulation of adipose tissue and inflammation that is characterized by the secretion of diabetogenic adipokine pattern, which contributes to the disruption of insulin action in skeletal muscle, brain, liver, and other organs are factors that connect obesity and dyslipidemia to T2DM[6]. Simultaneously, free fatty acids (FFAs) release is increased by insulin-resistant fat cells; high FFAs levels contribute to the production of triacylglyceroles (TG), which in turn stimulates the secretion of apolipoprotein B (ApoB) and very low-density lipoprotein cholesterol (VLDL-C)[7]. Hyperinsulinemia, in addition to high ApoB and VLDL-C, is associated with low

high-density lipoprotein cholesterol (HDL-C) levels[8]. Hyperglycemia also adversely affects lipoproteins (particularly LDL and VLDL) due to increased glycosylation and oxidation, reduces vascular compliance and promotes the development of aggressive atherosclerosis[9]. There is evidence to suggest that insulin also has a direct atherogenic effect on the vascular wall, and the production of LDL-C and TG is stimulated by hyperinsulinemia[10].

There are other diseases, in addition to well-known comorbidities linked to DM, associated with obesity, insulin resistance (IR), dyslipidemia and T2DM, including chronic pancreatitis (CP). Exocrine insufficiency of the pancreas, determined by the fecal pancreatic elastase-1 levels, was observed in 53.3% of all examined T2DM patients[11]. The development and progression of both CP and T2DM have common pathogenic factors, that is being the reason why these disorders can cause and exacerbate each other. It is noteworthy, that DM patients have about twice the risk of developing pancreatitis, and, conversely, about a third of patients with acute pancreatitis develop pre-diabetes and/or DM[12].

A wide range of therapies is available for the treatment of T2DM patients, and each class has advantages and disadvantages based on their mechanisms of action and clinical experience. The complexity of interaction between T2DM, comorbidities, and emerging complications requires a clinical approach that manages risk while maintaining indicated therapeutic goals[13]. The current methods of T2DM treatment are oral insulin secretagogues, sulfonylureas, repaglinide, nateglinide, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, pramlintide and exenatide[14]. The first choice for the treatment of T2DM, based on its well-defined efficacy, safety profile, low-cost and potential to reduce the risk of cardiovascular events is metformin[15], which inhibits hepatic glucose production and improves insulin sensitivity[11]. Insulin also can be used as hypoglycemic agent T2DM patients. If an initial glycated hemoglobin (HbA1c) level exceeds 9%, or if diabetes is uncontrolled despite optimal oral glycemic therapy, insulin therapy is recommended for T2DM patients[16,17].

The objective of the study was to analyse the frequency of mono- and combined glucose-lowering therapy assignment in T2DM patients with obesity and chronic pancreatitis and to assess the role of comorbidities in the choice of corrective therapy and its effectiveness.

Materials and methods

The retrospective study analysed 579 medical records of patients with T2DM hospitalized in the Endocrinology department of Ternopil University Hospital in 2018-2019, who were divided in the following groups: group 1- patients with normal body weight and without CP (n=67); group 2 – patients with normal body weight and with CP (n=32); group 3- overweight patients without CP (n=126); group 4 – overweight patients with CP (n=33); group 5 – obese patients without CP (n=262); group 6 – obese patients with CP (n=59).

The ethical principles included in the Declaration of Human Rights adopted in Helsinki, in 1975, and revised in 2008, were fully respected in our study. The enrolled subjects participated in this study voluntarily, completed and signed a written informed consent. The study protocol was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University, Ukraine.

The distribution of patients into the study groups is presented in Table 1. There was no significant difference in age and gender between the study groups.

Verification of T2DM was performed in accordance with the recommendations of the American Diabetes Association (ADA) (2019)[14]. The criteria for T2DM diagnosis were based on the value of HbA1c (≥6.5%), which was determined using an automatic biochemical analyzer COBAS 6000 (Roche Hitachi,

Table 1. Study groups (n = 579)

Group	*Patients cohort*	*n*	*% (95 % CI)*
1	T2DM patients with normal body weight and without CP	67	11.57 (8.97; 14.70)
2	T2DM patients with normal body weight and with CP	32	5.53 (3.78; 78.02)
3	Overweight T2DM patients without CP	126	21.76 (18.13; 25.91)
4	Overweight T2DM patients with CP	33	5.70 (3.92; 8.00)
5	Obese T2DM patients without CP	262	45.25 (39.94; 51.07)
6	Obese T2DM patients with CP	59	10.19 (7.76; 13.14)

Germany) and glucose concentration, which was determined using a standard set on an automatic biochemical analyzer BAS INTEGRA® 400 (Roche Diagnostics).

Verification of CP was based on the recommendations of the American Pancreatic Association[18].

The body mass index (BMI) was calculated by the formula: body weight (kg)/ height (m^2). Data were interpreted according to WHO recommendations: normal weight in the range of 20.0-24.9 kg/m^2; overweight (pre-obesity) 25.0-29.9 kg/m^2; class 1 obesity 30.0-34.9 kg/m^2; class 2 obesity 35.0-39.9 kg/m^2 and class 3 obesity > 40 kg/m^2.

Inclusion criteria: clinical, laboratory and instrumental signs of T2DM, CP and obesity, no sharp increase (not more than 3 times from the upper limit of normal) in the activity of alpha-amylase, lipase, alanine aminotransferase (ALT), transaminase (AST), alkaline phosphatase and gamma-glutamyltranspeptidase in blood serum.

Exclusion criteria from the study: signs of clinically significant neurological, mental, renal, hepatic, immunological, gastrointestinal, urogenital disorders, lesions of the musculoskeletal system, skin, sense organs, endocrine system (except T2DM) or hematological diseases that are uncontrolled, acute pancreatitis, unstable or life-threatening heart disease, patients with malignant neoplasms who have not been in complete remission for at least 5 years, medication (drug) dependence, alcohol addiction.

Metformin is the first-line medication in the treatment of T2DM in Ukraine, which is most often used in accordance with the recommendations of the American Diabetes Association and the European Association for the Study of Diabetes[19,20]. According to the analysis of medical records of patients, metformin was received in the minimum dose that ensures the effectiveness and maximum tolerability of the medication, 1500-2000 mg/day.

Combined therapy received by some patients included metformin and sulfonylurea derivative – gliclazide, the medication among the sulfonylurea the most commonly used in the treatment of T2DM due to its pricing policy[21].

When evaluating the effectiveness of the received therapy, the target value of HbA1c less than 7% was highly thought, according to the recommendations of the ADA for glycemic control[14,19].

The study results were analysed using STATISTICA 7.0 and MedCalc software. The Kolmogorov-Smirnov test was used to compare probability distributions. Quantitative values, because of their non-parametric distribution, are given in the form of median, lower, and upper quartiles, and compared using the Mann-Whitney test. For frequency values, the percentage ratio and its 95% confidence interval were calculated, and their comparative analysis was performed using Pearson's chi-square test and Fisher's bilateral test.

Results

The statistical analysis indicates the probability of differences between the study groups depending on the type of glucose-lowering therapy for T2DM patients and the influence on the choice of corrective therapy for comorbid pathology. Thus, majority of patients with T2DM, regardless of BMI and the presence of CP, received combined therapy. The highest percentage of patients on combined therapy was recorded in the T2DM+CP group (Table 2).

When analysing the frequency of different types of glucose-lowering therapy for T2DM, depending on the presence or absence of comorbid CP, it was found that 81.45% of patients with T2DM + CP received combined therapy (metformin + sulfonylurea derivatives), which exceeded the number of patients on metformin monotherapy, as well as the number of patients with T2DM without CP (Table 3).

When analysing the frequency of different types of glucose-lowering therapy for T2DM, depending on the body mass index, it was found that patients with T2DM and normal body weight most often received combined therapy. The highest percentage of patients on combined therapy was recorded at T2DM with normal body weight (Table 4).

There was no significant difference between serum glucose and HbA1c levels in patients with only T2DM and comorbid T2DM with CP and overweight/obesity with monotherapy vs combined glucose-lowering therapy. However, glucose and HbA1c levels in patients with only T2DM on metformin monotherapy were significantly lower, respectively, by 41.72% and 25.64%, compared to those in patients with comorbid T2DM with CP and overweight/obesity, who were also prescribed monotherapy (Table 5).

The obtained data indicate the influence of comorbidity on the choice of treatment for T2DM. Most of patients with T2DM+CP and T2DM with normal body weight received combined therapy (metformin + sulfonylurea derivatives).

Both the use of metformin as monotherapy and the use of combined therapy (metformin + gliclazide) in most of patients with only T2DM and comorbid T2DM with CP and overweight/obesity do not achieve the target levels of glucose and HbA1c (Table 6).

Table 2. Characteristics of glucose-lowering therapy for T2DM patients

Groups	*Monotherapy (metformin)*		*Combined therapy (metformin + gliclazide)*	
	n	*% (95 % CI)*	*n*	*% (95 % CI)*
Group 1	17	2.37 (14.78; 40.62)	50	74.63 (55.39; 98.39)
Group 2	4	12.50 (3.41; 32.00)	28	87.50 (58.14; 100.00)
Group 3	47	37.30 (27.14; 49.60)	79	62.70 (49.64; 78.14)
Group 4	6	18.18 (6.67; 39.57)	27	81.82 (53.92; 100.00)
Group 5	96	36.64 (29.68; 44.75)	166	63.36 (54.09; 73.76)
Group 6	13	22.03 (11.73; 37.68)	46	77.97 (57.08; 100.00)
χ^2 Pearson's, p	χ^2=16.82; p=0.005*			

Note. * – statistically significant results.

Table 3. Characteristics of glucose-lowering therapy for T2DM patients depending on the presence or absence of chronic pancreatitis

Groups	*Monotherapy (metformin)*		*Combined therapy (metformin + gliclazide)*	
	n	*% (95 % CI)*	*n*	*% (95 % CI)*
T2DM without CP (Groups 1+3+5)	160	35.16 (29.93; 41.06)	295	64.84 (57.65; 72.67)
T2DM with CP (Groups 2+4+6)	23	18.55 (11.76; 27.83)	101	81.45# (66.34; 98.97)
p	<0.001*			

Note. * – statistically significant results regarding the type of glucose-lowering therapy; # – statistically significant results regarding the presence or absence of CP

Table 4. Characteristics of glucose-lowering therapy for T2DM patients depending on the presence or absence of overweight/obesity

Groups	*Monotherapy (metformin)*		*Combined therapy (metformin + gliclazide)*	
	n	*% (95 % CI)*	*n*	*% (95 % CI)*
T2DM patients with normal body weight (Groups 1+2)	21	21.21 (13.13; 32.42)	78	78.79 (62.28; 98.33)
T2DM patients with overweight (Groups 3+4)	53	33.33 (24.97; 43.60)	106	66.67 (54.58; 80.63)
T2DM patients with obesity (Groups 5+6)	109	33.96 (27.88; 40.96)	212	66.04 (57.45; 75.56)
χ^2 Pearson's, p	χ^2=5.99; p=0.05			

Table 5. Glycemic and HbA1c indicators of T2DM patients depending on the type of glucose-lowering therapy

Indicators	*Monotherapy (metformin) (n=183)*	*Combined therapy (metformin + gliclazide) (n=396)*
	without comorbidity (Group 1)	
	n=17	n=50
Glucose, mmol/L	7.67 (5.90; 9.31)	8.46 (6.24; 10.32)
HbA1c, %	7.41 (5.56; 8.50)	7.68 (6.41; 9.05)
	with comorbidity (Groups 2+3+4+5+6)	
	n=166	n=346
Glucose, mmol/L	10.87# (8.90; 13.31)	9.70 (7.80; 12.94)
HbA1c, %	9.31# (8.30; 10.50)	8.70 (7.47; 10.00)

Note. There are no statistical differences depending on the type of glucose-lowering therapy (p> 0.05).
– statistically significant results regarding the presence or absence of comorbidity

Table 6. HbA1c levels of T2DM patients

Groups	*Level of HbA1c*			
	Target (<7 %)		*High (>7 %)*	
	n	*% (95 % CI)*	*n*	*% (95 % CI)*
	without comorbidity (Group 1)			
Patients receiving metformin (n=17)	6	35.29 (31.29; 39.29)	11	64.71 (59.98; 69.44)
Patients receiving combined therapy (n=50)	11	22.00 (17.27; 26.73)	39	87.00 (81.35; 92.65)
	with comorbidity (Groups 2+3+4+5+6)			
Patients receiving metformin (n=166)	27	16.27 (10.72; 22.47)	156	83.73 (71.69; 99.92)
Patients receiving combined therapy (n=346)	65	17.79 (12.67; 20.92)	331	82.21 (73.82; 92.09)
Fisher's criterion, p	p >0.05			

Discussion

The development of T2DM is based on relative insulin insufficiency which, in turn, occurs when the patient has two combined pathophysiological disorders – decreased sensitivity of peripheral tissues to insulin (insulin resistance (IR)) and deterioration of the insular apparatus of pancreatic β-cells. The activity and contribution of each of these two mechanisms to the etiology and pathogenesis of T2DM are different, regardless of the presence or absence of obesity[22,23]. It should be emphasized that T2DM is a progressive metabolic disease in which carbohydrate metabolism is deteriorated over time (due to the so-called phenomenon of "glucose intoxication")[24,25]. Therefore, appropriate glucose-lowering therapy allows not only to reduce glycemia, to achieve compensation for diabetes, to eliminate the clinical manifestations of the disease, but also to break the "vicious circle" caused by the phenomenon of "glucose toxicity".

For the treatment of T2DM, eight groups of glucose-lowering tablets are currently used – oral glucose-lowering agents[26]. However, according to various sources, 30-50% of patients diagnosed with T2DM receive insulin therapy[14,19]. According to the UK Prospective Diabetes Study (UKPDS), a landmark randomized multicenter trial of glycemic therapies in 5,102 patients with newly diagnosed T2DM, already at the stage of initial diagnosis, 5-10% of patients need constant insulin therapy, and after 10-12 years this indicator is already reaching 80%[27]. Most often, modern tactics of T2DM treatment, which involves the correction of chronic hyperglycemia by overcoming IR and improving β-cell function of the pancreas, are to prescribe a combination of biguanides and sulfonylureas[28]. Metformin belongs to biguanides, it inhibits the formation of glucose in the liver and reduces fasting glycemia, increases hepatic and peripheral insulin sensitivity (but does not affect its secretion), influences on insulin receptors. Thus, the effect of metformin helps to reduce IR at various levels: in the liver, skeletal muscle and adipose tissue. Metformin slows down the absorption of carbohydrates in the intestine, enhances glucose utilization by the cells of the intestinal mucosa and smooths glycemic peaks after eating[29].

In addition, metformin has anorexigenic effect. The drug slows down the development of T2DM, promotes weight loss and has a protective cardiovascular effect, improves lipid metabolism, with a decrease of FFAs levels, LDL-C and VLDL-C, an increase of HDL-C levels, inhibition of oxidative stress, improvement of vascular relaxation and a decrease of the proliferation of smooth muscle cells[29]. Thus, metformin is well tolerated, is not associated with hypoglycemia, promotes weight loss and is safe in the short- and long-term perspective; it may provide a protective effect against cardiovascular disease and certain types of cancer[30].

Sulfonylurea derivatives are considered first-line glucose-lowering drugs if the patient has a normal body weight, postprandial hyperglycemia predominates, moderate insulin deficiency is present, intolerance or contraindication to the use of metformin is determined, if rapid glycemic control is required. They are also recommended for combined oral therapy. Sulfonylurea derivatives stimulate insulin secretion by closing of ATP-sensitive potassium channels and, consequently, opening calcium channels. The accumulation of calcium in the cell triggers the process of insulin secretion[31].

T2DM is a disease that associates many comorbidities. On one hand, diabetes itself contributes to the development of comorbidities, and on the other hand, comorbidities have a serious impact on its course, treatment tactics and clinical outcomes[32-34].

The strategy for the treatment of comorbid diseases is the pathogenetic therapy and a personalized approach. These are the factors that determine the choice of the medication. Our analysis shows the influence of comorbid CP on the choice of treatment tactics for T2DM, particularly, 81.5% of patients with T2DM in combination with CP were prescribed combined therapy (metformin + gliclazide), while overweight/obesity is not a criterion for choosing mono- or combined glucose-lowering therapy.

For a long time, there has been a discussion about how CP and DM are related. In the case of their development in the same patient, should they be considered as two independent diseases, or one of them is a natural consequence of the other? Most studies of pancreatic exocrine function in diabetic patients have reported mild and moderate exocrine pancreatic insufficiency, which has been expressed in a relative decrease of bicarbonate and enzyme production, and severe pancreatic exocrine insufficiency with steatorrhea is relatively rare[35-37]. According to Sirchak et al, in patients with T2DM, CP is formed on the background of biliary pathology, while the functional capacity of the pancreas is greater than in T1DM[38]. There was an inverse correlation of the fecal elastase level with the duration of diabetes and the content of HbA1c, and a direct correlation with the concentration of C-peptide in the group of patients with T2DM[39,40]. In T2DM, the synthesis of amylase and trypsin is disrupted in 15–73% of cases, and there is a feedback of the activity of pancreatic enzymes with postprandial glycemia[41].

Several mechanisms of the development of exocrine pancreatic insufficiency in DM have been suggested[41-45]: insulin deficiency, leading to a decrease of pancreatic trophism, contributes to its atrophy; insulin deficiency reduces the secretion of pancreatic enzymes, in particular, there is a positive correlation between the residual β-cell function and the concentration of fecal elastase-1; change in incretion or imbalance of insulin and other islet hormones (glucagon, somatostatin, pancreatic polypeptide); autoimmune processes common to diabetes and CP: several studies in Japan have shown the presence of antibodies to various antigens of the exocrine pancreas at T1DM, for example, antibodies to pancreatic cytokeratin were detected in 39%, antibodies to lipase in 73.5% and antibodies to lactoferrin or carbonic anhydrase in 77% of all patients; diabetic angiopathy, presumably contributing to the development of pancreatic fibrosis; diabetic neuropathy and impairment of enteropancreatic reflexes.

The assessment of the comorbidity level in patients with T2DM can be clinically significant in predicting the achievement of individual treatment goals of a particular patient and in predicting the development of insulin demand. There was no significant difference between glucose and HbA1c levels in patients with only T2DM and comorbid T2DM with CP and overweight/obesity with glucose-lowering monotherapy vs combined therapy. However, glucose and HbA1c levels in patients with only T2DM on metformin monotherapy were significantly lower than in patients with comorbid T2DM with CP and overweight/obesity who were also prescribed monotherapy. However, in patients who were receiving combined therapy, there was no significant difference between glucose and HbA1c levels in case of only T2DM and comorbid T2DM with CP and overweight/obesity.

In this case, the level of comorbidity is an important criterion to be considered when determining target glycemic values. Predicting the effectiveness of treatment and medical rehabilitation of patients with T2DM allows for a personalized approach to diagnosis and treatment[33]. Our analysis shows that both the use of metformin as monotherapy and the use of combined therapy (metformin + gliclazide) in the vast majority of patients with only T2DM and comorbid T2DM with CP and overweight/obesity does not achieve the target levels of glucose and HbA1c. The obtained data raise concerns, because of the well-known importance of glycemic control in patients with comorbid pathology[32]. Tian et al. also note that long-term maintenance of the target HbA1c level in patients with coronary heart disease and DM reduces the incidence of coronary restenosis and improves the prognosis after percutaneous coronary intervention, and hyperglycemia that precedes stroke aggravates its course and increases the percentage of deaths. Moreover, hyperglycemia control for a relatively short time, preceding the stroke, does not reduce its risk and does not improve the prognosis[46].

Conclusions

It becomes increasingly important to demonstrate the differentiated approach to the glucose-lowering therapy in T2DM patients depending on comorbidities. According to our study, the presence of CP significantly affects the choice of treatment for T2DM, in special combination therapy (metformin + sulfonylurea derivatives), while overweight/obesity is not a criterion for choosing mono- or combined glucose-lowering therapy.

It is important to note that both the use of metformin as monotherapy and the use of combined therapy (metformin + gliclazide) in most of patients with only T2DM and comorbid T2DM with CP and overweight/obesity do not achieve the target levels of

serum glucose and HbA1c. Clinicians should focus on target-oriented nature of diabetes treatment and its effectiveness in individual patients.

Author Contributions:

Conceptualization, M.M.; methodology, U.H., S.D.; software, L.M., Y.D.; validation, U.H.; formal analysis, U.H., S.D.; investigation, U.H; resources, I.K., Y.D.; data curation, U.H.; writing original draft preparation, U.H., Y.D., S.D.; writing review and editing, I.K., M.M. L.M.; visualization, I.K.; supervision, M.M. All the authors have read and agreed with the final version of the article.

Compliance with Ethics Requirements:

"The authors declare no conflict of interest regarding this article"

"The ethical principles included in the Declaration of Human Rights adopted in Helsinki, in 1975, and revised in 2008, were fully respected in our study. The enrolled subjects participated in this study voluntarily, completed and signed a written informed consent. Study protocol was approved by the Ethics Committee of I. Horbachevsky Ternopil National Medical University"

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