CURRENT COMPLEX TREATMENT FOR TYPE 2 DIABETES MELLITUS IN OVERWEIGHT PATIENTS WITH COMORBIDITIES (LITERATURE REVIEW)

Olena Said,
post-graduate student,
Odesa National Medical University

Annotation. *Diabetes is one of the most important medical and social problems on a global scale. This is due to the widespread character of the disease, prevalent undiagnosed diabetes and multiple complications. Despite the progress in developing new hypoglycemics, only 12.5% of patients achieve a satisfactory glycemic control.*

Two of the most prevalent concurrent conditions in patients with type 2 diabetes (T2DM) are overweight and obesity which are also contributing factors to the development of diabetes and its progression. The role of chronic inflammation in the development of T2DM and obesity is subject of scientific research. Inflammatory processes are closely connected with increased speed of atherosclerosis development, hypertension and vascular diseases. Triggers for these mechanisms can include harmful eating habits, sedentary lifestyle and other lifestyle factors. These are connected to diabetes risk factors through intracellular changes which include stress of the endoplasmic reticulum and activation of stress-induced enzymes such as tumor necrotizing factor-α, interleukin-1β and interleukin-6 as well as high sensitivity C-reactive protein.

The discovery of adipose tissue inflammation phenomenon allowed for a detailed examination of the modulation of metabolic and immune processes, which are expressed exceedingly in visceral fat.

New therapeutic agents for treatment of T2DM were developed in recent years. Current approaches to T2DM treatment include traditional hypoglycemics, the focus of which is β-cell insufficiency and/or insulin resistance, however newer classes of drugs which influence other defects such as incretin insufficiency and include other metabolic glucose pathways appear to have a significant advantage.

Key words: *diabetes, overweight, obesity, cytokines, incretins, liraglutide, body mass index, review.*

Diabetes mellitus (DM) is one of the current most important medical and social problems and is a global issue. This is primarily due to the widespread character of the disease and a strong tendency towards increase in the number of patients.

According to the International Diabetes Federation (IDF) 2017 data, there are 425 million DM patients in the world aged 20 to 79 [1]. Morbidity of DM in different countries ranges from 1,67% to 37,27% [1,2]. Among the countries with the highest prevalence of DM are Micronesia (37,27%), Kuwait (23,86%), Saudi Arabia (23,38 %) and Qatar (23,33 %). Lowest prevalence of DM is in Mali (1,67 %), Gambia (1,97 %) and Moldova (2,73 %). Diabetes mortality in 2017 was 3.99 million patients, 50 % of which were under 60 years of age. More than 80 % of DM deaths, according to the WHO data falls under the lower and medium income countries. Cardiovascular pathology is

the cause of 50 % to 80 % of deaths among these patients [1, 3].

66 million people have DM in the European region, 38.2 % of which are undiagnosed. The incidence of undiagnosed diabetes in Ukraine is 43,4 % [1, 2].

Every year, more than 7 million of new cases of diabetes are diagnosed in the world. According to the current morbidity growth rate, IDF estimates an increase in diabetes patients to 629 million by 2045.

In 2017 2.836 million patients with type 2 DM (T2DM) were registered in Ukraine [1]. DM morbidity rates among the population of Ukraine is 7,1 %. According to official data, 41,5 thousands deaths in Ukraine occurred in 2017 due to DM complications. However taking into view European and world tendencies towards morbidity increase, we can estimate that the real figures could be much higher than the official ones.

According to WHO data, T2DM constitutes about 90 % of all diabetes cases [2]. This diabetes type is qualified as a chronic progressive disease with unavoidable loss of insulin secreting function of the pancreatic β-cells.

Current research is targeting effective preventive strategies that will allow to lower morbidity in a population as well as new treatment methods to prevent complications, improve quality of life and life expectancy of patients with DM [4-6].

Despite the constant progress in developing and implementing new hypoglycemic agents, only 12.5 % of patients achieve a satisfactory glycemic control and the prevalence of DM complications remains high and has a strong tendency towards further increase. The reasons for this could include widespread low patient motivation, insufficient availability of effective disease control and, primarily, an abundance of concurrent conditions [7].

One of the most prevalent concurrent conditions in patients with T2DM is overweight and obesity. According to different authors from 75 % to 85 % of these patients are obese [3,8]. This fact the grounds for “Global WHO Strategy on Diet, Physical Activity and Health” being the main addendum to the DM treatment and prevention program [3, 9-13].

Obesity is not only the most prominent concurrent condition in patients with DM, but also is one of the leading contributing factors to the development of DM and its progression [6]. The role of chronic inflammatory process in the development of T2DM and obesity is a subject of current scientific research [14-16].

The questions pertaining the pathogenesis, diagnostics and new effective control methods and complication prevention measures of T2DM, are still up for discussion regardless of the multiple research studies. Complexity and multiple levels of impairment in T2DM are the results of two main defects: insulin sensitivity decrease (or insulin resistance) and inadequate insulin secretion to overcome the barrier of insulin resistance [17].

Inflammatory processes are closely connected with increased speed of atherosclerosis development, as well as hypertension and vascular diseases [6, 14, 15]. Triggers for these mechanisms can include a variety of factors including harmful eating habits, sedentary lifestyle and other lifestyle factors. There is additional data that shows psychological

stress, environmental harms, infectious diseases and genetic variations to be additional factors in the immune response activation [18]. These stimuli are connected to the risk factors of T2DM through intracellular changes which include stress of the endoplasmic reticulum and activation of stress-induced enzymes such as tumor necrotizing factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) as well as high sensitivity C-reactive protein (hsCRP) [5, 17, 18]. Changes in the secretion in these in various tissue lead to increased concentrations of proinflammatory cytokines (PC) and histological changes which are characterized by immune cell infiltration of fatty tissue and pancreatic islets [19]. Persistence of these processes leads to chronic subclinical inflammation which is a known risk factor for insulin resistance, ß-cell dysfunction and finally T2DM [20-22].

The discovery of adipose tissue inflammation phenomenon allowed for a more detailed examination of the modulation of metabolic and immune processes, the expression of which was found to be the greatest in visceral fat [23, 24]. Acquiring more details on this is an important part of conducting preventive therapeutic measures [14, 15, 21, 22].

Cytokines, such as TNF-α, IL-1β, IL-6, transforming growth factor (TGF-β), etc play the key role in realization of the inflammatory reaction and monocyte-macrophagal chain immunity activation. Meanwhile, interleukin-10 (IL-10) is viewed as an effector inhibitor of inflammation [17, 18]. Elevated concentrations of inflammatory markers (CRP, TNF-α, IL-1β, IL-6) data and its connection to the severity of peripheral nervous system disturbances and endothelial dysfunction in patients with DM and obesity, nephropathy, retinopathy and cardiovascular form of autonomous neuropathy broaden and detail the understanding of immune-inflammatory disease model.

Cytokines are multifunctional molecules which directly take part in a wide spectrum of physiological reactions aimed primarily at defense. In addition to their role in immunity and inflammation, cytokines play the role of mediators of different pathological states of the central nervous system and peripheral nervous system and thus are neuroimmunomodulators. Besides, the immune system uses cytokine-like messengers, chemokines do recruit and activate specific types of white blood cells. There is a theory that some cytokines lead to functional depression of β-cells while others protect them from this interaction.

This systemic and subclinical inflammatory process can be characterized by elevated concentrations of the circulating PC, including hsCRP, IL-6, IL-1β and TNF-α. Different mechanisms through which these cytokines may lead to T2DM development were identified. For example, these cytokines can directly block insulin receptor signaling by activating the c-Jun aminoterminal kinase and inhibitor of the nuclear factor kappa-beta kinase which leads to phosphorylation of substrate-1 of insulin receptors. These cytokines were additionally found to be able to stimulate fatty acid synthesis in the liver thus producing an even higher amount of the acute phase proteins by the liver as well as activating a larger number of inflammatory cells in the fatty tissue and pancreatic ß-cells.

Interleukin 1-β is a powerful PC which is produced by the monocytes, macrophages

and dendrite cells. Interleukin 1-β upon immune system stimulation helps leukocytes to penetrate vascular walls into the inflammation site and leads to a reaction of fever by interacting with parts of the brain which are responsible for body temperature regulation. Patients with T2DM also experience elevated production of IL1-β. There is currently a discussion whether IL1-β is excessively produced and may be included in stress-induced obesity formation in multiple chronic stress [25].

There are studies which show that IL-1β concentrations in T2DM directly correlates with glucose levels which leads to inflammation progress and insulin resistance induction in obesity conditions [26, 27].

Interleukin-6 is produced by various types of cells. The main cell sources for IL-6 production are macrophages, fibroblasts and endothelial cells. Some other sources include T-cells, B-cells, eosinophils, mastocytes, glial cells and astrocytes. Interleukin-6 is pleiotropic and it functions as both a proinflammatory and anti-inflammatory cytokine. It is one of the key mediators of fever and acute phase response. Besides, high levels of IL-6 indicate an increased risk of future T2DM development [20-22].

C-reactive protein, however, was shown to be a stronger predictor than IL-6 in several studies which assessed both parameters [28-30]. These studies prove the existence of a connection but not a causal relationship. The connection between IL-6 and T2DM progression may just reflect an attempt to suppress the beginning of inflammation, which was induced by other mediators. IL-6 levels also reversely correlate with insulin resistance.

Elevated levels of IL-6 which is the main stimulator of production of most of the acute phase proteins, increase risk of T2DM development. However in addition to IL-6, IL-1β and TNF-α are central mediators of inflammatory response. It is well known that cytokines work as a framework in stimulating of acute phase protein production. Overweight and hyperglycemia leads to elevated concentrations of these inflammation markers. It needs to be noted that patients with obesity have higher concentrations of TNF-α and IL-6 compared to patients with normal weight and T2DM. However there is not enough data on the levels of these cytokines in overweight patients with T2DM.

Tumor necrotizing factor-α is a pleiotropic PC which is produced by monocytes, macrophages, NK-cells, astrocytes, Kupfer cells, T-cells, B-cells, glial cells, basophils and eosinophils.

The main role of TNF-α is immune cell regulation. TNF-α can also induce apoptosis, cause inflammation and inhibit tumor genesis and virus replication.

Research into the role of TNF-α as well as mechanisms with which this factor reduces sensitivity to insulin at the adipose and muscle tissue level is scientifically relevant. Many researchers see TNF-α as a mediator for insulin resistance in obesity.

C-reactive protein is considered to be one of the main PC which functions as a nonspecific defense mechanism in response to tissue damage or infection. CRP activity which is synthesized primarily in the liver is stimulated by other cytokines, especially IL-6, IL-1β and TNF-α. It becomes attached to different other molecules and is a powerful activator of the classic complement system.

Several studies have shown that CRP elevation had a reverse correlation with insulin sensitivity and is an important prognostic factor for patients with metabolic syndrome [29, 30]. There is also a hypothesis that notes insulin sensitivity decrease in the conditions of elevated CRP expression through lowering of physiological immunomodulation of insulin and acute phase protein genes transcription [31].

Therefore, PC don't only influence insulin resistance but can also induce apoptosis and beta-cell insufficiency causing T2DM. These cytokines are part of a family of cytokines which are produced in the adipose tissue, so called adipokines and may be the link between obesity and T2DM [14,15,19,20].

Among etiological factors of T2DM, it needs to be noted that chronic subclinical inflammation cannot be viewed as a singular primary cause for the development of this disease in the absence of other risk factors. But regardless of that it constitutes an important mechanist which is a connective link between the primary causes of T2DM and its manifestation. Due to an existing association of systemic chronic inflammatory process and DM development it seems probable that anti-inflammatory therapy would lower the cumulative risks among the patients with T2DM. Cytokines as mediators of an inflammatory process may be the target for realizing of pharmacodynamics of the new hypoglycemic agents, such as glucagon-like peptide-1 (GLP-1). Determining the mechanism of action of the latter considering the dynamics of lipid and carbohydrate metabolism markers, allows an increase in treatment efficacy, lower the risks of complications, and develop an individualized treatment plan for patients with T2DM especially in obese patients.

Many new therapeutic agents for treatment of T2DM were developed in the recent years. Current approaches to T2DM treatment continue to include traditional hypoglycemic agents classes, the focus of which is beta-cell insufficiency and/or insulin resistance, however newer classes of hypoglycemic agents which influence other defects such as incretin insufficiency and include other metabolic glucose pathways (i.e. excretion via kidneys) have a significant advantage. The effects of these therapeutic approaches on comorbidities, such as dyslipidemia, hypertension and obesity is subject of further research.

However, not very many medications for the treatment of T2DM directly influence the level of inflammation despite the fact that many different approaches aimed at DM prevention have a proven anti-inflammatory effect.

Recent discovery of the role of kidneys in glucose homeostasis lead to the development of a new class of medication, so called type 2 sodium-glucose co-transporter inhibitors. Although this class of hypoglycemic has a high cardiovascular safety profile, these medications primarily influence only one pathogenesis link of T2DM and are known to have a range of adverse events.

Recent years have seen significant developments in the incretin-oriented theory, such as studying the role of gastrointestinal hormones in the regulation of insulin secretion and glucose homeostasis as a whole.

Incretins are gastrointestinal hormones which are secreted in response to food

intake. Two of the incretins which have been extensively studied are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP).

Glucagon-like peptide-1 is secreted by the L-cells of the small intestine in response to food intake. Its effects include insulin synthesis stimulation and glucagon production decrease which also leads to gluconeogenesis decrease in the liver. Native GLP-1 also stimulates pancreatic β-cell proliferation and neogenesis [32, 33]. However, native GLP-1 cannot be considered to be a promising therapeutic agent due to it's short half-life of under 2 minutes as a result of degradation by dipeptidyl peptidase-4 (DPP-4) and quick elimination with the kidneys.

There are two ways to influence incretin levels in patients with T2DM. One class of medications causes DPP-4 inhibition thus leading to native GLP-1 levels preservation. However, in the conditions if incretin defect which is commonly seen in patients with T2DM, replenishing physiological concentration of GLP-1 is not always adequate for proper glucose homeostasis.

Glucagon-like peptide-1 analogues mimic the effects of the endogenous GLP-1 which regulates plasma glucose by stimulating the synthesis and secretion of insulin, decrease production of glucagon while slowing down gastric emptying and reducing the volume of food consumed. Based on these mechanisms of action, GLP-1 analogues influence blood glucose levels and have an additional capacity for weight loss.

Liraglutide is a synthetic GLP-1 analogue that is 97 % homologous to the endogenous GLP-1 by its aminoacid components.

According to the clinical trial data, liraglutide can lead to a decrease in hypertriglyceridemia as well as lower concentrations of cardiovascular risk markers, such as plasminogen activator inhibitor-1 (PAI-1) and hsCRP [33-35].

Study results show that liraglutide administration leads to weight loss in patients with T2DM and obesity. Weight loss is usually accompanied by a decrease in abdominal circumference, which could be an indicator of a decline in visceral fat content. Weight loss noted with liraglutide administration could be explained by the activation of the hypothalamic appetite controlling center which lead to a decrease in food intake volume and calories consumption [36,37,38,39].

Liraglutide is also characterized by additional angio- and cardioprotective properties (i.e. positive inotropic effect). This cardioprotective effect has theoretical basis. It is a well known fact that GLP-1 receptors are not only expressed in the β- and α-cells of the pancreas, but also in the human and animal heart tissue. There are studies that show that GLP-1 administration in myocardial infarction and congestive heart failure increases myocardial sensitivity to insulin and glucose uptake, increases cardiac output and therefore decreases left ventricular end-diastolic pressure as well as decreasing the area of myocardial infarction, renewing left ventricular function and shortening the duration of hospital stay and in-hospital mortality following myocardial infarction.

In patients with congestive heart failure, GLP-1 administration increases ejection fraction and improves physical exercise tolerance [40-42]. There was also a note of decrease in endothelial dysfunction signs when GLP-1 was administered to patients

with T2DM [43,44,45]. One more effect of liraglutide which is drawing the interest of clinicians is lowering the blood pressure levels. Antihypertensive effect of liraglutide is linked to endothelial dysfunction which is an important factor which leads to decrease in systolic blood pressure [43-46].

Liraglutide therapy allows to reach satisfactory glycemic control along with a variety of positive non-glycemic effects, such as rare hypoglycemia episodes (along with lower risks of weight gain due to hypoglycemia compensation and hypoxic encephalopathy); as well as the ability of liraglutide to influence factors that form metabolic syndrome [4, 33, 34].

However there is insufficient data on the influence of liraglutide on PC concentrations in overweight and obese patients with T2DM. Therefore, it is relevant to conduct a deeper investigation into the actions of hypoglycemic agents, specifically on the PC levels, which can have positive metabolic effects, improve glycemic control in patients with T2DM as well as be a preventive measure for the development of cardiovascular disease, especially in overweight patients.

All of the above became the basis of a more profound research into the problem of T2DM in overweight patients which is a question on the verge of two directions of scientific research – on one side, it's a study of metabolic pathology a bright example of which is overweight and obesity and T2DM and on the other side is the further development of the concept of prevention of cardiovascular events which arise as a result of metabolic disturbances.

Our research into the assessment of efficacy of complex treatment of overweight patients with T2DM show a high level of efficacy of a combination of liraglutide and metformin as part of a complex treatment regimen which included lifestyle modification as well as differentiated dosed controlled physical exercise. Thus, the main treatment patient group, who received a combination of liraglutide and metformin saw a statistically significant decrease in body weight index (BMI) as a result of treatment from 28,48±2,1 kg/m2 to 23,9±1,8 kg/m2 ($p<0,05$), whereas the liraglutide monotherapy group noted a statistically significant, however less pronounced decrease in BMI from 28,59±2,5 kg/m2 to 25,87±2,3 kg/m2 ($p<0,05$).

Similar tendency was seen in the analysis of visceral fat content. The patient group receiving a combination of liraglutide and metformin saw a decrease in abdominal fat by (35,1±3,8) %, whereas the liraglutide monotherapy group the decrease was less prominent – (24,84±2,5) % ($p<0,05$). There was also noted a direct moderate strength correlation between BMI and abdominal fat content among the patients of both groups ($r1= 0,467$; $p<0,05$, $r2= 0,328$; $p<0,05$).

During assessment of the quality of life dynamics in patients receiving different hypoglycemic agents, there were significant changes among both patient groups. However, the patients receiving a combination of liraglutide and metformin saw an increase of the physical health component (PH) by (31,2±2,8) % ($p<0,05$), whereas the group of patients which received liraglutide monotherapy the increase consisted only of (22,7±2,5) % ($p<0,05$). Similar tendency was noted towards the mental health component

(MH). The group of patients with combination treatment of liraglutide and metformin noted an increase in MH by (35,9±3,1) % ($p<0,05$), whereas the group with liraglutide monotherapy saw a less pronounced but significant increase by (25,8±2,7) % ($p<0,05$).

Therefore, a combination of liraglutide and metformin leads to better results in T2DM management in overweight patients than monotherapy which is also additionally aided by the pleiotropic effects of liraglutide, thus positively influencing weight loss and quality of life parameters [47-53].

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