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Short Communication

The Role of Metformin in the Treatment of Type 2 Diabetes and Obesitys

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SUMMARY

Topic: Mutual association and connection study between the obesity, visceral obesity, insulin desensitation (with the conesquential hyperinsulinemia), type 2 diabetes, dyslipoproteinemia and anthropometric characteristics of the patients with the metabolic syndrom are the subject of many epidemiological studies. However, it is noticed that there are certain disagreements and contradictions in defining the anthropometric and metabolic risk factors for the occurance of the cardiovascular, cerebrovascular and other vascular diseases, especially in population of the obese patients with type 2 diabetes.

Topic position in medical public: Theoretically, metformin achieves a good glicoregulation preciselyinthe visceral obese patients. This is explained by a higher glucometabolic activity of the visceral adipose tissue in regard to the subcutenaus tissue.

Futher action: More efficient reduction of the visceral adipose tissue inpatients with achieved better glucoregulation, under the affection of the metformin is a result of its complex effect mechanism. Metformin plays a significant role in the reduction of the cardiovascular risk that comes from a higher visceral obesity, parallel to the achievement of the good glicoregulation in obese, type 2 diabetes patients.

Keywords: metformin, diabetes mellitus, type 2, obesity, adipose tissue

TOPIC

For the obesity development, as well as for the development of the mentioned metabolic deseases, answering how or in which way does it come to the increasement of the body adipose tissue has a great clinical significance. There are two ways of increasing body adipose tissue in obesity – proliferation or adipose hypertrophy.

TOPIC POSITION IN MEDICAL PUBLIC

There are reports that say that the adipose in type 2 diabetes persons and with positive calory balance, compared to the obese persons without the diabetes, have lower chance for fat storage with cellular proliferation because of the decreased genes expression responsible for the adipogenesis [1,2]. However, clinical significance in the obesity patogenesis does not reflect only in the fact how, but also where does the body adipose accumulate and store [1,3,4]. According to the place – region where the adipose accumulates, the adipose tissue is divided to the visceral and subcutenaus adipose tissue. The visceral adipose tissue is adipose more

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metabolically active compared to the subcotenaus adipose tissue. Bigger metabolic activity of the visceral adipose tissue, compared to the subcutaneous, is reflected in the schedule and the amount of the receptors in the adipocytes, disballance between the lipogenesis and lipolysis, difference in the secretion of the adipokines, cytokines and other mediators of inflammation, as well as the difference in the hormone and protein release [3].

The appearance of the visceral adipose tissue in the omentum, mesentery, liver, muscles, pericardially and other organs is marked as ectopic and often combines with the high insulin concetration in blood and insulin resistence that is measured by hyperinsulinemic euglycemic clamp or other techincs that measure fast responses of the aimed organs, primarily muscels, to the insulin action [5,6]. It is also shown that the acummulation of the visceral adipose tissue in abdomen is combined with the accelerated aterosclerosis development [7].

The connection od the insulin resistence and excess accumulation od the visceral adipose tissue still has not been clarified. There are few theories about the connection between the insulin resistence and overaccummulation of the visceral adipose tissue, one of which is "portal" or "lipolitic" theory. This theory implies that the intra-abdominal visceral adipose tissue has anatomic and metabolic charachteristics that are unique compared to the adipose tissue of other localization, and, which is very interesting, it is especially regarded to the regions that are drained via the portal circulation (omental and mesenteric adipose tissue) [8].

According to this theory, the connection between the insulin resistence and visceral adipose tissue is in the fact that the visceral adipose tissue has a bigger activation of the β3 adrenergic receptor with polymorphism of the gene allele responsible for the expression of β3 receptors [9]. Bigger β3 receptors activity leads to the increasement of the lipolitic activity, circulating non-esterfied adipose acids increase, dislipoproteinemia (increased levels of triglycerides with reduced levels of high-density cholesterol) and insulin resistance with a consequent reduction in glucose tolerance.

Alternative to the "portal theory" is "hormone-inflammatory theory" in whose base is that the visceral adipose tissue is rich in macrophages that increasingly produce proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6, while leading to the decreased protective adipokines secretion, among which adiponectin should be noted [10].

Also, it was demonstrated in animal models that visceral fat affects hormone production higher resistin, which got its name based on being established that it causes resistance to insulin [11]. For mentioned abdominal visceral fat it has been presented, both in humans and in animal models, that these tissues compared to the subcutaneous adipose tissue produce significantly more interleukin-6, [12] while the excessive secretion of TNF-α could be produced only in animals, but not in the human population [13]. It has been shown that interleukin-6 possess great induction potential of C-reactive protein (CRP) in the liver, so the interleukin-6 and CRP have become important predictors of visceral obesity, insulin resistance syndrome and type 2 diabetes [14]. Studies that have pointed to the importance of the links between genetic factors, excessive food intake, reduced physical activity, insulin resistance, visceral obesity, inflammation and endothelial dysfunction of blood vessels in the development of atherosclerosis in patients with type 2 diabetes are especially important [15].

Also in animal models has been shown that by specific inhibitors of tyrosine kinases (substances among which there are also some drugs that are mainly used in certain leucosis treatment, but are also being tested the treatment of type 2 diabetes resistant to other forms of treatment) reduces insulin resistance and insulinemia [16]. It was found that their use increases the takeover and use of glucose, associated with the reduction of proinflammatory cytokines and proliferation of macrophages in the mesenteric adipose tissue. All of this was accompanied by a reduction of the insulin receptor substrate 1, which has be proven, next to the tyrosine kinase of the insulin, that can be phosphorylated and serine / threonine kinases, activated by mediators of chronic inflammation or stress.

Certain newly discovered substances with hormonal action, such as visfatin, which is largely secreted in visceral adipose tissue, has been shown to act like insulin via a tyrosine kinase, and that visfatin and insulin have equal insulin effect [17]. It has also been suggested that there is no competition between visfatin

and insulin, so it was concluded that they bind to different subunits of the insulin receptor.

Great advance in the research of the pathogenetic link between insulin resistance, central type obesity, intra-abdominal obesity, chronical inflammation, atherosclerosis, dyslipoproteinemia and type 2 diabetes, has an increasing clinical importance, for at least two reasons. The first reason certainly is awareness of the role of intra-abdominal visceral adipose tissue in insulin resistance and type 2 diabetes, which led to the improvement and development of new anthropometric measurement methods and visceral obesity diagnosis in the general human population of different age, gender, ethnicity and race [18,19]. While some authors emphasize the importance of the morphological measurement of visceral adipose in patients with type 2 diabetes with nuclear magnetic resonance imaging, computed tomography or ultrasound, [19] others emphasize the ease of measurement of waist circumference as a measure of abdominal obesity, but also the most important predictor of vascular events in these patients [20]. The latter authors showed that in patients with type 2 diabetes and waist circumference > 90 cm (for men) or > 85 cm (for women), as well as with the level of serum triglycerides ≥ 2 mmol/L (hypertriglyceridemic waist), multiply increases the risk of a cardiovascular disease.

Second, but not less important reason to clarify the role of increased visceral obesity in type 2 diabetes is that these findings started to apply critically in monitoring the effects of pharmacotherapy drugs in type 2 diabetes and its prevention, but also in control of its non-pharmacological treatment, which primarily involves the implementation of strict dietary measures with the programmed physical activity increase [21-23].

In newly diagnosed type 2 diabetes patients first step in the treatment is a change of lifestyle that is reflected in the reduction of patient body weight (if overweight) and increasing physical activity. However, such therapeutic measure, even if it leads to a reduction in glycated hemoglobin (HbA1c) by 1-2%, it becomes insufficient to maintain the achieved glucometabolical effect already in the first year of non-pharmacological intervention [24].

The next step in the type 2 diabetes treatment is conducting therapy with metformin, which is only contraindicated in patients with renal insufficiency (creatinine concentrations > 132 mmol/L for men and > 124 mmol/ L for women) [25]. The expected reduction in the level of HbA1c in patients with type 2 diabetes on metformin monotherapy is 1% -2% [26,27]. Metformin is an oral anti-diabetic agent from the group of biguanides. The bioavailability of metformin is 50% -60%. It is absorbed mainly from the small intestine, and estimated time of resorption him 0.9 hours to 2.6 hours. After 1-2 hours from the oral dose taken from 500 mg -1000 mg, maximum drug concentrations in plasma are 1-2μg/mL. About 90% of metformin is eliminated in the urine within 12 hours. Is evenly distributed in all tissues, in concentrations close to those in the peripheral plasma, while it achieves high concentrations in the liver and kidneys. Metformin achieves the highest concentrations in the salivary glands and in the intestine wall.

The metformin treatment increases insulin sensitivity, which is reflected by reducing fast glucose and insulin circulating concentrations. Metformin has no effect in the absence of insulin [28]. In patients with type 2 diabetes, the effect in reducing the glycemia by metformin is mainly explained by the mechanism of reducing hepatic production and increasing peripheral glucose uptake. Several other mechanisms of metformin action also contribute to the reduction of blood glucose, such as increasing intestinal glucose utilization and reducing adipose acid oxidation. Metformin decreases glucose production in the liver in patients with type 2 diabetes, in which it must be borne in mind that this is a very important mechanism of action on reducing fast glucose [29].

In isolated liver cells metformin increases suppressing gluconeogenesis by insulin and lowers glucagon-stimulated gluconeogenesis [30]. In most studies, metformin also increases the availability of glucose which was confirmed by hyperinsulinemic, euinsulinemic clamp or hyperglycemic clamp procedures in patients with type 2 diabetes, where the muscles were central site of metformin action [27]. In animals, metformin increases muscle glucose takeover stimulated by insuline, resulting in a glycogen synthesis increase and the glucose oxidation in peripheral tissues, but not in increasing the production of lactate [31].

Metformin also increases the takeover and oxidation of glucose in adipose tissue, and equally well encourages lipogenesis [32]. However, the metformin in vitro effect in

the peripheral tissues depends on the amount of its concentration, so it's very slow at the beginning. Metformin increases insulin binding to its receptors by increasing the phosphorylation and the tyrosine kinase activity on the insulin receptors in vivo, so this could lead to a reduction in plasma glucose, which could not be reproduced in vitro [33]. It also increases the possibility of translocation of the GLUT-1 and GLUT-2 glucose transporter isoforms in various types of cells [34] and thus prevents the occurrence of the insulin resistance in hepatocytes and adipocytes cultures, which are exposed to high concentrations of insulin for a longer period of time [35].

In the case of long-term use, metformin reduces the concentration of plasma lipoproteins (particularly triglycerides, and, to a lesser degree, cholesterol) in patients with hyperlipoproteinemia, especially Type IV, and II-B [36]. It is considered to be the drug of choice in obese patients with type 2 diabetes, primarily because it does not increase the body weight of patients, but on the contrary, it can reduce adipose tissue [29].

A significant contribution to the elucidation of the mechanism of the metformin action was given by Zhou et al 2001 [37]. They showed that metformin activates the hepatic and muscle adenosine monophosphate-activated protein kinase (AMPK), an enzyme that normally resides adenosine monophosphate-activated, being result of the adenosine triphosphate decomposition. AMPK also gets triggered by the cell signaling for increased energy requirements. Hepatic AMPK activation results in phosphorylation and inhibition of acetyl coenzyme A carboxylase, which catalyzes lipogenesis. Since furthermore there is a blockage in the synthesis of adipose acids, their oxidation is being stimulated. In addition, the activation of hepatic AMPK reduces the expression of a sterol-regulatory element-binding-protein-1 (SREBP-1), normally an important transcription factor that participates in the pathogenesis of insulin resistance, dyslipidemia, and type 2 diabetes. Reduction of SREBP-1 expression leads to a decrease of gene expression of the lipogenic enzymes that later contribute to the reduction of synthesis of triglycerides and hepatic steatosis occurence.

However, it must be noted that although there is a common view that metformin reduces obesity, with special emphasis on visceral obesity in patients with type 2 diabetes, there is a lack of studies that could confirm this and / or possibly show the correlation of the reduction of abdominal visceral obesity with a parallel increase in insulin sensitivity, glikoregulation recovery or dislipoproteinemia correction in type 2 diabetes patients.

In our earlier work, we showed that in obese type 2 diabetes patients, metformin reduces unproductive fast insulin secretion and increases its productive postprandial secretion [38]. It also increases the suppression of gluconeogenesis by insulin and lowers glucagon-stimulated gluconeogenesis [30]. Metformin increases takeover and oxidation of glucose inadipose tissue [32]. Under the action of metformin in omental adipocytes, the expression of SREBP-1 inhibits with an increase in AMPK [39].

All these mechanisms of metformin action, showed that it has a great potential in reducing visceral obesity that combines with insulin resistance. The metformin impact on AMPK increase and SREBP-1 inhibition in visceral adipose tissue, is particularly highlighted in the review reports as a potentially important mechanism in the prevention and reduction of cardiovascular risk in patients with type 2 diabetes and insulin resistance [40].

On the other hand, there are few and contradictory reports about the impact of other oral antidiabetics on the visceral obesity in patients with type 2 diabetes. There are only individual detailed reports that certain drugs called insulin sensitizers, such as thiazolidinediones, after the first three months of application in patients with type 2 diabetes, although leading to a reduction in HbA1c levels, lead to an increase in overall obesity, increase of subcutaneous adipose tissue, with no changes in visceral obesity [23]. Our previous results indicate that the three-month application of metformin in obese patients with type 2 diabetes, and patients with impaired glucose tolerance more often led to normalization of HbA1c levels in patients with pretherapy level of HbA1c $< 8\%$ compared to patients with HbA1c $\geq 8\%$ [41,42].

FURTHER ACTION

In spite of the clear implications that metformin is the drug of choice in the treatment of obese patients with type 2 diabetes, there is a lack of the pharmacoepidemiological and clinical studies that document the effects

of metformin on the redistribution of body adipose as well as its impact on the reduction of abdominal and / or visceral obesity. Generally speaking, the effects of oral antidiabetic agents in different forms of obesity are imperative for further research, as the current good clinical practice reduced to monitoring of metabolic and anthropometric variables that define obesity, including abdominal obesity, without the actual insight into the visceral obesity.

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Uloga metformina u tretmanu dijabetesa tipa 2 i gojaznosti

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KRATAK SADRŽAJ

Tema: Međusobna udruženost i proučavanje povezanosti između gojaznosti, visceralne gojaznosti, smanjene osetljivosti na insulin (sa posledičnom hiperinsulinemijom), dijabetesa tip 2, dislipoproteinemija i antropometrijskih karakteristika pacijenata sa metaboličkim sindromom, predmet su mnogih epidemioloških studija. Međutim, primećuje se da postoji neslaganje i kontradiktornost u definisanju antropometrijskih i metaboličkih faktora rizika za nastanak kardiovaskularnih, cerebrovaskularnih i drugih vaskularnih oboljenja, posebno u populaciji gojaznih pacijenata sa dijabetesom tip 2.

Pozicioniranost teme u medicinskoj javnosti: Teorijski, metformin postiže dobru glikoregulaciju upravo kod visceralno gojaznih bolesnika. Ovo se objašnjava većom glikometaboličkom aktivnošću visceralnog masnog tkiva u odnosu na supkutanu mast.

Buduće aktivnosti: Efikasnija redukcija visceralnog masnog tkiva kod pacijenata sa postignutom boljom glikoregulacijom pod uticajem metformina, rezultat je njegovih kompleksnih mehanizama dejstva. Metformin igra važnu ulogu u smanjenju kardiovaskularnog rizika koji potiče od povišene visceralne gojaznosti, paralelno sa postizanjem dobre glikoregulacije kod gojaznih bolesnika sa dijabetesom tip 2.

Ključne reči: metformin, dijabetes, tip 2, gojaznost, masno tkivo

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