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Choosing the most appropriate drug regarding pathogenetic features of type 2 diabetes

Dobór najlepszego leku w oparciu o cechy patogenetyczne cukrzycy

Starting with "Standards of diagnosing and treatment of type 2 Diabetes Mellitus" (Ukraine 2007) and according to "Clinical recommendations for diabetes treatment" (Poland 2006) it is enthusiastically recommended to keep good prescribing standards according to the pathogenetic stage of type 2 Diabetes Mellitus (DM2). Existing obesity or its absence is the only criterion mentioned in both documents in favour of choosing the most appropriate drug. Unfortunately, until now there have been no special laboratory criteria to choose the most appropriate hypoglycaemic drug, first of all regarding insulin resistance. Insulin resistance as we know it plays a prominent role in type 2 diabetes. Sub-clinical inflammation is also present. At the same time, a growing number of medicaments (metformin, pioglitazone, glimepiride, etc) calls for more profound understanding of their usage while their advertisment based on serious investigations announce the unique influence on insulin resistance and inflammation. This study was undertaken to find criteria for good standards in prescribing pioglitazone, metformin, and glimepiride regarding insulin resistance, dislipidemia and inflammation.

MATERIAL AND METHODS

A randomized, active controlled, cross-over study was performed on 56 overweight (BMI>26 kg/m^2) patients (mean age 44.8±10.8, 21M/35F) with inadequate glycaemia (HbA1c>7%) to explore the effects of each 3 mo. treatments with pioglitazone, metformin, and glimepiride in a sequence on insulin resistance, dislipidemia and sub-clinical inflammation. No other drugs were used by those patients. Patients started with 15 mg/day of pioglitazone, titrated to maximum tolerated doses in 15 mg increments to a maximum of 45 mg. After 3 months from the beginning of the investigation such treatment was switched to 1.0 g/day of metformin, titrated to a maximum tolerated dose of 2.5 g/day. After 6 months passed, the patients received glimepiride titrated to a maximum dose of 3 mg/day. Mean follow-up was 9 months. Laboratory assessments was made for liver function, like alanine aminotransferase (ALT), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides and inflammatory markers. Such laboratory tests as tumour necrosis factor α (TNF-α), C-reactive protein (CRP), glycated haemoglobin (HbA1c) were performed every visit.

RESULTS

HbA1c achieved a normal level after glimepiride (6.1±1.3%) and metformin (6.3±1.5%) in comparison with randomization baseline 9.1±0.9%. The results show that there was a general shift toward normalization of ALT values under pioglitazone ($p<0.001$), less with metformin ($p<0.05$). HDL was statistically significant following pioglitazone treatment ($p<0.001$) in comparison with metformin ($p=0.05$) and glimepiride treatment ($p>0.05$). LDL levels statistically increase after pioglitazone ($p<0.05$) and show no effect after glimepiride and a slightly positive decrease after metformin ($p<0.05$). Triglycerides decrease in both treatment approaches: pioglitazone ($p<0.02$), metformin ($p<0.05$) with no changes after glimepiride. TNF-α was significantly reduced after pioglitazone treatment (4.2±0.76 pg/ml vs 16.7±4.2 pg/ml, $p<0.05$) and metformin approach (3.8±0.68 pg/ml vs 16.7±4.2 pg/ml, $p<0.05$) while CRP shows more reduction with glimepiride treatment (0.8±0.08 vs 4.2±0.4 μ/ml, $p<0.05$). Metformin significantly decreased total cholesterol ($p<0.05$) and revealed significant changes in ALT levels ($p=0.05$).

DISCUSSION

Pioglitazone is the drug belonging to thiazolidinediones. Thiazolidinediones are synthetic peroxisome proliferators-activated receptor-[gamma] (PPAR-γ) agonists that decrease insulin resistance. PPAR-γ is present in the target tissues of insulin: fat, skeleton muscles and liver. *In vivo* studies PPAR-γ-agonists promote beta cell survival and regranulation as well as maintenance of beta cell mass and reduction in amyloid deposition. Thiazolidinediones bind with PPAR-γ and influence the GLUT genes, lipoprotein lipase and TNF- α (β) expression [2, 5]. PPAR-γ-agonists slow down gluconeogenesis, lead to proinsulin, C-peptide and insulin levels reduction, raise adiponectin concentration [3, 7]. Our investigation confirms the ability of PPAR-γ-agonist to significantly decrease TNF-α, triglycerides and low HDL levels following pioglitazone use with C-peptide and insulin tendency to descent.

Metformin, as the only permitted medicine from the group of biguanides, connects with phospholipids in mitochondrial membrane (mostly in the intestines and liver) and changes its electrical potential into a more positive one. This inhibits the electron transport in the cellular respiratory chain with the further weakening of ATP synthesis and a corresponding rise of the inner cell content of ADP and AMP. This results in glycolysis acceleration which is associated with a reduction of glycogen stores and an increase in lactate. The conditions of hypoxia stimulate glucose penetration into cells. According to the mechanism of action, the physiological manifestations of Metformin include [3–5, 7]: reduction of gluconeogenesis, decrease in the circulating triglycerides, diminishing of the serum cholesterol level by the suppression of synthesis in the intestinal wall and greater excretion through the intestines, reduction of endogenous insulin level, suppression of protein glycation. In our study we observed a significant shift of TNF-α, triglycerides and LDL like that of pioglitazone. At the same time we discovered the property of metformin to decrease ALT. Some articles mention that ALT is an independent marker of insulin resistance [6]. Therfore, ALT diminishing even in its normal range should be considered as beneficial.

Glimepiride, the latest sulfonylurea agent, has a mild effect on insulin secretion. It was established that Glimepiride improves both first and second phases of insulin secretion, but not insulin sensitivity in patients with type 2 diabetes [1]. In another research it was confirmed that Glimepiride remarkably improves insulin resistance, promotes reduction in HbA1c without changing extrapancreatic β-cell function. It was also found out that Glimepiride increases plasma adiponectin and decreases plasma

TNF-α which may underlie the improvement of insulin resistance [7]. In our study we established a prominent potency of glimepiride to modulate CRP elevation.

CONCLUSIONS

We achieved the compensation level of HbA1c (<6.5%) following every treatment. Pioglitazone turned out to be a good choice for patients with type 2 diabetes and high TNF-α, triglycerides and low HDL levels. A tendency to a decline of C-peptide and insulin were also documented. Metformin proved beneficial when diabetics have high TNF-α, triglycerides, LDL and total cholesterol. ALT diminishing in its normal range, presented by metformin may show its additional independent ability to improve insulin resistance. Glimepiride will be a better choice in the situations when CRP is elevated.

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SUMMARY

A randomized, active controlled, cross-over study was performed in 56 overweight patients with inadequate glycaemia to explore the effects of each 3 months' treatment with pioglitazone, metformin and glimepiride. These findings indicate that even if glucose levels are normalised, other pathophysiological processes like insulin resistance, dislipidemia and inflammation still are present. Choosing the most appropriate drug according to such challenges is the current problem.

STRESZCZENIE

Przeprowadzono randomizowane, aktywnie kontrolowane badania w modelu *cross-over* u 56 pacjentów z nadwagą i nieadekwatną glikemią w celu poznania efektów leczenia z zastosowaniem pioglitazonu, metforminy i glimepirydu. Wyniki badań wskazują, że mimo normalizacji poziomów glukozy u pacjentów nadal występują inne procesy patofizjologiczne, takie jak oporność na insulinę, dyslipidemia i stan zapalny. Z tego też powodu, dobór właściwego leku nadal stanowi istotny problem w farmakoterapii cukrzycy.