Comparative effects of oral hypoglycemic drugs on serum YKL-40 level in type 2 diabetic patients.

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Abstract:

Background: The prevalence of Type 2 diabetes mellitus and its associated micro and macro-vascular complications are globally rapidly increasing. Studies show that most diabetic complications are associated with an inflammatory response. YKL- 40, a novel biomarker for acute and chronic inflammation, has been proved to have a role in these complications. Many classes of antidiabetic drugs may have modulatory effects on inflammation beyond their glucose-lowering activity. So, inThis study we evaluate comparative effects of metformin and glimepiride on ykl-40 serum level in type2 diabetic patients.

Patients and method(s): In a parallel-group, randomized trial setting, 46 newly diagnosed, medication-naïve type 2 diabetes patients were assigned to metformin (in divided doses, 500 -850 mg tablets three times daily) (n = 23) or glimepiride (1-4 mg once daily) (n = 23). Serum concentrations of YKL-40, along with HbA1c were measured at baseline visit and after 4 months.

Result(s): Both drugs were equally effective to achieve glycemic control. However, metformin caused more significant reduction in YKL-40 concentrations after 4 months when compared to glimepiride ($P < 0.05$).

Conclusion: /From the present study it is hypothesized that metformin is more effective than glimepiride in reduction of YKL-40 level (inflammatory diabetic complications).

Keywords: Diabetes mellitus, YKL-40, Metformin, Glimepiride, Inflammation.

Introduction:

Diabetes mellitus (DM) is a heterogeneous group of metabolic diseases resulting from defects in insulin secretion, insulin action, or both, resulting in hyperglycemia.Uncontrolled chronic hyperglycemia in DM is associated with many macro and micro-vascular complications***(American Diabetes Association, 1997)***.

Subclinical systemic inflammation and abnormalities in different systemic inflammatory markers have been reported in type-2 DM***(Kolb&Mandrup-Poulsen, 2005).***

YKL40, a novel marker for acute and chronic inflammatory conditions, has beenproved to have a putative role in development of diabetic micro and macro-vascular complications***(Rathcke& Vestergaard, 2006).***

YKL-40, also named human cartilage glycoprotein-39,is secreted by a

variablehuman cell including activated neutrophils, chondrocytes, synovial cells and osteoblasts.YKL-40 also mainly secreted from vascular smooth muscle cells (VSMCs) and macrophages***(Volck et al., 1998).***

Both genders have the same plasma level its median level in healthy individuals is~40 µg/l***(Johansen, 2006).***

Optimal anti diabetic treatment has beneficial effects that can help to prevent diabetic micro and macro-vascular complications, in addition to providing good glycemic control***(Krentz&Bailey, 2005).***

Available researches suggest that metformin andglimepiride, two commonly prescribed oral hypoglycemic drugs can alleviate inflammatory processes by significant reduction in CRP levels***(Satoh et al., 2003).***

However, it is not clear whether these drugs exert similar effects on YKL-40 inflammatory marker in type-2 DM patients.

Aim of the work:

The study aims to examine the comparative effects of metformin and glimepiride on YKL-40 concentrations in type 2 diabetes patients (inflammatory complications of diabetes).

Patients and method:

Study design:parallel-arm, randomized clinical trial.

Patients:

This study was carried out on46 newly diagnosed medication naïve type 2 diabetes patients (20 males and 26 females)recruited and simply randomized; with the aid of a randomization software, from the diabetes outpatient clinic of Qena university hospital for 4 months duration. All study patients have the following inclusion criteria:(1) recent diagnosis of type 2 diabetes mellitus; diabetes was diagnosed according to diagnostic criteria of the American Diabetes Association (ADA) ***(American Diabetes Association, 2013)***; (2) negative past history for taking oralhypoglycemic drugs of any class or insulin; (3) negative history for anti-oxidant or vitamin supplementation and (4) absence of chronic illnesses of the heart, lungs, or kidneys of any clinical significance. patients having the following criteria were excluded:(1) Age below 18 years old;(2) History of chronic illness and (3)History of takinganti-diabetic drugs of any class or insulin.All patients were subjected to the following: 1-Full history taking;2-Clinical examination and 3-Investigations including:liver enzymes (AST, ALT), renal function tests (urea, creatinine) and Random blood glucose.

Methods:

Patients are classified into 3 groups: **Group 1**: Patients receiving metformin (in divided doses, 500 -850 mg tablets three times daily according to patient glycemic control) >> (n = 23).**Group 2**: patients receiving glimepiride (1-4 mg once daily before breakfast according to patient glycemic control)>> (n = 23).**Group 3**: patients before treatment in each study arm (positive control) >> (n =23).

(A)Sampling collection and preparation:after informed consent was obtained from each patient,a venous blood sample (6 ml) was withdrawn from each individual under aseptic conditions using

sterile disposable syringe (at the baseline visit and at a second visit 4 months after the baseline visit) and then dispensed into two tubes: (A) 2 ml of blood were delivered into tube containing K-ethylene-diamine Tetra acetate (K-EDTA) for HbA1c and (B)4 ml of blood were delivered into another plain tube in which serum was separated by centrifugation on 3000 rpm for 10 minutes and the serum used for assessment of YKL-40 (by ELISA).The serum obtained from patients at the baseline visit was preserved immediately after separation in Eppendorf tubes at -80 °C to be used later (after 4 months at the next visit).

(B)Analytic methods: HbA1c assays were done using Cobas C311, Hitachi, and Roche Diagnostics, Germany. Serum YKL-40 was determined by enzyme-linked immune sorbent assay (ELISA) (Molecular Devices, Sunnyvale, California, USA).

(C) Statistical analysis: The results data have been represented as the group means ± standard error of the mean (S.E). All statistical analysis had been calculated with prism software (Graph-Pad Software, version5, San Diego Ca, USA).

Results:

There was significant decrease in HbA1c in both metformin (P=0.001) or glimepiride (P=0.001) treated groups for 4 months duration compared with its level in positive control group (patients before treatment in baseline visit) as shown in (Table 1 &2)

There was no significant difference between metformin treated group andglimepiride treated group regarding glycemic control (P=0.136); both drugs achieve good glycemic control as shown in (Table 3)

Table (1): HbA1c expressed as Mean ±SE in Metformin arm.

HbA1c	Patients before treatment	Patient after metformin treatment
	7.47 ± 0.11	6.38 ± 0.13*

* Significant difference as compared to the positive control group (P < 0.05).

Table (2): HbA1c expressed as Mean ±SE in Glimepiride arm.

HbA1c	Patients before treatment	Patient after glimepiride treatment
	9.01 ± 0.18	6.72 ± 0.18*

* Significant difference as compared to the positive control group (P < 0.05).

Table (3): comparison between effect of Metformin and Glimepiride on HbA1c expressed as Mean ±SE

	Metformin	Glimepiride
HbA1c	6.38 ± 0.13	6.72 ± 0.18×

× No significant difference as compared to Metformin arm (P > 0.05).

There was significant reduction in YKL-40 serum level in groups treated by metformin(P=0.001)or glimepiride(P=0.001) in comparison with its level in positive control group as shown in (Table 4&5).

However, there was significant difference between the amount of reduction in serum ykl-40 metformin treated patients' arm and glimepiride treated patients' arm (P=0.001); indicating that metformin is more effective than glimepiride in reduction of YKL-40 serum levels as shown in (Table 6).

Table (4): YKL-40 expressed as Mean ±SE in Metformin arm.

Serum YKL-40	Patients before treatment	Patient after metformin treatment
	251.96 ±10.95	85.40 ± 4.78*

* Significant difference as compared to the positive control group (P < 0.05).

Table (5): YKL-40 expressed as Mean ±SE in Glimepiride arm.

Serum YKL-40	Patients before treatment	Patient after glimepiride treatment
	334.22 ± 13.78	164.80 ± 15.08*

* Significant difference as compared to the positive control group (P < 0.05).

Table (6): comparison between effect of Metformin and Glimepiride on YKL-40 expressed as Mean ±SE

Serum YKL-40	Metformin	Glimepiride
	85.40 ± 4.78	164.80 ± 15.08 *

* Significant difference as compared to Metformin group (P < 0.05).

Discussion:

Type2 diabetes is a metabolic disorder characterized by chronic hyperglycemia resulting from a progressive insulin secretory defect on the background of insulin resistance, usually leading to absolute insulin deficiency, which results in complex phenomena exacerbated by central obesity, and increases the risk for micro and macro vascular complications such as atherosclerosis and related cardiovascular disease***(American Diabetes Association, 2014).***

Chitinase-3-like protein 1 (CHI3L1), also known as YKL-40, is a secretedglycoprotein and its pattern of expression is associated with pathogenic processes related to inflammation such as type 2 diabetes***(Eurich et al., 2009).*** In the present study, there was a strong correlation between type2 diabetes and serum YKL-40, so serum YKL-40 level is considered a good indicator for inflammatory processes which increase with micro-vascular complications of diabetes.

Our findings are consistent with data from ***(Rathcke et al., 2009)*** who found that patients with type1 diabetes and also patients with type2 diabetes have elevated serum YKL-40 levels. Also, our findings are consistent with ***(Johansen et al., 2006)*** who reported that plasma concentrations of YKL-40 are often elevated, compared to healthy subjects, in patients with diseases characterized by inflammation such as type 2 diabetes.

Another study of ***(Paarivalavan et al., 2015)***for showing the role of plasma and urinary YKL 40 in early diagnosis of nephropathy in type 2 Diabetic Patients, they found that both plasma and urinary YKL 40 levels were significantly higher in type 2 diabetes mellitus patients compared to healthy controls and that is in agreement with our study.

Proper anti diabetic treatment has additive beneficial effects in preventing diabetic micro and macro-vascular complications, besides providing good glycemic control***.(Krentz&Bailey, 2005).*** Therefore, reduction in YKL-40 by pharmacological intervention may be effective in decreasing the prevalence of these complications.

In our study we found that ykl-40 serum levels in type 2 diabetic patients group taking metformin for 4 month regimen have been significantly reduced in comparison to its high levels in the same group before taking the drug as well as there was significant reduction in their glycated hemoglobin (HbA1c) and this in agreement with the randomized clinical trial made by ***(Esteghamati et al., 2014)*** which conclude that metformin is more effective in reduction of YKL-40 concentration than pioglitazone after 3

months and this effect even seems to be independent of degree of glycemic control.

In the Diabetes Prevention Program, treatment with metformin in patients with impaired glucose tolerance (IGT) for 12 months decreased C reactive protein (CRP) levels as compared to placebo***(Haffner, 2005).***

Krysiak and Okopien found that patients with IGT treated with metformin have decreased release of many pro-inflammatory cytokines from monocyte and lymphocytes ***(Krysiak&Okopien, 2013).***
However, in contrast, LANCET trial found that treatment with metformin for 14 weeks failed to decrease CRP or other inflammatory biomarkers in T2DM patients, in spite of glucose regulation ***(Pradhan et al., 2009).***

Regarding glimepiride, our study also shows that T2DM patient groups treated by the drug have significant reduction in ykl-40 level as well as HbA1c in comparison to the same groups at baseline visit before treatment. This is in line with ***(Mavridis et al., 2008)*** who reported that T2DM patients treated with sulfonylureas had significantly lower inflammatory cytokine levels than the insulin-treated. Sulfonylurea can suppress cytokine production from activated macrophages by blocking the K^+ channels ***(Kewcharoenwong et al., 2013)***.

In the present study when we compared between metformin and glimepiride regarding their effect on improving HbA1c in T2DM patient after 4 months regimen, there was no significant difference between the 2 drugs. Both metformin and glimepiride were effective in treating T2DM for glycemic control and this is consistent with ***(Zhu et al., 2013)***randomized controlled clinical trial.

However, our results showed that amount of reduction in YKL-40 levels in patients group treated by metformin was more than in that treated by glimepiride, this is in line with ***(Erem et al., 2014)***controlled clinical study, in which improvement in markers of inflammation and endothelial dysfunction was less marked with glimepiride than with either metformin or pioglitazone, despite similar glucose control.

It is notable that while glimepiride appears to have some effect in the expression of many inflammatory cytokines, its anti-inflammatory effect is less potent than metformin ***(Xourgia et al., 2019).***

Conclusion:

Oral hypoglycemic drugs (metformin &glimepiride) show anti-inflammatory effects by reduction of YKL-40 inflammatory markerbeside their ability to achieve glycemic control in type2 diabetic patients. Metformin seems to be more potent than glimepiride regarding reduction of serum YKL-40 (inflammatory complications of diabetes).

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