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Original Article

EFFECTS OF METFORMIN AND GLIBENCLAIMIDE COMBINATION IN IRAQI OBESE PATIENTS WITH METABOLIC SYNDROME

HAEDAR ABDULHAFITH AL-BIATI[1], AHMED SALIH SAHIB[2*], SAJIDA HUSSEIN ISMAIL[3]

[1]Department of Clinical Pharmacy, College of pharmacy, University of Bagdad, Iraq, [2]Department of Pharmacology, Al-kindy College of Medicine, University of Bagdad, Iraq, [3]Department of Pharmacology and Toxicology, College of pharmacy, University of Bagdad, Iraq. Email: ahmedsalih73@yahoo.com

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ABSTRACT

Objective: The prevalence of diabetes mellitus and obesity was increased world-wide as well as in Iraq. Inflammation plays important role in pathogenesis of obesity and type 2 DM. The aim of this study was to investigate the serum levels of the inflammatory markers, insulin resistance, and BMI and lipid profile in obese type 2 diabetic Iraqi patients treated with metformin and glibenclamide.

Methods: This cross sectional study was conducted at Baquba Teaching Hospital, Diyala, Iraq; from January - April 2014. Fasting blood of glucose and insuline levels, lipid profile (S. cholesterole,S. triglyceride, and S. HDL),S. Interleukin 6 (IL-6) and C-reactive protein were determined in 30 subjects; 15 healthy control and 15 diabetic obese patients.

Results: There was statistically significant difference in BMI, fasting blood sugar, insulin resistance and lipid profile between obese diabetic and control group; inflammatory markers were also significantly elevated in diabetic obese patients compared to healthy control.

Conclusion: There is augmented inflammatory response in Iraqi diabetic obese patients which plays role in higher insulin resistance in these patients. Levels of inflammatory markers are increased and related to BMI and dyslipidemia in these patients.

Keywords: Type 2 DM, Obesity, Inflammation, Interleukin-6 (IL-6).

INTRODUCTION

The prevalence of diabetes mellitus (DM) world-wide was estimated to be 171 million people in the year 2000 and this is projected to increase to 366 million by the year 2030 (1), the prevalence of diabetes mellitus and obesity was increased world-wide as well as in Iraq. Inflammation plays important role in pathogenesis of the disease and inflammatory markers including interleukins and C-reactive protein (CRP), are found to be increased in type 2 DM (T2DM) patients (2).

Adipocytes secrete inflammatory cytokine; in addition they develop macrophage infiltration (adiposities) which is the source of most of the IL-6 in adipose tissue along with other inflammatory markers (3). Not only obesity but hyperinsulinism per se, seen in metabolic syndrome and type 2 DM, can induce rise in inflammatory markers including IL-6, and CRP. High levels of IL-6 have been reported to be associated with insulin resistance in adipocytes, hepatocytes and myocytes (4).

Raised serum IL-6 level in type 2 diabetic patients was found to be associated with increased BMI, fasting insulin levels and insulin resistance (5). In a prospective study in American females, the baseline CRP and IL-6 levels were significantly higher in those who later developed T2DM (6) Few studies have been done in Iraqi T2DM patients for CRP. No study so far has been done on serum levels of IL-6 level in T2DM patients. The present study was done to evaluate the serum levels of the inflammatory markers, insulin resistance and BMI and lipid profile in obese type 2 diabetic Iraqi patients treated with metformin and glibenclamide.

MATERIALS AND METHODS

This cross sectional study was conducted at Baquba Teaching Hospital, Iraq, from January 2014- April 2014. Approval from ethical committee of Ministry of Health, Iraq, was obtained before undertaking the research project. 15 healthy control male subjects and 15 diabetic male patients who were already on oral hypoglycemic agents (metformin and glibenclamide); age being 54.33± 2.52 year for control group and 55.67± 4.13 year or diabetic patients were included in the study as in table 1.

The diabetic group (n = 15) were diagnosed cases of type 2 diabetes mellitus of maximum duration of 5 years. The control group (n = 15) comprised of normal healthy individuals. The subjects were selected in accordance with inclusion and exclusion criteria. The inclusion criteria comprised of T2DM patients diagnosed according to 2013 WHO Diabetes criteria. Smokers, type 1 diabetic patients, patients on insulin therapy, patients with diabetic complications and patients with acute or chronic inflammatory disease were excluded from the study.

All study patients had proper history; physical examination. All subjects were informed about the nature, significance, implications and consequences of the study. They were appraised regarding investigational procedures. They were advised not to do any exercise or take any non-steroidal anti inflammatory drugs (NSAIDs) for two weeks prior to the blood sampling. The written informed consent was obtained, and personal particulars informed consent was obtained and personal particulars of each subject were noted and each was evaluated on the basis of detailed medical history, physical examination and laboratory tests. 10 ml of venous blood sample was drawn from antecubital vein under aseptic conditions in a disposable syringe from each individual. Blood was allowed to clot for 30 minutes at room temperature. After retraction of the clot, serum was separated by centrifugation at 3000 cycles per second for 15 minutes. Serum was then transferred to small sterile tubes and stored at - 20 °C prior to biochemical analysis. Blood C- reactive protein was performed on sysmex automated analyzer, Total cholesterol (TC), and triglycerides (TGs) by calorimetric method, and high density lipoprotein (HDL); calculated by Freidewald formula. IL-6 were determined by Enzyme Amplified Sensitivity Immunoassay (EASIA). Insulin resistance was calculated by Homeostatic Model of Assessment of insulin resistance (HOMA-IR). Statistical analysis was done utilizing program package of SPSS-17.

IL-6 assay

Quantitative measurement of IL-6 was done by use of a commercial EASIA kit; 'Bioscience Human IL-6 EASIA kit' (Catalogue no KAC1751, BioSource Europe S. A. Rue de I'Industrie 8 B-1400 Nivelles Belgium).

The assay is a solid phase Enzyme Amplified Sensitivity Immunoassay performed on microtiter plate. The minimum detectable concentration was estimated to be 2 pg/ml. The intra-assay and inter-assay coefficient of variation for IL-6 were 5.6% and 7.5% respectively.

RESULTS

Table 1 showed that there is non-significant difference between the ages of obese diabetic patients compared to that of healthy subjects, while there is a highly significant difference between the two groups concerning the BMI. The fasting blood glucose and fasting insulin levels in addition to insulin resistance were differ significantly in diabetic obese patients compared to healthy subjects table 1.

Table 1: Baseline data of healthy subjects and diabetes obese patients

Variables	Healthy subjects (n=15)	Diabetic obese patients (n=15)
Age (year)	54.33±2.52	57.65±4.138
BMI (kg/m^2)	21.17±1.62	39.59±2.55*
F. B. S (mmole/l)	5.95±0.67	12.89±2.1*
F. S. Insulin mIU/L	9.34±0.93	7.02±0.71*
HOMA-IR	2.46±0.33	4.04±0.79*

Results represents mean±SD; *=significant difference ≤ 0.05 ; BMI=body mass index; FBS=fasting blood glucose; HOMA-IR= Homeostatic Model of Assessment of insulin resistance.

While the values of total serum cholesterol and serum triglycerides were significantly higher in diabetic obese patients compared to healthy control, the value of high density lipoprotein was significantly lower in diabetic obese patients compared to healthy control, table 2.

The results of inflammatory markers studied were shown in table 3, IL-6 and C-reactive protein as; the serum levels of both inflammatory markers were significantly higher in diabetic obese patients compared to healthy controls.

Table 2: Lipid profile of healthy subjects and diabetes obese patients

Variables	Healthy subjects (n=15)	Diabetic obese patients (n=15)
S. Cholesterol (mg/dl)	141.73±13.64	219±27.68*
S. Triglycride (mg/dl)	124±16.35	272.2±59.3*
S. HDL (mg/dl)	47±4.72	40±3.81*

Results represents mean±SD; *=significant difference ≤ 0.05 ; S. HDL=serum high density lipoprotein.

Table 3: Inflammatory markers of healthy subjects and diabetes obese patients

Variables	Healthy subjects (n=15)	Diabetic obese patients (n=15)
IL-6 (pg/ml)	2.16±0.65	4.04±0.98*
CRP (mg/L)	2.7±0.65	9.65±1.2*

Results represents mean±SD; *=significant difference ($P \leq 0.05$); IL-6=interleulin-6; CRP=C-reactive protein.

DISCUSSION

Obesity is associated with a chronic inflammatory response, characterized by abnormal adipokine production, and the activation of some pro-inflammatory signaling pathways, resulting in the induction of several biological markers of inflammation (7). The key finding of this study is the close and significant relationship between levels of fasting glucose and CRP, Interleukin -6, and insulin resistance and changes in lipid profile. These findings in fact indicate that higher levels of these parameters in obese individuals lead to increased blood glucose. In support of these findings, some clinical studies support a close relationship and the role of CRP and other inflammatory markers such as IL-6, in hyperglycemia phenomenon in relationship with abnormal lipid profile (8, 9). Preliminary human studies demonstrated that central obesity is a risk factor for decrease in insulin sensitivity, although the molecular mechanisms for this are less understood (10). Obesity has been associated with elevated levels of CRP as an inflammation marker and elevated in serum cholesterol and triglyceride and predictor of cardiovascular risk (11). Recent epidemiologic studies have demonstrated associations of elevated serum levels of C-reactive protein with obesity, visceral adiposity, and insulin resistance, suggesting that a chronic inflammatory state is associated with hyperglycemia and diabetes through obesity or increased insulin resistance (12, 13, 14). The rise in the inflammatory cytokines is the essential step in glucotoxicity and lipotoxicity induced mitochondrial injury, oxidative stress and beta cell apoptosis in type 2 DM (15).

Our study found higher levels of, C-reactive protein,and IL-6 in diabetic obese patients compared to healthy controls that agreed with other studies (16, 17) indicating the role of inflammation in pathogenesis of the disease; administration of oral hypoglycemic agents in current use such as Metformin and Glibeneclamide to diabetic obese patients were unable to correct the glycemic control or changes in lipid profile beside increased level of inflammatory markers; targeting of these changes may represents an important strategy in the treatment of diabetic obese patients that may improve the overall situation of such patients.

In conclusion, there is augmented inflammatory response in Iraqi diabetic obese patients which plays role in higher insulin resistance in these patients. Levels of inflammatory markers are increased and related to BMI and dyslipidemia in these patients. This is the first study reporting the association of inflammatory cytokines with dyslipidemia and poor glycemic control in diabetic obese Iraqi patients.

CONFLICT OF INTERESTS

Declared None

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