Evaluation of lipid profile and inflammatory parameters in female diabetes type2 induced rabbits treated with glimepride,bromocriptine and fluoxtein

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Summary

This study was performed to evaluate the improvement in serum lipid profile and inflammatory parameters in female diabetic rabbits after two month treatment with glimepride, bromocriptine and fluoxtein in order to decrease cardiovascular diseases risk related to type 2diaetes mellitus. Twenty five local female rabbits divided equally in to five groups, four groups were diabetes type 2 induced by alloxan 120 mg/kg and nicotinamide 50 mg/kg and the fifth group was control negative (Cv-).The animal were allocated to different treatment regimen ,dosed orally on daily base for two months treatment, as following, T1 (glimepride 0.11mg/kg),T2 (glimepride 0.11+bromocriptine 0.04 mg/kg),T3 (glimepride 0.11+fluoxtein 0.29 mg/kg), control positive group(Cve+) diabetic without treatment and the fifth group was control negative group (Cve-) dosed with distall water. Lipid profile, interleukin-6,C-reactive protein were determined after diabetes induction and at the end of experiment. IL-6 significantly reduced in T2,while C-Reactive Protein non-significantly reduced. All treated groups showed nearly similar total cholesterol level, T1demonstrate the higher level of High Density Lippoprotein -C level . In the same time all treated groups showed non-significant decrease in Low Density Lippoprotein-C, T2 showed superiority in reducing Very Low DennsityLippoprotein-C and triglyceride level over all other diabetic groups .

Conclusion:Diabete agonist (Bromocriptine)+glimepride demonstrate the superiority over the combination therapy glimepride +flouxtein and glimepride as monotherapy in improving diabetes type 2 related cardiovascular complications.

Key words: Lipid frofile, diabetes type 2, Bromocriptine.

Introduction

Diabetes mellitus(DM) is a group of metabolic diseases characterized by elevated blood glucose levels hyperglycemia resulting from defects in insulin secretion, insulin action or both. Insulin is a hormone manufactured by the beta cells of the pancreas, which is required to utilize glucose from digested food as an energy source. Chronic hyperglycemia is associated with microvascular and macrovascular complications that can lead to visual impairment, blindness, kidney disease, nerve damage amputations, heart disease, and stroke. In 1997 an estimated 4.5% of the US population had diabetes direct and indirect health care expenses were estimated at $98 billion(1).The worldwide prevalence of diabetes has continued to increase dramatically. Globally, as of 2011, an estimated 366 million people had DM, with type 2 making up about 90% of the cases(2). The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries (3). The International Diabetes Federation (IDF) estimates that by 2030, patients with diabetes will double to current estimates of

up to 59.9 million in the middle east and north Africa (MENA) region (4). In recent years, several studies have been published that implicate subclinical chronic inflammation as an important factor for pathogenesis in the development of insulin resistance and type 2 diabetes. This opens new perspectives for diagnosis and treatment of early insulin resistance and incipient glucose intolerance. Surrogate markers for this low-grade chronic inflammation include IL-6 ,CRP (5). On the other hand, Alloxan used to induce diabetes,is a small molecule that resembles glucose, that binds the GLUT-2 glucose transporter, and enter cells via the GLUT-2 glucose transporter (6). It generates super-oxide and hydroxyl radicals; since beta cells have relatively weak defenses against oxidative stress, they are especially sensitive to free radical-mediated damage by alloxan and undergo necrotic cell death within (48) hours postinjection (7).

Material &Methods

Total number of twenty five locally female rabbits were used in the experiment. The experimental animals rang weight were 1200-1420gm,raised and bred in the animal house of Collage of Veterinary Medicine, Baghdad University, where the study was performed the animals were kept in cages of (100*50*50) cm in dimensions in average 2 female rabbits in each cage. In optimum conditions of breeding at 22±3 c° with about 14/10 hours (light /dark)cycle. Standard pellets and water provided ad libidum (8). Diabetes type 2 was induced in rabbits according to (9) in which alloxan at dose 120 mg/kg and nicotinamide 50 mg/kg were given IP to the different dosing diabetic animal groups. Twenty five adult female rabbits nearly at the same age and weight were divided equally in to 5 groups, 4 diabetic groups and one non diabetic group. The first group (T1) in which the 5 diabetic female rabbits were administered 0.11 mg/kg glimipride, (10) daily, orally for 2 months, the second group (T2) in which 5 diabetic female rabbits were administered 0.11mg mg/kg glimipride (10 and 0.04 mg/kg (11) of dopamine D2 agonist bromocriptine, daily, orally for 2 months. The third group (T3) in which 5 diabetic female rabbits were administered 0.11mg/kg glimipride (10) and 0.29 mg/kg (12) of selective serotonin reuptake inhibitors (fluoxetine), daily, orally for 2 months. The fourth group (Cve+) included 5 diabetic female rabbits without treatment for 2 months and the fifth group (Cve-) include 5 non diabetic female rabbits administered distilled water orally for 2 months. Directly after induction of type 2 diabetes and once again at the end of study, serum was obtained from all experimental groups and then Interleukin -6 concentration was measured according to instruction of commercial kit, in addition to measurement of C-Reactive protein concentration according to commercial kit (BIOTEC), also total cholesterol concentration, HDL-C concentration and triglyceride concentration was determined according to commercial kit (ELITech clinical system), While determination of VLDL-C concentration was according to (13) by to the following equation VLDL = 1/5 *triglyceride.

Determination of LDL-C was obtained according to (13) by the following equation:- LDL-C = Total cholesterol –HDL-C –VLDL-C. Statistical analysis of data was performed on the basis of Two-Way Analysis of Variance (ANOVA) using a significant level of ($P<0.05$). Specific group differences were determined using least significant differences (LSD) as described by (14).This study was performed under the rules of ethics for management of laboratory animals submitted by University of Baghdad /College of veterinary Medicine.

Results and Discussion

The result of interleukin 6 level revealed that T1,T3 and Cve+ at the end of study showed significant increase ($P\leq0.05$) in comparison with period directly after induction of diabetes type 2. While T2 showed significant decrease ($P\leq0.05$) at the end of study in comparison with period directly after induction of diabetes type 2. At the end of study T1,T3 and Cve+ showed significant increase ($P\leq0.05$) and only T2 showed significant decrease in comparison with control group (Cve-) as listed in table (1).

Table, 1: Interleukine-6- level pg/ml in induced diabetic rabbit groups dosed orally for two months with glimepride ,bromocriptine and fluoxtein .

period / group	Interleukin -6 levels pg/ml directly after diabetes induction M±SE	Interlukin-6 levels pg/ml two months after treatment M±SE
T1 (Glimepride)	54.78±3.37 Ab	72.93±4.04 BCa
T2 (Glimeprid+bromocriptine)	55.18±5.32 Aa	26.07±2.56 Db
T3 (fluoxtein)	58.57±2.84 Ab	79.42±7.65 Ba
Cve+(without treatment)	62.33±0.62 Ab	93.76±1.67 Aa
Cve- (D.W)	62.08±6.92 Aa	63.72±1.65 Ca
LSD 0.05	13.962	

- M±SE =Mean± Standard error
- Different capital letters represent significant differences (P≤0.05) between groups
- Different small letters represent significant (P≤0.05) between periods.

In recent years, several studies have been published that implicate subclinical chronic inflammation as an important pathogenetic factor in the development of insulin resistance and type 2 diabetes. Surrogate markers for this low-grade chronic inflammation include C-RP, IL-6 (5).

Data from our study suggest that bromocriptine may reduce inflammatory response that may implicated in type 2 diabetes pathogenecity after 8 weeks treatment through reducing IL-6-. Its reported by (15) that bromocriptin may be produce anti- inflammatory effect.

It has been suggested that type 2 diabetes is the final result of an acute phase reaction during which cytokines are released in large amounts from adipose tissue (16), as well as from macrophages recruited into adipose tissue, sustaining inflammation and impaired adipocyte function (17).It need more investigation to clarify if it is necessary to included anti-inflammatory medications within the strategy to control this metabolic disease.

C-RP concentration : The result of C-RP revealed that, at period directly after induction and at the end of study all treated groups(T1,T2,T3 and Cve+) showed significant increase(P≤0.05) in comparison with control group(Cve-). Within the periods only T1 and T2at the end of study showed significant decrease, While T3 and Cve+ groups showed significant increase in comparable to the period directly after induction of DM 2 as listed in table(2).

(Table .2) C- Reactive protein level mg/ml in induced diabetic rabbit groups dosed orally for two months with glimepride ,bromocriptine and fluoxtein .

period / group	C-reactive protein levels directly after diabetes induction M±SE	C-reactive protein levels two months after treatment M±SE
T1 (Glimepride)	16±4.14 Aa	9.20±3.13 Bb
T2 (Glimeprid+bromocriptine)	14.8±3.72 Aa	8±3.09 Bb
T3 (fluoxtein)	9.2±3.13 Bb	19.2±3.49 Aa
Cve+(without treatment)	14.8±3.72 Ab	20.4±2.4 Aa
Cve- (D.W)	2±0 Ca	2±0 Ca
LSD 0.05	9.901	

- M±SE =Mean +Standard error
- Different capital letters represent significant differences (P≤0.05) between groups
- Different small letters represent significant (P≤0.05) between periods.

It has been shown that the serum levels of C-RP, IL-6, fibrinogen، PAI-1 (plasminogen activator inhibitor 1), amyloid A and sialic acid are increased in patients with type 2 diabetes، and that the magnitude of the increase correlates with the degree of hyperglycemia (17). If this hypothesis is correct, it may have consequences for treatment: drugs that inhibit the acute phase

reaction and the ensuing inflammation could potentially increase insulin sensitivity and retard the development of diabetes(5). Rsearchers (18) reported their study which was conducted on type 2 DM subjects, they conclude that the hs-C-RP was higher in healthy controls, who are at the risk of developing DM and CVD (Intermediate risk)(18). In type-2 DM, insulin resistance is the primary event, followed by increasing degree of β-cell dysfunction (19). Chronic, systemic subclinical inflammation has also been identified as a driving force for insulin resistance, metabolic syndrome ،and type 2 DM (20). The process of inflammation induces hepatic synthesis of various acute phase proteins such as serum ferritin and high sensitivity C-reactive protein (hs-CRP), which is believed to play a role in insulin resistance as well as atherosclerosis (21). In our study the decrease in C- reactive protein in T1, may be due its effect of glimperid through increasing secretion of insulin, although it is still controversial issue but insulin may has anti-inflammatory effect as reported by(22). In addition the decrease in C-RP noticed in T2 after 2 months treatment with (glimeprid and bromocriptin) and the significant increase in C-RP noticed in T3 after 2 months treatment with (glimeprid and flouoxtein) may be correlated to body weight changes beside the suggested anti-inflammatory effect of bromocriptin. Effective weight loss has been shown to reverse elevated hs-C-RP levels in diabetic and nondiabetic populations(23). Favorable effects on the inflammatory response, including a decrease in hs-C-RP levels, have also been seen with physical activity interventions(23). Raised base-line C-RP values are also associated with many features of the insulin resistance or metabolic syndrome (24), up to and including frank diabetes mellitus (25). This may reflect, in part, the fact that adipocytes are the source of a substantial portion of base-line IL-6 production (26) and perhaps also synthesize and secrete some of the baseline C-RP itself (27). On the other hand the increase in C-RP in T3 group that reported in our current study after administration of antidepressant (Fluoxtein (selective serotonin reuptake inhibitor) may be attributed to the atherogenic effect of serotonin which lead to initiate atherogensis process that may be lead to formation of arthroma inside the vessels which indicated by high C-RP level which is used as predictor for cardiovascular disease. Serotonin promotes further platelet recruitment and activates the coagulation pathway. The blood vessels in which platelets aggregate are exposed to high concentrations of 5-HT (28).

At the end of treatment the results of lipid profile test demonstrated that all diabetic groups except Cve+ group showed nearly the same level in total cholesterol to that of Cve-,T1has the significance (P≤0.05) over other diabetic groups in elevating HDL-C level. All treatment groups showed non-significant decrease while Cve+ still recorded high levels of LDL-C. T2 demonstrate significant decrease(P≤0.05) over all other diabetic groups in VLDL-C and triglyceride level as listed in table (3)

(Table.3) lipid profile mg/dl in induced diabetic rabbit groups dosed orally for two months with glimepride ,bromocriptine and fluoxtein .

Parameter	Period / group	directly after diabetes induction M±SE	At the end of study M±SE
Total cholesterol mg/dl	T1(glemipride)	124.8±1.98 Aa	107.6±2.63 Bb
	T2(glemipride+bromocriptie)	124.6±1.53 Aa	101.2±2.03 Bb
	T3(glemipride+fluoxtein)	122.2±1.01 Aa	108.2±3.48 Bb
	Cve+(without treatment)	123.2±2.26 Aa	128.4±2.58 Aa
	Cve-(D.W)	107.8±2.85 Ba	108.4±5.2 Ba
LSD0.05		9.083	
HDL-C mg/dl	T1(glemipride)	22.4±1.74 ABb	27.2±1.15 Aa
	T2(glemipride+bromocriptie)	20.80±0.86 Ba	22.40±0.92 Ba
	T3(glemipride+fluoxtein)	21.40±2.27 ABa	23±1.48 Aba

	Cve+(without treatment)	20±0.54 Ba	21.6±0.67 Ba
	Cve-(D.W)	25±1.04 Aa	25.4±5.2 ABa
LSD0.05	4.492		
LDL-C mg/dl	T1(glemipride)	76.92±4.03 Aa	54.32±2.45 Bb
	T2(glemipride+bromocriptie)	79.92±2.33 Aa	56.72±2.29 Bb
	T3(glemipride+fluoxtein)	77.44±1.04 Aa	60±1.48 Bb
	Cve+(without treatment)	75.36±1.99 Aa	78.32±1.79 Aa
	Cve-(D.W)	62.80±4.73 Ba	62.68±7.51 ABa
LSD0.05	8.527		
VLDL-C mg/dl	T1(glemipride)	25.08±0.44 Aa	25.08±0.39 Ba
	T2(glemipride+bromocriptie)	23.88±1.93 Ba	21.96±0.50 Ca
	T3(glemipride+fluoxtein)	25.36±0.47 Aa	25±0.43 Ba
	Cve+(without treatment)	24.88 ±0.34 ABb	31.44±0.60 Aa
	Cve-(D.W)	21.76±0.28 Ba	20.32±0.70 Ca
LSD0.05	2.494		
Triglyceride mg/dl	T1(glemipride)	125.4±2.24 Aa	125.4±1.98 Ba
	T2(glemipride+bromocriptie)	119.4±1.36 Aa	109.8±2.51 Cb
	T3(glemipride+fluoxtein)	126.8±2.39 Aa	125±2.16 Ba
	Cve+(without treatment)	124.4±1.72 Ab	157.2±3 Aa
	Cve-(D.W)	108.8±1.42 Ba	101.6±3.54 Db
LSD0.05	7.596		

- M±SE =Mean ±Standard error
- Different capital letters represent significant differences (P≤0.05) between groups
- Different small letters represent significant (P≤0.05) between periods.

The results of lipid profile might indicate (dyslipidemia) seen directly after induction of DM2 is due disturbance in lipid metabolism . It is proposed that underutilization of glucose is associated with changes in lipid profile. Changes in lipid profile are also well related with severity of DM(29). Diabetic dyslipidemia or atherogenic dyslipidemia is characterized by low HDL, high TG and high low density lipoprotein LDL (30). Data from our study demonstrate that after glimepride administration, caused remarkable improvement in lipid profile results, reducing in total cholesterol, LDL-C and elevation in HDL-C without affecting triglyceride level, this may be due to anti-atherogenic effect of glimiprid which is may be associated with its anti-glycemic effect. Data from our study agree to far extent with the study result of (31),which showed that BMI and plasma lipid profile, TC, TG, HDL improved by Glimepiride treatment probably, they suggest that ,the mechanism for improvement may be related to decrease in plasma TNF α levels & increase in plasma adiponectin which is a specific plasma Glycoprotein which has anti atherogenic, anti-inflammatory and apoptotic effects(32). Also in their studies showed that, Glimepiride possibly has anti atherogenic activity by inhibiting platelet aggregation via suppression of arachidonic acid metabolism. Most of the anti-diabetic drugs besides their hypoglycemic effect, they are having to some extent the anti-atherogenic influence by bringing fluctuations in the lipid profile features, but this effect is variable. In case of Glimepiride comparatively influence on the lipid profile is a significant feature associated with hypoglycemic effect (33). While the result of T2 which was administered(glimiprid +Bromocriptin (D2 agonist) showed a comparable results in total cholesterol, HDL and LDL glimeprid monotherapy group, beside that there was a better improvement in the results of VLDL-C and triglyceride while glimepride as amonotherapy did not affect neither VLDL-C and nor triglyceride.This may be attributed to the suggested anti –inflammatory effect (reducing IL-6) that documented in our study. It is well known that proinflammatory cytockine will increase triglyceride production via promoting lipolysis and decrease triglyceride clearance by suppressing lipoprotein lipase (34). On the other hand it suggest that , Bromocriptin demonstrate improvement in lipid profile may be via suppressing prolactin level. While the result of T3 which administered glimeprid +Fluoxtein

(serotonin reuptake inhibitors) demonstrate a comparable results to that of T1 which administered glimperid only, so its seems that flouxtein have no effect or minor effect that counteract the demonstrated effect of glimeprid in improving lipid profile in DM2, may be through the suggested negative work of fluoxtein occur through suppressing endogenous dopamine and cause elevation of prolactin. A variety of other modulators of prolactin secretion act at the hypothalamic level by either disinhibiting of the dopaminergic tone (e.g. serotonin, GABA, oestrogens and opioids) or by reinforcing it (e.g. substance P)(35). In conclusion: D2 agonist (Bromocriptine)+glimepride demonstrate the superiority over the combination therapy glimeprid + flouxtein and glimeprid as monotherapy in improving diabetes type 2 related cardiovascular complications.

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تقيم الدهون والمقايس الالتهابية في في داء السكري من النوع الثاني المستحدث في اناث الارانب المعالجة بعقار الكليمبرايد,بروموكريبتين وفلوكستين

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الخلاصة:

تم اجراء هذه الدراسة لغرض تقيم الدهون والمقايس الالتهابية في اناث الارانب المصابة بداء السكري بعد فترة علاج شهرين بعقار الكليمبرايد,بروموكريبتين و فلوكستين لغرض تقليل خطر الاصابة بامراض القلب والاوعية الدموية المرتبطة بالاصابة بداء السكري. حيث ان خمسة وعشرين انثى من الارانب المحلية قسمت بشكل متساوي الى خمس مجاميع ,اربع مجاميع تم فيها استحداث داء السكري من النوع الثاني عن طريق حقن مادة الوكزان بجرعة 120ملغم/كغم و مادة النيكوتين آمايد بجرعة 50 ملغم/كغم,والمجموعة الخامسة هي مجموعة سيطرة سلبية .حيوانات التجربة قسمت لأنظمة علاج مختلفة وبتجريع يومي لمدة شهرين كالاتي ,المجموعة الاولى ,جرعت فيها الحيوانات عقار الكليمبرايد بجرعة0,11 ملغم/كغم,المجموعة الثانية جرعت عقار الكليمبرايد بجرعة0,11 ملغم/كغم +عقار البروموكريبتين بجرعة 0,04 ملغم/كغم,المجموعة الثالثة جرعت فيها الحيوانات عقار الكليمبرايد بجرعة0,11 ملغم/كغم+ عقار الفلوكستين بجرعة 0,29 ملغم/كغم و مجموعة رابعة (مجموعة السيطرة الايجابية مصابة بالسكري ولكن بقينت من دون علاج) و مجموعة خامسة مجموعة السيطرة السلبية جرعت فيها الحيوانات ماء مقطر .كمية الدهون ,الانترلوكين -6 و السي رياكتف بروتين تم حسابهم مباشرة بعد استحداث داء السكري وفي نهاية التجربة ايضاً.حيث ان الانترلوكين -6 سجل ارتفاعاً معنويا في المجموعة الثانية بينما السي رياكتف بروتين سجل انخفاضاً غير معنوياً.كل المجاميع المعالجة سجلت تقريبا نفس مستوى الدهون.المجموعة الأولى سجلت أعلى ارتفاع بمستوى الكوليستيرول النافع ,في نفس الوقت كل المجاميع المعالجة سجلت انخفاضاً غير معنوياً في مستوى الكوليستيرول الضار .المجموعة الثانية اظهرت تفوقا على بقية المجاميع المصابة بالسكري في خفض نسبة الكوليستيرول جدا منخفض الكثافة والدهون الثلاثيةز ننستنتج البروموكربتين +الكليمبرايد اظهر تفوقا على العلاج بالفلوكستين +كليمبرايد و العلاج بالكليمبرايد فقط في خفض نسبة الاصابة بامرض القلب الوعائية الناتجة عن مرض السكري من النوع الثاني .

الكلمات المفتاحية: تقييم الدهون، مرض السكري من النوع الثاني، بروموكريبتين.