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The impact of metformin adding therapy on type 2 DM patient on insulin treatment

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Abstract

Background:

The need for strict glycemic, lipid and blood pressure control to avoid or delay the development of cardiovascular and other complications in those with type 2 DM has been well established.

Aim of study:

To assess the the role of metformin medication on the blood glucose control, improvemen of lipid profile, blood pressure contole and body weight of patient with type 2 diabetic patients .

Patient and method:

A cohort study was done to assess 50 patients of type 2 diabetes mellitus , on insulin therapy , seen at diabetic Centre of Al Sadr city in Al-najaf Alashraf . All patients were followed up monthly for 3 months to insure regular treatment and occurrence of any complication .

Results

Fifty patients with type 2 diabetic were studed by using a paired analysis study those patient ordinerary on insulin therapy then we added maximum dose of metformin therapy on insulin then followed after 3 monts 3 after metformin therapy (combination insulin and metformin therapy) to assess and evaluate the effect of metformin as combination therapy with insulin on the blood glucose control, Triglyceride level ,total cholesterol and blood pressure . in addition to assessment of HA1C and blood glucose level we also assess other parameter including metformin therapy effect on systolic and diastolic blood pressure ,Waist ciecumfrence, body mass index(BMI),lipid profile for each patient.This study was a cohort study to review and asess type 2 DM patients on insulin . in this study we found that blood glucose level was significantly improved ($P < 0.001$) after the introduction a amaximum dose of metformin therapy (2000 mg/day), and a 30 % of the fifty type 2 diabetic patients reaching HbA1c levels less than 7%, and 50% of patients reaching HA1c values (7-8%) . There was also significant reduction of triglyceride level with ($P < 0.05$) and TG (286.8 ± 56.6 to 221.04 ± 33.43 mg/dL) and reduction of waist circumference (124.5 ± 11.8 to 117.4 ± 9.4 cm) but there was no significant improvement in total cholesterol level , HDL cholesterol, blood pressure and body mass index .

Conclusion:

This study evaluate the effect of metformin adminstration with insulin therapy simultaneously without important negative side effects with significant glycemic and TG control and waist circumference reduction.

Introduction:

Diabetes mellitus (DM) refer to as a common metabolic disorders that charactarised by acomon symbtoms of hyperglycemia. there are many types of DM that result from interaction of environmental factors ,genetic and heredetary factors. there are many mechanisem causing elevation of blood glucos elevel includind a reduction in insulin prodection and secresion, impairement of bllood glucose metabolism and utilisation ,also increased glucose syntheses . DM has many adverse effect on several organ and system in the body of patient with diabetic mellitus that burden on the diabetic patients and on the health care systems [(1)] .

Type 2 DM is a group of disorders that lead to the common phenotype of hyperglycemia in type 2 DM and have important therapeutic effect on pharmacologic agents that available to treat specific metabolic disorders [(2)].

The prevalence of DM has increases over the last 2 decades, from an estimated 30 million patient in 1986 to 286 million in 2011. Based on the International Federation of DM showed that 439 million people will have DM at the 2030 year . the occurence of type 2 DM is rising dramaticly , mostly due to prevalence of obesity, dicrease excersise(sedentary life stile) and the improvent the age of the people[(3)].

Furthermore, Type2 DM are associated with increased cardiovascular ischemic risk factors such as hyperlipidemia, obesity and hypertension [(4)] .most of (more than 50%) of deaths among type2DM patients were caused by cardiovascular ischemic disease [(5)] .

Treatment of type2DM including management of hyperglycemia in addition to treatement of other associated disorder such as dyslipidemia,obesity and hypertention.

metformin medication that proved to be more effective in dicreasing insulin therapy resistance[(6)].there are several reseaches are undertaken to study the effect of metformin therapy on total blood cholesterol , bllood triglycerides level , and HDL- levels, and its effect on obesity and BP .

Because of type 2 DM is a progressive disease so that , an important percentage ofthose patients eventually will end with insulin therapy, at this moment most of the physicians are recommended to continue on using metformin therapy with insulin or other medications . The advantage behind of using a combination therapy related to beneficial metformin metabolic effects, such as decreasing glycemic blood levels and body weight of patient [(8)] . The prospective Diabetes Study of The United Kingdom suggested a beneficial metformin effect when compared with dietary controle, on ischemic heart disease and mortality of type 2 diabetic patient after 10 years follow up [(9)].

at first time of patient with type 2DM there is sparing insulin in pancrease so that there is agood response to oral hypoglycemic agent . However, the progressive nature of the diabetic disease with its reduction in endogenous insulin result in progression of disease lead to advanced disease more closely similar to type 1 diabetes [(10)].

Metformin therapy is usually regarded as first drug in type 2 DM.[8]The mechanism action of metformin medication is that mostly causing inhibition of mitochondrial respiratory chain (complex I), inhibition of glucagon-induced elevation in the level of cyclic adenosine monophosphate (cAMP),activation of AMP-activated protein kinase (AMPK), and this mechanism will lead to activation of protein kinase A (PKA), inhibition of mitochondrial glycerophosphate dehydrogenase [(11)]. Activation of AMPK, this enzyme has an important role in human insulin signaling, regulate the metabolism of plasma glucose level ,body energy regulation, and fatty tissue distribution[(12)], these was required for inhibitory action of metformin therapy on the liver production of glucose [(13)].

Also metformin therapy may antagonize the glucagon hormon action in the body, as aresult metformin reduce fasting blood glucose levels[(14)]. In addition to decreasing hepatic production of glucose , metformin improve tissues sensitivity to insulin, enhancing peripheral tissue uptake of glucose (by inducing the phosphorylation of GLUT4 enhancer factor), decreases insulin effect on fatty acid oxidation, and reduces GIT absorption of glucose [(15)]. metformin also Increasing the peripheral utilisation of glucose,this is may be due to improvement of insulin binding to its receptors[(16)].

The metformin treatment also reduces the gluconeogenesis by over one-third in type 2DM[(17)].

The metformin synthesis , initially described at 1922 which is formed by the reaction of dimethylamine hydrochloride and 2-cyanoguanidine (dicyandiamide) by heating[18].

Peak plasma level of metformin occure after 1-3 hrs after taking immediate-release therapy and 4-8 hrs after taking extended release therapy[19].

The plasma protein that binding to metformin after absorbtion is neglected this is due to high volume distribution of drugs in the body . Steady state of metformin level in the plasma is mostly reached after 1-2 day. Metformin is a medication that is not well metabolized so that it will be excreted mostely unchanged from the urinary tract. The half-life of metformin therapy in the body is about 6.3 hrs [20].

the type 2 DM in pregnant women as well as gestational diabetic women are treated effectivelly and less side effect by metformin therapy and have less effect on body weight in pregnant women than those patients on insulin therapy . The newnate of pregnent diabetic mother that received metformin therapy have less body fat and weight, this will lead to decrease the percentage of insulin resistance and DM in later life[21].

The lactic acidosis is very rare effect of metformin therapy and can be prevented . Metformin should not be used in patients with renal impairement (GFR < 60 mL/min), acidosis, congestive heart failler , hepatic broplems, and severe hypoxemia[22].

Type 2 DM have an important health care problem due to increased risk of ischemic heart disease [23]. The importance of bllood glucose control in reducing microvascular diseae, cardiovascular adverse effect with increasing morbidity and mortality has been shown in the UK Prospective DiabetIC Study (UKPDS)[24]. metformin lead to an important improvement of HbA1c so that reducing the complication of microvascular and macrovascular disease[25].In addition, the UKPDS study find alogic answer ,whether there is a preferred treatment in order to achieve good blood glycaemic control [26]. in This study after a follow up of 11 year, the treatment with intensive metformin therapy lead to an important reduction of diabetes mellitus -related mortality , and cardiovasculr complication in type 2 DM patients when compared with insulin therapy or other hypoglycemic drugs, inspit similar blood glucose control.

Type 2 DM causing several metabolic derangement in lipid and fatty metabolism and leading to lipoprotein metabolic abnormalities, such as decreasing HDL , increase of small dense of low density lipoprotien particles, and increasing TG plasma level [27].

There is strict evidence that each of these dyslipidemic metabolic disorder is associated with important risk of ischemic heart disease and CVA and death in type 2 DM[28].

Any changes in the TG-rich lipoprotein metabic disorder has crucial effect in the pathogeneses of the atherosclerosis in diabetic patient ,these metabolic alteration including the increasing of liver secretion of VLDL-cholesterol and reduce clearance of VLDL-cholesterol and Chylomicron . An important sequele of metabolic clearance is prolonged bllood retention of VLDL cholesterol and postprandial Chylomicron as partially lipolyzed particles . These remnants particles, involve cholesterol enriched (IDLs), wich is regarding as atherogenic particles in humans and in animal [29].

Insulin resistance mechanism in type 2DM play an important role in the dyslipidemia that causes by several factors such as increase efflux of free fatty acids from fatty tissue, increase fatty acid influx to the liver and impaired insulin mediated skeletal muscle uptake of free fatty acids[28] .

Methods and Material :

Collection of data :

This is a cohort study was done to assess 50 patients with T2DM, on insulin therapy without metformin had been rolled in this study, seen at diabetes Centre of Al-Sadr city in Alnajaf Alashraf . All patients were chosen randomly and followed up monthly to insure regular treatment and occurrence of any complication.

Method:

The selected patients was on 2 doses of insulin injection then metformin added to a maximum 2000 mg daily to their therapy and follow up for 3 months .

Inclusion criteria:

*Aged 35-70 years
*Treatment with insulin only
*HbA1c more than or equal to 7%
* high TG levels (TG > 150 Mg/DL).
* waist circomfrence (female : > 88 Cm; male : >102 cm).

Exclusion criteria:

* any evidence of renal impairment(serum creatinine >1.5 mg/dl in males or >1.4 mg/dl in females).
*heart failure or myocardial infarction.
* liver impairment.
*sever symptom that indicate gastropareses.
*History of recent acute illness in previous 6 weeks.
*Unhealed diabetic foot.
*Patients on lipid lowering agent.

Variables studied

BMI(Body mass index) , WC(waist circomflex) , the lipid blood profile (Total Cholesterol ,TG , HDL-C), HbA1c, blood glycemic level (FBG), doses of injectable insulin therapy , Bood pressure (BP), were measured in all patients when the metformin was started and 3 months after combined insulin and metformin therapy.

weight of patient was measured by using digital scale with a precise measurement of up to 100g. the length of patient was calculated by a tape measure with aprecise measurement of up to 1mm precision . For waist circumfelerence was measured by a tape measure, the patient was in standing position, with a relaxed abdomen , and the tape measure was placed horizontally but without any compression on the tissue of the abdomen .

Blood pressure was measured by a well calibrated mercury sphygmomanometer and BP was measured on the left arm ,with 2 times BP measurement for each patient with in 5 mints interval, with the patient in the sitting position.

Total chlesterol level (TC), triglyceride (TG) ,HDL-C, and fasting BG levels were measured by using the colorimetric methods. HbA1C was perforeformed accurately by using high-performance liquid chromatography technique .

Statistical analysis of data

The data are collected as percentages (%) , 95% confidence intervals (95% CI) and means ± SD, . the significant level was at $P < 0.005$.

A paired *t*-test with 95% confedence interval (CI) was used for the mean of study variable after adminstration of metformin therapy to type 2 DM patiens. If there is any difference in *t*-test value for any variable studied then torson's correlation test was calculated to check for any possible intervening variables (co-variance) by the analysis of the coefficient of determination (r 2) and r 95% CI.

GraphPad InStat, version 3.06 was The statistical package of Windows (San Diego, CA,USA) were used in this study for analyses of data .

Results

A fifty Patients were analyzed in this study.

A blood glucose level are significantly improved ($P < 0.0001$) after the adminstration of metformin medication , with a dicrease of HbA1c levels as shown in (Table 1).

Table 1. Comparison of glycemic control after 3 months of metformin adding therapy on insulin .

variables	before	after	95 % CI	PV
HbA1c (%)	8.8 ± 1.03	8.18 ± 1.01	o.21 - 1.03	0.0032
BG (mg/dL)	215.3+/-28.1	189.3+/-27.4	15 - 37.13	0.0001
insulin doses IU/kg	0.83 ± 0.39	0.79 ± 0.36	0.11 to -0.19	0.597

A thirty percent of the DM patients reached HbA1c of less than or equal 7%, 50% had HbA1c values of 7-8 % and 20% had unsatisfactory blood glucose control. before introduction of metformin and 88% of diabetic patients had HA1C >7% Table(2) .

Table(2).Comparison of glycemic control after 3 month of metformin therapy.

HbA1c	Before metformin			After metformin		
	No.of patients	percentage	SD	No.of patients	Percentage	SD
</=7%	6	12%	6.45±0.45	15	30%	6.51±0.29
7-8%	20	40%	7.41± 0.19	25	50%	7.39±0.36
>8%	24	48%	9.12± 1.95	10	20%	8.9± 0.7

Table(3).comparison between male and female before and after treatment with metformin of patient with T2DM

Male			Female	
Variables	Before	After	Before	After
HbA1c	8.75 ± 1.03	8.13 ± 1.01	8.9 ± 1.03	8.20 ± 1.01
TG	280.8± 55.5	218.04 ± 31.5	290.8± 58.6	225.04 ± 32.6
BMI	31.7 ± 5.5	29.9 ± 4.0	29.7 ± 5.2	28.1 ± 3.8
WC	126.6 ± 11.9	119.3 ± 9.5	123.5 ± 11.5	116.3 ± 9.1

There was a significant dicrease of the triglycerid after 3 months of metformin treatment. Although there was an elevation in HDL-C but its value was not statistically significant. While TC decreased in most of the patients but the total result was not significant. as shown in(table-4).

Table 4. Comparison of lipid profile after 3 months of metformin treatment.

variables	Before metformin	After metformin	95% CI	PV
cholesterol lvel (mg/ dL)	230.0 ± 29.6	218.3 ± 25.1	0.12 - 21.8	0.0525
HDL level (mg/ dL)	32.6 ± 5.98	35.1± 6.98	-5.1 - 0.091	0.0584
Triglycerides (mg/dL)	286.8± 56.6	221.04 ± 33.43*	47.2 - 84.0	0.00016

Regarding waist circumference there was significant changes but Neither blood pressure, nor BMI show significant alteration. As demonstrated in below (table-5).

Table 5. Comparison of laboratory and clinical data after 3 months of the metformin treatment .

variables	before metformin	after metformin	95% C I	P value
BMI (index) (kg/m2)	30.8 ± 5.3	29.1 ± 4.1	- 0.12 - 3.6	0.0787
WC (cm)	125.1 ± 11.8	117.4 ± 9.4	3.08 - 11.5	0.0009
systolic BP (mmHg)	159 ± 26	1567 ± 18.0	- 6.7 - 10.7	0.65
Diastolic BP (mmHg)	923 ± 12	91 ± 14.0	-3 - 7	0.43

The correlation test showing that HA1c dicreased independently of reductions in waist circumference, and body mas index which are detailed in(table-6).

Table 6. Pearson's Correlation test that applied to the data.

Variable	Pvalue	r	95% C I	r^2
HA1C and BMI(index)	0.057	0.253	-0.0071- 0.482	6.3 %
HA1C and WC	0.927	0.013	-0.273 - 0.248	0.01 %

However there are a mild correlation between dicreasing of trigyceride and BMI(index) (r^2 = 12.6 %), also with triglyceride and waist circumference (r= 8%). these data are assessed by using the coefficients and 95% C I as demonstrated in (Table-7).

Table 7. Pearson's correlation test applied to variables.

Variable	Pvalue	r	95 % C I	r^2
Triglyceride and HA1C	0.606	0.071	-0.194 - 0.325	0.5 %
triglyceride and BMI	0.008	0.353	0.102 - 0.562	12.6 %
triglyceride and WC	0.034	0.283	0.023 - 0.505	8 %

Discussion:

The management of type2DM must include pharmacological treatment that able to correct blood glucose levels and other risk factores such as blood pressure , blood lipid profile levels, and body mass index .

metformin treatment are proved to dicrease insulin resistance effectivelly[6].Also there are several rsearchs were undertaken to stdy and assess the effects of metformin therapy on TG ,total cholesterol ,triglycerides (TG), and HDL-cholesterol blood levels, and also its effect on blood pressure and body mass index .

This study showed the effect of addition of metformin therapy to insulin and this will improve glycemic level of patient with type 2 DM after 3 months, where over half of patients reached HbA1c levels 7-8%, 30% of patient had ideal glycemic level (HbA1c up to 7 %), and 20% of patient had their HbA1c more than 8%. as already shown in other studies.

JaberLA , NowakSN and SlaughterRR in 2002 studied that Insulin whith metformin as a combination treatment shwed a significant reduction in HA1c blood level with a mean reduction value of 1.5 % +/- 1.2 % ($p = 0.001$) . FBG reduced significantly ($p < 0.005$) by 1 month after insulin-metformin treatment [32].

UK is Prospective Diabetes melitus Study (UKPDS) Showed the Median glycemic level (HbA1c) = 7.4% in diabetic patient on metformin therapy group when compared with HA1c 8.0% in the cother diabetic group with out metformin therapy [9] .

Douek IF et al studied in a double-blind randomized trial studied that Continuation of metformin therapy when starting insulin treatment in type 2 diabetes group. Over 12 months, metformin was associated with a greater reduction in HbA1c and a lower insulin requirement[34] .

The improvement of HbA1c levels in this study demonstrate that that metformin enhance action and sensitivity of insulin therapy by several mechanisms such as reduction of liver gluconeogenesis [45]. enhances peripheral tissues for uptake of suger , decreases the suppression of fatty acid oxidation by insulin action, and decreases GIT absorbtion of glucose [15].

There was a significant decrease in the TG levels after metformin treatment. Although there was an elevation in HDL-C and decrease in TC but its value was not statistically significant.

WulffeleMG et al in 2004 studied The role metformin therapy on BP, BLOOD cholesterol level and TG in type 2 DM. when compared with other control treatment, however, metformin therapy reduce a blood TG, total blood cholesterol and LDL l significantly[7] .

Some studies, in agreement with the result of the present study, reported reduction in TG levels as in UK Prospective Study (UKPDS) group (1998)[9].while others study showed a decrease of Total blood Cholesterol and triglyceride with an increase of blood HDL-C according to Lamanna C et al study.[35] Still there are other studies demonstrate no sgnificant improvement in blood lipid profile as in Riddle MC study[10].

An important possible cause for these discrepancy of study results may be due to that the clinical studies that analyzed these variables from independent samples. In the current study, this problems were dicreased and avoided byusing paired data analysis, in which each patient was had his own control data , so that improving the power of the statistical analysis. the triglyceride reduction that found in the study underwent interference from body mas index and waist circumfrence .

Janine J. Geerling and Mariëtte R. Boon show that Metformin decrease bllood TG by enhancing triglyceride secreation from brown adipose tissue in mouse.this study was Accepted in November 17, 2013. © 2013 by the American Diabetes Association. this study the underlying mechanisms in APOE*3-Leiden.CETP of mice, a well-established model for human-like lipoprotein metabolism. They found that metformin markedly lowered plasma triglyceride blood levels . metformin did not affect liver VLDL-TG production, VLDL composition and liver lipid composition but selectively improve clearance of glycerol tri[^{3}H]oleate.

In current study there was a significant reduction in WC(p value=0.0009) ,while BMI reduction was insignificant(p

value=0.0787) These results are consistent with other studies that showe the effect of metformin therapy to reduce body mas index and WC [6].

George bray et al in 2009 studied the Effect of Metformin therapy on Weight and WC in the Diabetes Prevention Program Outcomes Studies**,** and Instituted by Rockville, MD. During the early tow years of the double-blind phase, body mas index decreased more in the metformin therapy than in the placebo group (2.3% decrease for metformin group versus 0.06% increase for placebo group,p <0.001). An early dose-related decrease in WC was also noticed.

According to Douek IF et al studied in a double blind randomized placebo controlled study that studied the Continuing of metformin therapy after starting insulin therapy in type 2 diabetic patients . Over 12 months, metformin was associated with less weight changes than placebo with significant decrease in waist circumference.

This study showed that patient with metformin group did not controle blood pressure ,this fact agree with Riddle MC study[10].

The most explanation for this discrepancy may be due to that not all diabetic patient who lose body weight experience decreasing in their blood aldosterone and renin level [17].

WulffeleMG et al in 2004 studied The effectiveness of metformin therapy on BP When compared with a control group, metformin therapy effect on booth systolic BP and diastolic BP and HDL were not significant[7].

The relationship between tissue resistance of insulin and elevatated BP has encourage several studies on the using of metformin medication in the improvement of BP. The results of these trials are more conflicting as in Giugliano et al study ,this reported that metformin therapy may improve hypertension and insulin tissue sensitivity in obesity but non-diabetic and hypertensive .[31]While another study by Snorgaard et al. showed that metformin therapy had mild and clinically not significant effect on hypretensive patient in non-diabetic group [32].

Conclusion:

This study showe that a beneficial effect of metformin add on therapy in T2DM on insulin therapy together with significant glycemic and TG control. There was reduction in waist circumference but no changes in weight and less effect were on HDL level l or BP.

Recommendations:

Based on this study a patient of type2 diabetes mellitus should be advised to continue on metformin with insulin after failure of other oral hypoglycemic agents to achieve good glycemic control.

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