EFFECTS OF LIPOPHILIC STATIN ON GLUCOSE INDICES IN OBESE HYPERLIPIDEMIC PATIENTS WITH TYPE 2 DIABETES

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ABSTRACT

80 patients with type 2 diabetes (55 males & 25 females), ranged between 32-56 year old, insulin resistant, hypercholesterolemic patients divided into 2 groups randomly, and 24 non-diabetic, age- matched, normocholesterolemic patients were enrolled as control group. While maintaining their usual eating habits, fasting blood samples were collected at baseline and at the end of the 12 weeks period of treatment. After 3 months of treatment significant reduction (p <0.05) of BMI were observed in group I (28.33 ±1.1) and group II (29.53 ± 1.34) compared with baseline level and also significant reduction (p <0.05) of FPG, FI & HOMA-IR in group I were observed while in group II only FPG, HOMA-IR were reduced significantly, contrarily, non significant decrease in FI was observed in group II because of the effect of metformin on glucose metabolism, were neutralized by atorvastatin, which resulted in significant increases in fasting insulin. Significant (p <0.05) improvement in dyslipidemia from baseline level were observed in both groups. This study proved that atorvastatin is effective in improving of dyslipidemia but increase biochemical insulin resistance in patients with type 2 diabetic

KEYWORDS: diabetic, metformin, glucose metabolism, atorvastatin, dyslipidemia etc.

INTRODUCTION

Insulin acts on cells through its cell surface receptor, which is a heterotetramer made up of 2 α, β dimers linked by disulfide bonds (12), which belongs to a family of α1 – helix protein (5). Any change in binding of insulin to its receptor or in post binding signal cascade could theoretically lead to reduced cellular response to insulin, hyperinsulinemia & consequently insulin resistance (6), which is mediated through serine phosphorylation, rather than autophosphorylation on specific tyrosine residues activity (5). Insulin resistance is a common feature & central to the pathogenesis of Type 2 diabetes mellitus (TIDM) and contributes to impaired regulation of circulating lipoprotein and glucose levels (6,7). Hyperglycemia increases the risk of microvascular complications (6), while dyslipidemia is a major risk factor for macrovascular complications in patients with TIDM (9, 10). Dyslipidemia, an established risk factor for CVD, is strikingly common in patients with type 2 diabetes, affecting almost 50% of this population and remains largely uncontrolled in patients with TIDM (11), it is increasingly recognized that insulin resistance contributes to the characteristic dyslipidemia associated with TIDM (7) and disturbance of lipid metabolism appears to be an early event in the development of TIDM, potentially preceding the disease by years (12). Impaired insulin action at the level of the adipocyte is believed to result in defective suppression of intracellular hydrolysis of triglycerides (TGs) with the release of nonesterified free fatty acids (NEFAs) into the circulation (6), this increased influx of NEFAs to the liver promotes TG synthesis and secretion of large very low density lipoproteins VLDL; also impairment in the ability of insulin to suppress hepatic production of VLDL (13), this results in elevated plasma VLDL levels and postprandial hyperlipidemia that is compounded by impaired lipoprotein lipase activity (Both TNF-α and IL-6 inhibit lipoprotein lipase activity and decrease its production in adipocyte cell) (14). When low density lipoprotein (LDL) particles become small and dense, they are more prone to oxidation and more readily adhere to and subsequently invade the arterial wall, contributing to atherosclerosis; these particles therefore regarded as more atherogenic than their larger precursor (6). Elevated plasma LDL-c and TGs concentrations and low plasma HDL-cholesterol levels very frequently occur in TIDM (15), the hyperlipidemic state is characterized by an increase in oxidative stress and proinflammatory cytokines, which may play an important role in the initiation and progression of atherosclerosis (16). Statin therapy is recommended as the initial pharmacological treatment for lowering LDL-C levels in patients with type 2 diabetes (17). Atorvastatin is a lipophilic HMG-CoA reductase inhibitor. Inhibition of this enzyme decreases de novo cholesterol synthesis, increasing expression of low-density lipoprotein receptor on hepatocytes & increasing LDL uptake, decreasing the amount of LDL-c in the blood & increasing HDL-c (18). Atorvastatin have pleiotropic actions that might cause unfavorable metabolic effects such as reduction of insulin secretion and exacerbation of insulin resistance (19). Studies showed that treatment with statins is associated with an increase in plasma glucose levels in diabetic and non-diabetic patients (20, 21), and the risk of worsening glucose homeostasis differs between different statins (22). Metformin is the most commonly used insulin sensitizer worldwide in the treatment of TIDM and insulin resistance. It is as considered an insulin sensitizer since it lowers plasma glucose levels without increasing insulin secretion, it’s a biguanide derivative (23).
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affects glucose metabolism by increasing intracellular glucose transport, insulin receptor binding, peripheral glucose utilization, oxidative and non-oxidative glucose metabolism and decrease hepatic glucose production (24). Metformin has been shown to reduce LDL-C, TC, and TG levels and increase HDL-C levels (25).

SUBJECTS & METHODS

80 patients were enrolled in the study (55 out of these were males & the other 25 were females), ages ranged between 32-56 y old, diabetic patients (26). Insulin resistant (indicated by HOMA index) (27), hypercholesterolemic (28). In addition, another 24 age- matched non-diabetic, normocholesterolemic patients were enrolled as control group.

Groups’ randomization and type of treatments

1- Group I includes 37 Patients

These patients received metformin 850mg b.i.d for 12 weeks.

2- Group II includes 43 Patients

These patients received metformin 850mg b.i.d & Atorvastatin 40 mg/day for 12 weeks.

3- Control includes 24 healthy persons

The study protocol was approved by the ethical & scientific committee at AL kindy College of Medicine.

Exclusion criteria

Patients with hepatic dysfunction, renal dysfunction, uncompensated heart failure and uncontrolled hypertension were excluded.

| TABLE 1: Comparison of mean between control, baseline & after 3 months treatment |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| **Analytes**                    | **Controls**   | **Group I n=37**     | **% Of changes** | **Group II n=43**     |
| **N=24**                        | **Baseline**   | **After tx**        |                  | **Baseline**   | **After tx**        |
| **BMI (kg/m2)**                 | 25.97± 2.1     | 30.79 ±1.22*       | 8%               | 31.46 ± 0.97*   | 29.53 ±1.34*       | 6.2%               |
| **Insulin level (µU/ml)**       | 12.74 ± 0.56   | 19.29 ±3.67*       | 22.75%           | 18.58 ± 3.72*   | 16.83 ±2.805*      | 9.5%               |
| **FBG (mmol/L)**                | 4.51 ± 0.17    | 6.42 ±0.32*        | 40%              | 4.9 ± 0.39*     | 3.31 ± 0.11*       | 32%                |
| **Triglycerides (mmol/L)**      | 3.75± 11.3     | 5.67 ±0.14         | 20.5%            | 3.83 ± 0.14*    | 2.15 ± 0.24*       | 43%                |
| **HDL-c (mmol/L)**              | 1.91± 0.02     | 1.1 ± 0.8*         | 33%              | 1.57 ± 0.09*    | 2.12 ± 0.65*       | 35%                |
| **LDL-c (mmol/L)**              | 1.45± 0.31     | 3.93±0.47*         | 37.4%            | 3.82 ± 0.14*    | 1.17± 0.79*        | 69.3%              |

Data are expressed as Mean ± SD

P<0.05 for comparison with control group

**Statistical analysis**

The data was expressed as mean ±SEM. The results were statistically analyzed using student’s t-test, statistical significance was set at (p<0.005).

1- Effect of treatment on BMI

As presented in table 1, significant increment (P<0.05) in mean BMI (Kg/m2) of baseline level in group I (30.79 ±1.22) & group II (31.46 ± 0.97) compared with control group (25.97± 2.1) and it was decreased significantly (P<0.05) after 3 months of treatment to (28.33 ± 1.1) in group I & to (29.53 ± 1.34) in group II compared with baseline level, and the percent of decrement were 8% in group I and 6.2% in group II.

2- Effect of treatment on Insulin, FBG, and HOMA- IR

Insulin level ( µU/ml) showed that significant increment (P<0.05) in mean baseline level in group I & group II (19.29 ± 3.67& 18.58 ± 3.72 respectively ) compared with control group (12.74 ± 0.56) and it was decreased significantly (P<0.05) after 3 months of treatment to (14.9 ± 3.09) in group I & non significantly to 16.83 ± 2.50 in group II compared with baseline level . The percent of decrement were 22.75% in group I and 9.5% in group II.

Fasting glucose level (mmol/L) in table 1, showed that significant increment of baseline level (P<0.05) (6.42 ± 0.32) in group I & (5.93 ± 0.31) in group II compared with control group (4.51 ± 0.17) and it was decreased significantly (P<0.05) after 3 months of treatment to (4.96±0.53) in group I& (4.83 ± 0.35) in group II compared with baseline level. The percent of decrement were 22.75% in group I and 18.5% in group II.

The study showed that significant increment of mean HOMA- IR baseline level (P<0.05) in group I (5.5 ± 0.25) compared with control group (4.5 ± 0.27) and it was decreased significantly (P<0.05) after 3 months of treatment to (3.72 ± 0.57) in group II compared with baseline level . The percent of decrement were 37.4% in group I & 39.6% in group II.

3- Effect of treatment on TG and HDL levels

Table 1: Comparison of mean between control, baseline & after 3 months treatment

**Sampling**

While maintaining their usual eating habits, fasting blood samples were collected at baseline and at the end of the 12 weeks period of treatment & transferred into plain tubes, left for 30 minutes for clotting, centrifuged and then serum was separated and used for measurement of glucose, insulin level, lipid profile. Insulin resistance score by homeostasis model assessment of insulin resistance (HOMA-IR).

**Laboratory analysis**

Serum insulin level determined by enzyme linked immunosorbent assay (ELISA kits). Fasting glucose level (27), total cholesterol (28), triglycerides, (29), and HDL-c (30) levels were measured enzymatically. LDL-c was calculated using the (Friedewald equation): LDL-c =Total Cholesterol – HDL-c-TG/5 (31).

Homeostasis model assessment (HOMA) was computed with the following formula: HOMA index = [FPG (mmol/L) × fasting plasma insulin (µU/mL)]/22.5. Insulin resistant patients were defined as having HOMA > 2.7; Low HOMA values indicate high insulin sensitivity (27).

Body mass index (BMI) = (weight) Kg/ (height) M 

**RESULTS**

Table 1: Comparison of mean between control, baseline & after 3 months treatment.
& group II (4.9 ± 0.19) compared with control group (2.55 ± 0.14) and it was decreased significantly (P<0.05) after 3 months of treatment to (3.28± 0.23) in group I & (3.31 ± 0.11) in group II compared with baseline level. The percent of decrement were 40% in group I and 32% in group II.

3- Effect of treatment on lipid profile

As presented in table 1, significant increment (P<0.05) in mean total cholesterol (mmol/L) of baseline level in group I(5.67 ± 0.14) & group II(6.16 ± 1.18) compared with control group (3.75±1.13) and it was decreased significantly (P<0.05) after 3 months of treatment to(4.51 ± 1.49) in group I& (3.72 ± 1.57) in group II, and the percent of decrement were 20.5% in group I and 39.6% in group II.

Table 1, showed that significant increment of baseline level (P<0.05) of TG in group I (3.2 ± 0.5) & group II (3.83 ± 0.14) compared with control group (1.93 ± 0.05) and it was decreased significantly (P<0.05) after 3 months of treatment to (2.88± 0.19) in group I& (2.15 ± 0.24) in group II. The percent of decrement were 10% in group I and 43% in group II.

Also there is significant decrement of baseline level (P<0.05) of HDL-c in group I (1.1 ± 0.8 ) & group II (1.57 ± 0.09) compared with control group (1.91± 0.02) and it was increased significantly (P<0.05) after 3 months of treatment to (1.47± 0.53) in group I& (2.12± 0.65) in group II. The percent of increment were 33 % in group I and 35 % in group II.

For mean LDL-c (mmol/L) table 1, showed that significant increment of baseline level (P<0.05) in group I (3.93± 0.47) & group II (3.82 ± 0.14) compared with control group (1.45± 0.31) and it was decreased significantly (P<0.05) after 3 months of treatment to (2.46± 0.72) in group I& (1.17± 0.79) in group II, and the percent of decrement were 37.4% in group I and 69.3% in group II.

DISCUSSION

After 3 months treatment with metformin a significant (p <0.05) reduction in BMI were observed, because metformin lead to decrease the caloric intake by suppressing appetite (35) and this effect may be independent of the gastrointestinal side effects of metformin. The percent of reduction was in consistence with many investigators who reported that 4-10% reduction in BMI in response to metformin treatment (36), but it’s less in group II because atorvastatin may counter act effect of metformin on improvement of glycemic control & lead to increase insulin resistance (37). Rajpathak et al, calculated that the incidence of diabetes was 13% higher in statin recipients, which was statistically significant (38).

This quality is interesting and important since it has shown that different adipose compartments can have varying effects on endocrine and metabolic factors, and visceral fat is the main fat tissue in the body responsible for insulin resistance observed in obesity (39). After 3 months of treatment a significant reduction (p <0.05) of FPG, FI & HOMA- IR in group I were observed because metformin lead to increase glucose utilization, decrease hepatic glucose production, increase insulin receptor binding and insulin receptor tyrosin kinase activity, it was consistent with previous findings (24,40); While in group II only FPG, HOMA- IR were reduced significantly, contrarily, non significant decrease(9.5%) in FI was observed in group II because the effect of metformin on glucose metabolism (24,40) were neutralized by atorvastatin, which resulted in significant increases in fasting insulin and glycated hemoglobin levels (41), it was reported that lipophilic statins have pleiotropic actions that might cause unfavorable exacerbation of insulin resistance (42). Recent large-scale, controlled clinical trials have raised the possibility that lipophilic statins might increase the rate of new onset diabetes (43, 44). The mechanisms by which statins may influence glucose metabolism suggested that statins may alter glycemic control by decreasing various metabolites, such as isoprenoid, farnesyl pyrophosphate, geranylgeranyl pyrophosphate, and ubiquinone, which enhance glucose uptake via glucose transporter type 4 in adipocytes and impair insulin release (20). Randomised trials and large-scale observational studies have shown that treatment with statins is associated with an increase in plasma glucose levels in diabetic and non-diabetic patients (20, 21), and that the risk of worsening glucose homeostasis differs between different statins (42). Statins reduce cardiovascular morbidity and mortality to a degree beyond what is expected from reduction in LDL-C level alone (45, 46). The present study demonstrates a significant (p <0.05) increase of TC, TG & LDL-c baseline value of group I &II compared with control & significant decrease of HDL-c in both groups compared with control, these results were compatible with other studies as metabolic consequences of TIIDM & patients would be predicted to be at high risk for dyslipidemia because they are frequently obese, hyperinsulinemic and insulin resistant, consequently hyperinsulinemia inhibits lipolysis with a subsequent increase in levels of non esterified fatty acids, high levels of nonesterified fatty acids lead to increased triglyceride levels and reduced HDL-c levels. Low HDL-c levels are frequent in those with obesity, &TIIDM, in which TG metabolism is abnormal (47). After 3 months treatment a significant (p <0.05) reduction in TC, TG & LDL-c were observed in both groups from baseline. Antidiabetes agents (metformin) that directly improve insulin resistance may have effects on lipid levels, especially TG levels. Although there may be no effect on HDL-C levels, these agents may instead alter the ratio of lipoproteins in HDL towards more anti-atherogenic HDL particles (48). Effect of metformin was in consistence with other studies (49). The main mechanisms due to suppressing of hepatic glucose production, and insulin-sensitizing actions which primarily mediated through the weight loss that frequently occurs during therapy (50), also it was reported that metformin have modest favorable effect on serum lipids, and decrease TG level by 16%, total cholesterol by 5%& LDL-c by 8% (51). Effect of atorvastatin in the present study was concurred with other studies reported that in mixed hyperlipidemia, when both TG and LDL are elevated, statins were very effective in reducing LDL-c and TG (52, 53), but the percent of decrement of these parameters in group II was higher because of the synergistic effect of combination of metformin and atorvastatin. HDL-c significantly increased in both groups I and II after
treatment, in group I metformin has been shown to reduce LDL-C, TC, and TG levels and increase HDL-C levels (25), but in group II, combination of metformin and atorvastatin lead to increase HDL-c by (35%). Atorvastatin effects was in agreement with other study by Giuseppe P. etal (15) & Gentile el al (54) who recorded increments in HDL-c of 7.1–7.4% with atorvastatin treatment and the percentage changes are greater in patients with low baseline levels, including those with the common combination of high TG and low HDL-c. The most likely explanation is a reduced rate of CETP-mediated flow of cholesterol from HDL (52). Guerin et al., 2000 showed that atorvastatin reduced circulating levels of CETP and the rate of CETP-mediated CE transfer from HDL to VLDL secondary to reduction in the VLDL (55).

CONCLUSION
This study proved that atorvastatin is effective in improving of dyslipidemia & increase biochemical insulin resistance in patients with TIDM after treatment.

REFERENCES


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