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Original Research Article

# Evaluation of the Effect of Atorvastatin on Insulin Sensitivity at Tertiary Care Hospital, Telangana State

**G. Swapna[1], K. Udaya Bindu[2], B. Jeevitha Naik[3]**

[1]Assistant Professor of General Medicine; Government Medical College / Hospital, Mahabubnagar, Telengana State

[2]Assistant Professor of Cardiology; Government Medical College / Hospital, Kurnool, Andhra Pradesh

[3]Assistant Professor of Medicine, Osmania Medical College / Hospital, Hyderabad, Telangana State.

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**Corresponding author: Dr. B. Jeevitha Naik**

**Conflict of interest: Nil**

**Abstract:**

**Aim of the Study:** To evaluate the effects of Atorvastatin on insulin sensitivity.

**Material & Methods:** The patients were randomized into two groups, of 34 patients each, by a random selection process. The experimental group consisting of 34 dyslipidaemic and hypertensive patients receiving atorvastatin 10mg/day and atenolol 50 mg/day at the Hypertension OPD at Government Tertiary Care Hospital, Telangana State are chosen as volunteers and are compared with another group of 34 hypertensive patients receiving atenolol 50 mg/day only.

**Results:** The anthropometric and biochemical characteristics of the subject in the control and Atorvastin treated groups at the start of the study. It is found that in the group receiving atenolol and atorvastatin (experimental group), T Cells is reduced from initial values of 280 +/- 20 mg/dl to 202 +/- 12 mg/dl (p = 0.05). HDLC is increased from 45 +/-10 mg/dl to 52 +/- 12 mg/dl (p = 0.04). LDLC reduced from 180 +/-20 mg/dl to 148 +/-12 mg/dl (p = 0.05). VLDLC, Triglycerides values remain almost same, and changes are statistically insignificant. In the control group receiving atenolol only, it is observed that TC is from initial values of 140 +/-20 mg/dl to 112+/-8 mg/dl. HDLC changes from 40 +/-10 mg/dl to 44 +/-9 mg/dl. LDLC changes from 110 +/-30 mg/dl to 95 +/-13 mg/dl. VLDLC, TG and FBS values remain almost same, and all the value changes are statistically insignificant.

**Conclusion:** Since statins are used for the treatment of hypercholesterolemia in clinical practice, it is important to know their effect on insulin sensitivity. If further studies confirm the observation that statins improve insulin sensitivity and reduce the onset of type 2 diabetes, the perceived benefit of cardiovascular intervention in clinical trials could be greatly increased and the long term cost-benefit analysis of those interventions may be more positive than previous studies have estimated.

**Keywords:** Dyslipidaemic; Atorvastatin; Insulin Sensitivity.



## Introduction

The 3-Hydroxyl-3 methyl glutaryl Coenzyme A (HMG CoA) reductase inhibitors or statins have been a primary force in the management of hypercholesterolemia for many years and are important in the primary and secondary prevention of heart disease. However, increasingly it is being shown that the statins have clinical benefits that appear to be greater than those one would expect from improvement in the lipid profile alone. These pleotrophic actions include direct effects on vascular tissue, kidney, bone and glucose metabolism [1].

The hyperinsulinaemic / insulin resistant states is a metabolic condition linked to widespread and heterogeneous clinical syndrome like hypertension, obesity, type-2 diabetes, dyslipidaemia, atherosclerosis and coronary vascular disease. About 25% of the non-diabetic population shows abnormalities of insulin sensitivity and compensatory hyperinsulinaemia [2]. The South Asian population is known to be at risk of a atherosclerosis, even though the subject does not have clinical evidence of coronary heart disease.

In India, population is vast, and there is heterogenecity of origin or race, geography and habit, socioeconomic status, dietary habits, methods of cooking and preservation, use of pesticides etc. These factors along with known variables like age, sex etc. influence lipid profile of individuals [3].India is facing a diabetic explosion.

It has the world's largest diabetic population about 25 million, and the number is predicted to rise to 35 million by 2010 and to 57 million by 2025. The exact nature of the increase in prevalence of type 2 diabetes is unknown, and both genetic and lifestyle factors are being blamed. The urbanization tendency of rural India puts the incidence of diabetes with all its complications and mortality on the rise. Insulin resistance is supposed to play a major role in the development of diabetes. Considering the magnitude and severity of hyperinsulinaemic / insulin resistant state, pharmaceutical measures are initiated early in an Indian [4].

Clinical trials and animal studies (invivo and invitro) have shown that statins reduce cardiovascular disease risks and events, progression of nephropathy, development of diabetes and fracture rates, these are benefits that go beyond lipid lowering alone. These agents improve insulin sensitivity and reduce the likelihood of persons progressing from impaired glucose tolerance to type II diabetes [5].

Various studies have observed the effect of statins on insulin sensitivity in Type 2 Diabetic mellitus. Since statins are commonly used for the treatment of hypercholesterolemia in clinical practice, it is important to know their effect on insulin sensitivity.

**Aims of the Study:** To evaluate the effects of Atorvastatin on insulin sensitivity.

## Material and Methods

The study deals with the effect of Atorvastatin on insulin sensitivity conducted at Hypertension outpatient department of Government Tertiary Care Hospital, Telangana State. Ninety patients are screened for the study from a random population of 110 hypertensive patients receiving atenolol as anti-hypertensive drug, by a random selection process, from which 68 patients are considered based on patient compliance, intelligence to understand dietary prescriptions and directions and whether free from any other disease on initial medical testing.

The patients were randomized into two groups, of 34 patients each, by a random selection process. The experimental group consisting of 34 dyslipidaemic and hypertensive patients receiving atorvastatin 10mg/day and atenolol 50 mg/day at the Hypertension OPD at Government Tertiary Care Hospital, Telangana State are chosen as volunteers and are compared with another group of 34 hypertensive patients receiving atenolol 50 mg/day only. Uniform diet pattern is prescribed to all of them.

**Inclusion Criteria:** Dyslipidaemia, Hypertension, Age 40 to 50 years, not receiving any drugs other than mentioned above, not suffering from any other diseases.

**Exclusion Criteria:** Those patients not satisfying the inclusion criteria are excluded.

## Results

**Table 1: Anthropometrical, Clinical and Biochemical characters of volunteers**

| | Experimental Group (34) | Control Group (34) |
|---|---|---|
| Age | 45 + 4 | 43 + 3 |
| Males | 21 | 21 |
| Females | 13 | 13 |
| BMI | 27.3 + 12 | 27.5 + 2.1 |
| SBP | 154 + 16 | 146 + 24 |
| DBP | 100 + 12 | 94 + 8 |
| T. Cholesterol | 280 + 20 | 140 + 20 |
| LDL | 180 + 20 | 110 + 20 |
| HDL | 45 + 10 | 40 + 10 |
| VLDL | 40 + 5 | 35 + 15 |
| TGL | 220 + 20 | 120 + 20 |
| FBS | 106 + 6 | 96 + 6 |
| Fasting Insulin | 20 + 5 | 18 + 5 |

**Table 2: Values of Blood parameters of Experimental Group**

| | 0 mins | 1 min | 2 mins | 3 mins | 4 mins | 5 mins | 6 mins | 7 mins | 8 mins | 9 mins | 10 mins | 11 mins | 12 mins |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| T. Cholesterol | 2.80 ± 20 | 276 ±18 | 270 ± 16 | 260 ± 15 | 256 ± 16 | 248 ± 18 | 240 ± 16 | 234 ± 12 | 226 ± 11 | 218 ± 13 | 212 ± 12 | 208 ±102 | 202 ± 12 |
| HDL | 45 ± 10 | 45 ±12 | 46 ± 12 | 46 ± 13 | 47 ± 12 | 48 ± 16 | 48 ± 8 | 49 ± 11 | 50 ± 14 | 50 ± 10 | 51 ± 13 | 51 ± 11 | 52 ± 12 |
| LDL | 180 ± 20 | 178 ±18 | 17 ± 12 | 172 ± 11 | 172 ± 12 | 168 ± 18 | 166 ± 10 | 164 ± 8 | 160 ± 12 | 160 ± 8 | 158 ± 10 | 15 2 ± 8 | 148 ± 12 |
| VLDL | 40 ± | 40 | 40 ± | 39 ± | 39 ± | 39 ± | 39 ± | 39 ± | 39 ± | 39 ± | 39 ± | 39 ± | 39 ± |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 | ± 3 | 2 | 6 | 5 | 6 | 5 | 4 | 2 | 4 | 3 | 4 | 3 |
| TGL | 220 ± 20 | 218 ±18 | 218 ± 16 | 214 ± 10 | 214 ± 8 | 216 ± 8 | 212 ± 10 | 210 ± 11 | 210 ± 12 | 206 ± 6 | 214 ± 8 | 208 ± 8 | 212 ± 6 |
| FBS | 106 ± 6 | 106 ± 5 | 105 ± 3 | 103 ± 4 | 103 ± 3 | 101 ± 4 | 98 ± 5 | 98 ± 6 | 96 ± 5 | 93 ± 4 | 92 ± 5 | 90 ± 3 | 88 ± 4 |

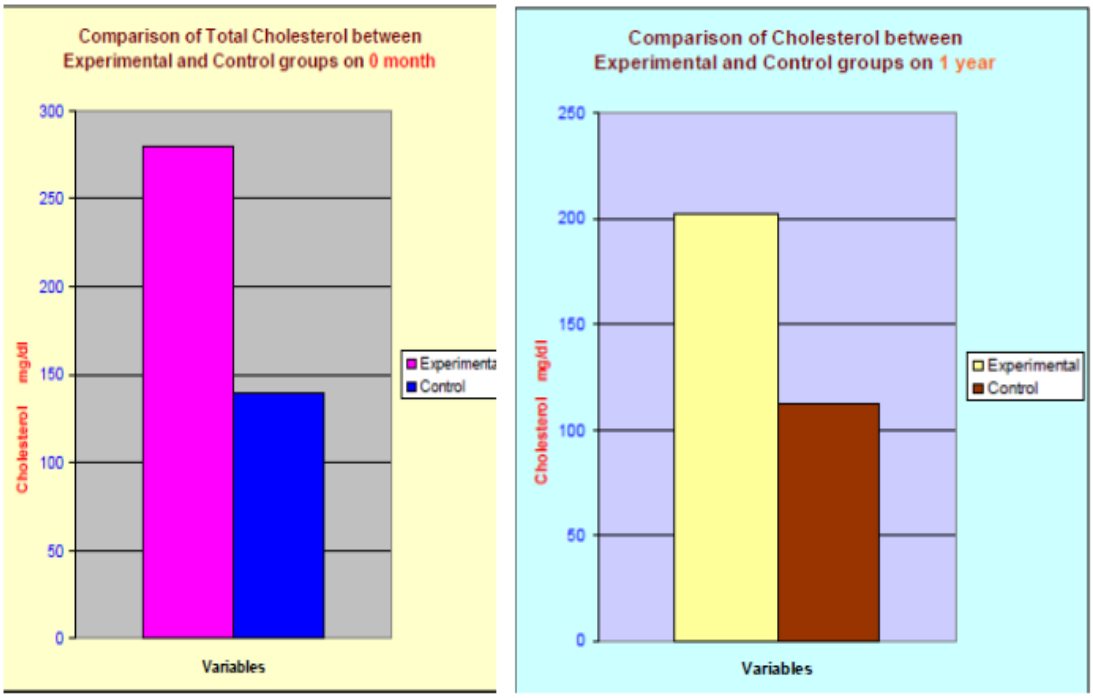
**Table 3: Values of Blood parameters of Control Group**

| | **0 mins** | **1 min** | **2 mins** | **3 mins** | **4 mins** | **5 mins** | **6 mins** | **7 mins** | **8 mins** | **9 mins** | **10 mins** | **11 mins** | **12 mins** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **T. Cholesterol** | 140 ± 20 | 138 ± 8 | 136 ± 16 | 134 ± 15 | 132 ± 15 | 130 ± 16 | 128 ± 8 | 125 ± 10 | 123 ± 8 | 120 ± 12 | 117 ± 6 | 115 ± 6 | 112 ± 18 |
| **HDL** | 40 ± 10 | 40 ± 8 | 41 ± 9 | 41 ± 7 | 41 ± 5 | 42 ± 6 | 42 ± 7 | 42 ± 7 | 42 ± 6 | 43 ± 8 | 43 ± 9 | 43 ± 8 | 44 ± 9 |
| **LDL** | 110 ± 30 | 110 ±12 | 108 ± 18 | 108 ± 16 | 108 ± 14 | 106 ± 12 | 106 ± 13 | 106 ± 13 | 102 ± 11 | 100 ± 18 | 98 ± 16 | 97 ± 10 | 95 ± 13 |
| **VLDL** | 35 ± 15 | 35 ± 9 | 35 ± 8 | 35 ± 7 | 35 ± 8 | 35 ± 10 | 35 ± 10 | 35 ± 8 | 35 ± 12 | 35 ± 14 | 35 ± 11 | 35 ± 6 | 35 ± 8 |
| **TGL** | 120 ± 20 | 120 ±11 | 120 ± 8 | 119 ± 12 | 120 ± 14 | 118 ± 12 | 118 ± 12 | 116 ± 15 | 118 ± 8 | 118 ± 8 | 110 ±12 | 116 ± 12 | 116 ±13 |
| **FBS** | 96 ± 10 | 96 ± 8 | 94 ± 6 | 94 ± 5 | 92 ± 8 | 94 ± 8 | 94 ± 8 | 92 ± 6 | 92 ± 9 | 92 ± 8 | 96 ± 7 | 94 ± 8 | 94 ± 6 |

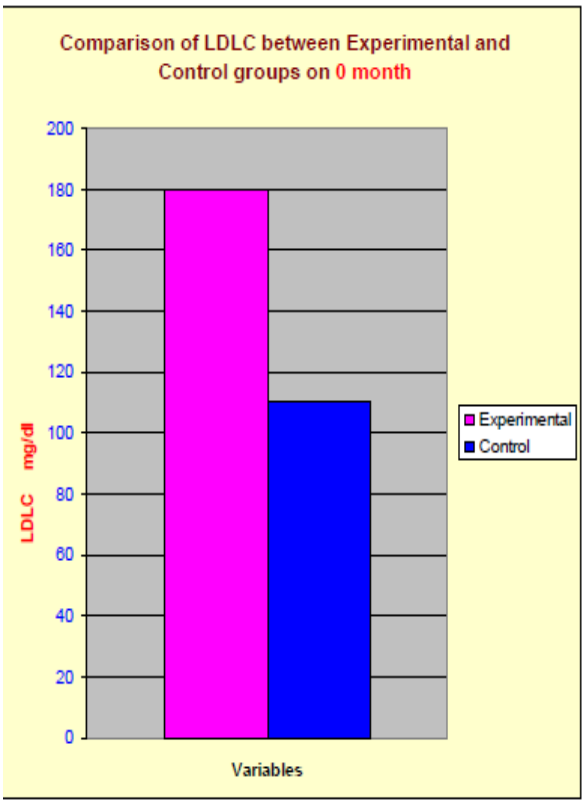
**Table 4: Showing Serum Insulin and HOMA – IR 2 values of Different Group**

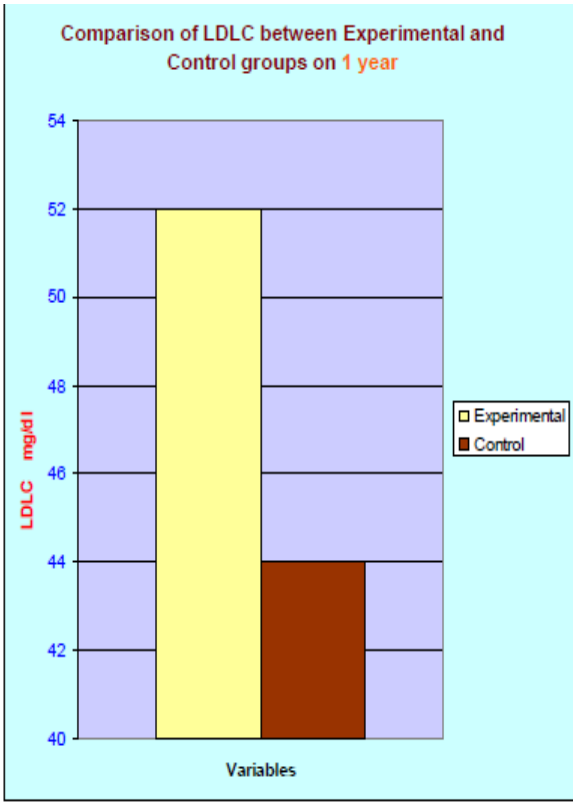
| | **S. Insulin initial value** | **S. insulin end value** | **Homeostasis model assessment of insulin resistance 2 –IR (initial value)** | **HOMA – 2 IR end value** |
|---|---|---|---|---|
| Experimental Group | 20 + 5 | 18 + 3 | 4.3 + 0.5 | 3.7 + 0.4 |
| Control Group | 18 + 5 | 18 + 5 | 4.3 + 0.3 | 4.3 + 0.2 |

**Graphs: Comparison of different variables between experimental groups and Control Groups**

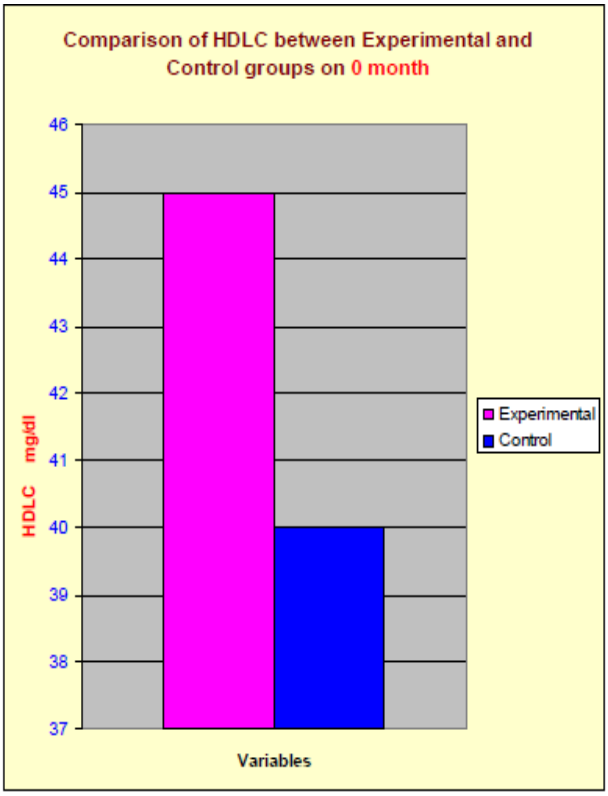


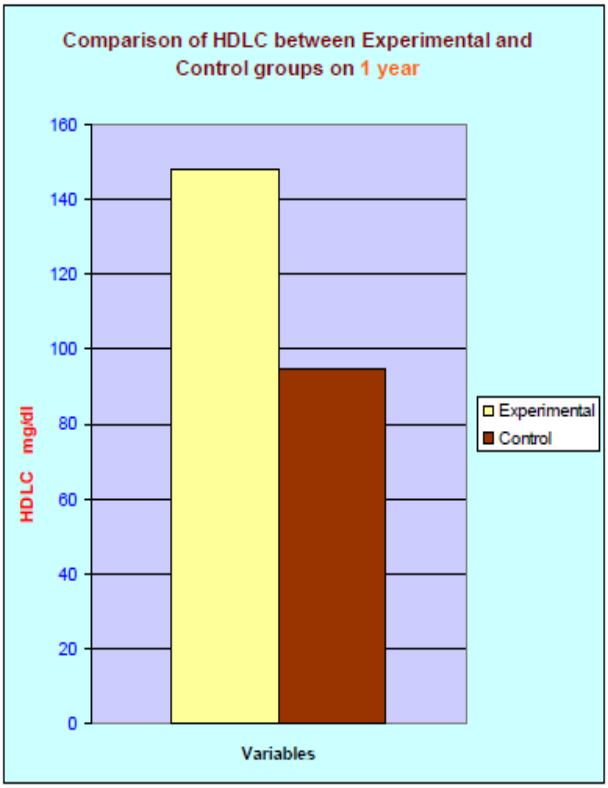

**Graph 1:**



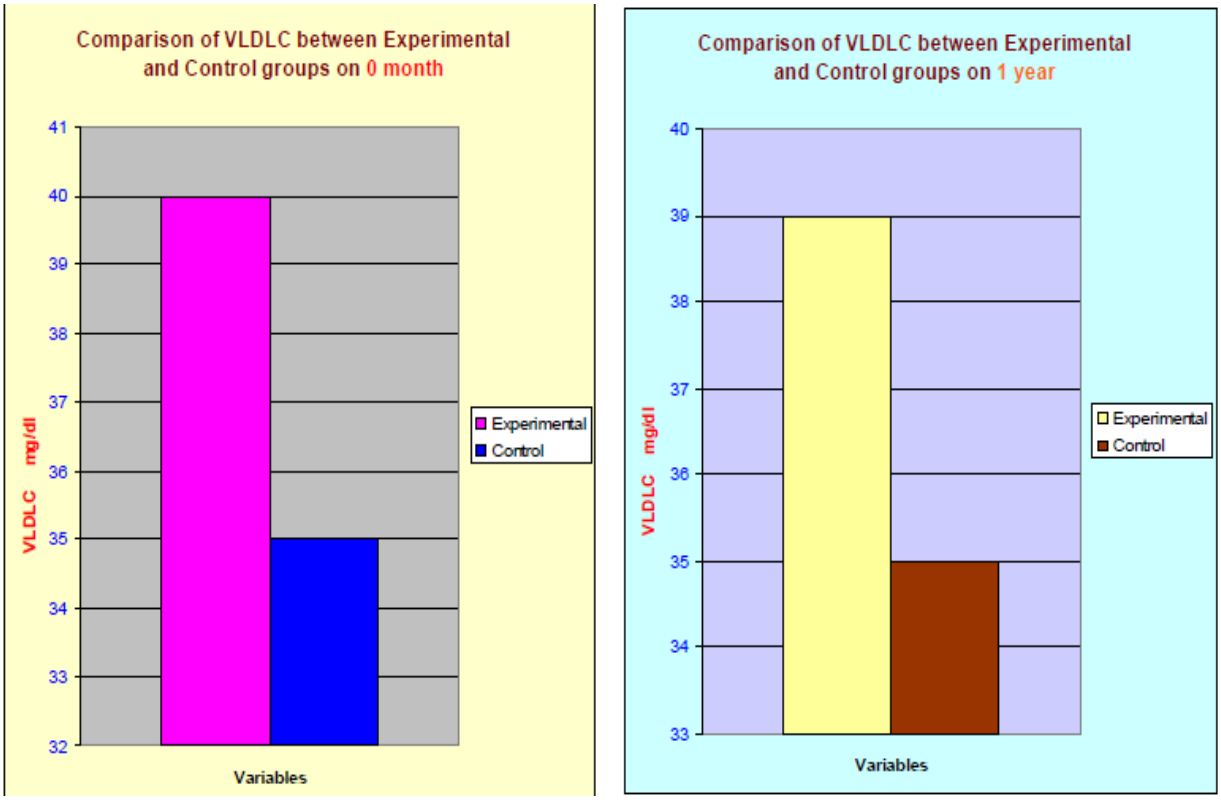




**Graph 2:**

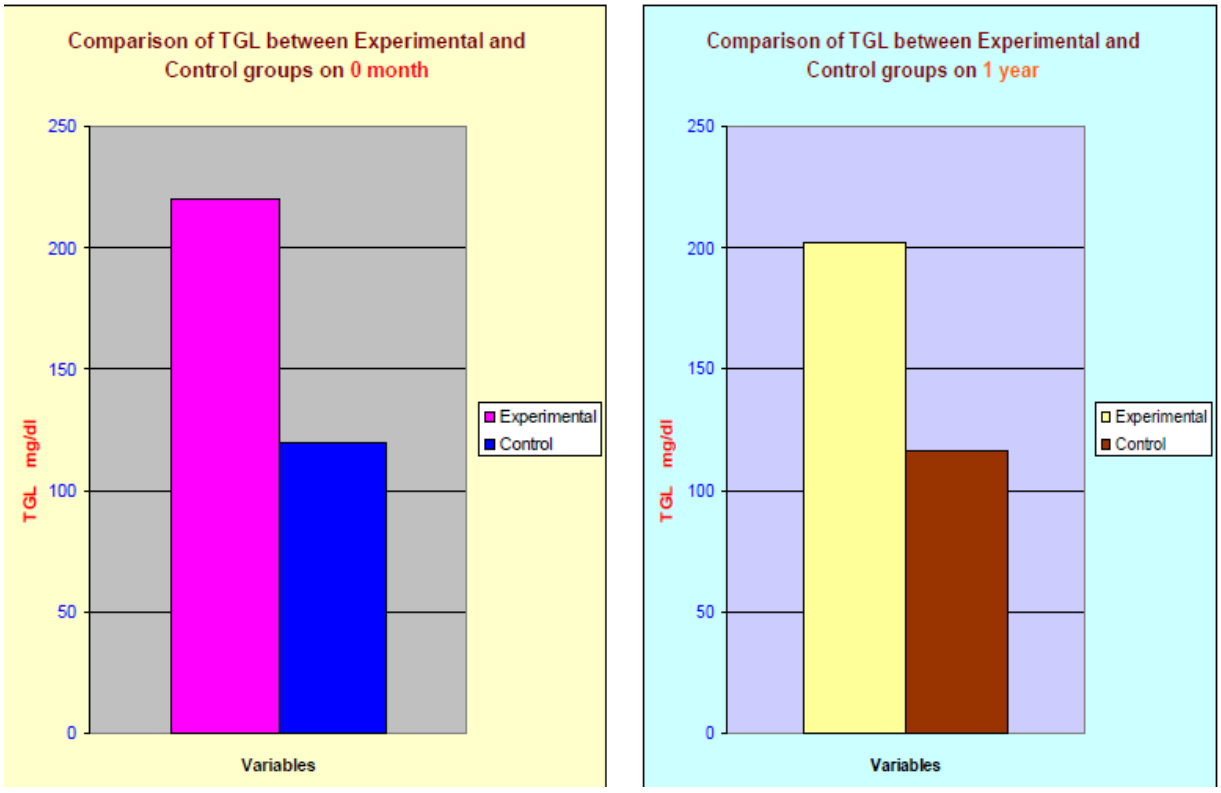


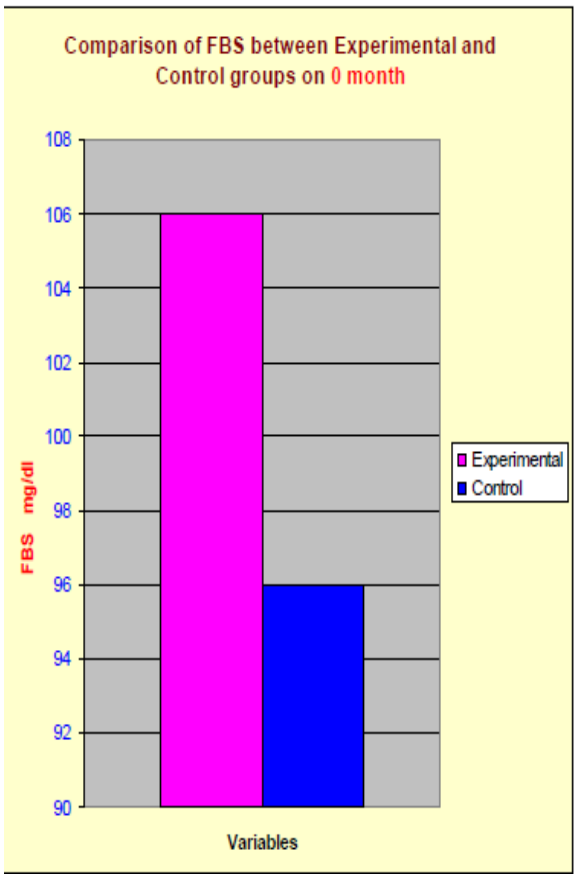

**Graph3:**

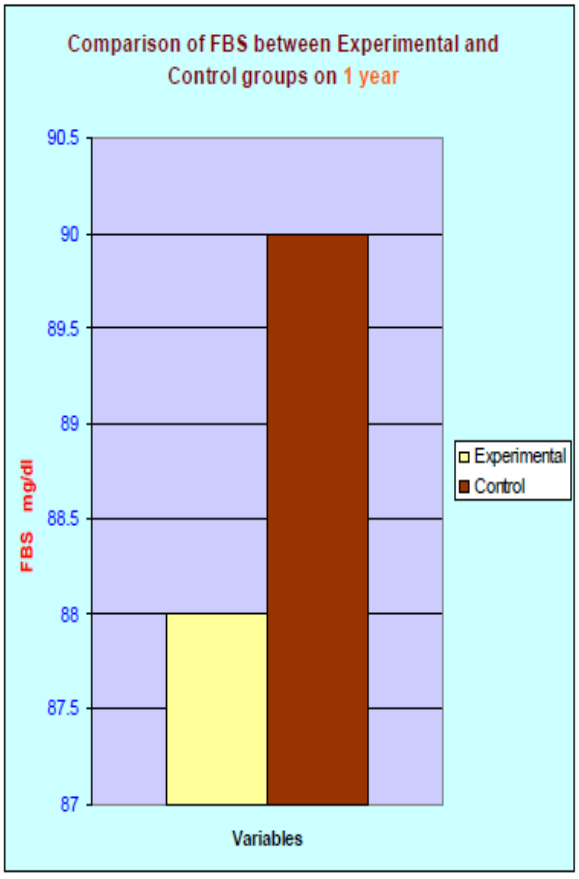



**Graph4:**

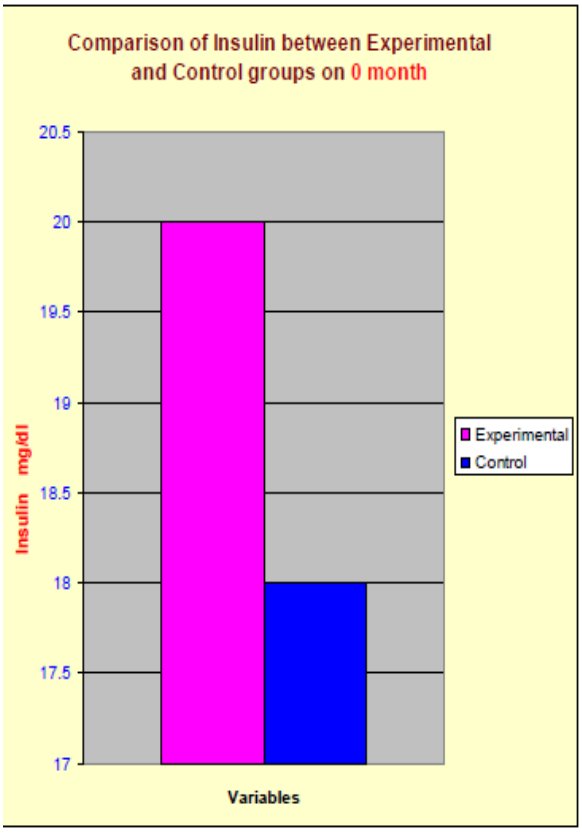


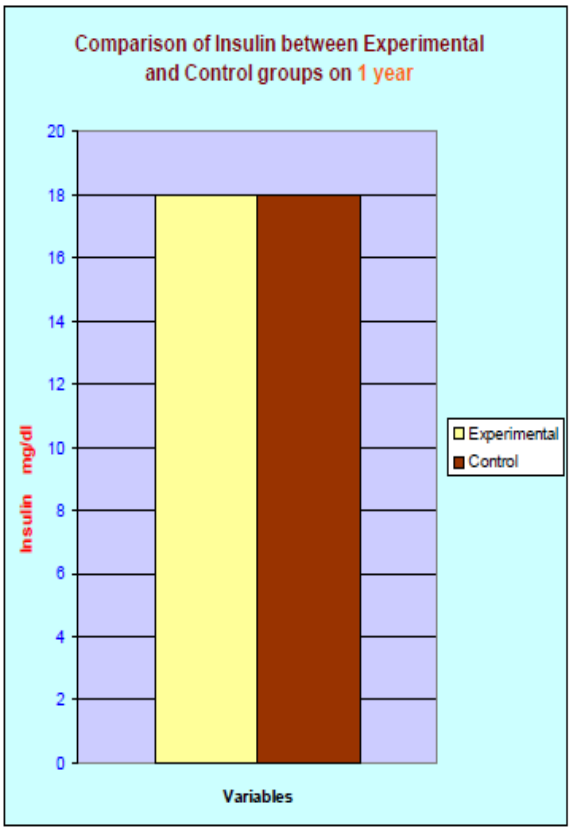

**Graph5:**




**Graph6**




**Graph7:**

## Discussion

The study shows that atorvastatin increases insulin sensitivity in normal subjects. Compared with placebo, treatment with atorvastatin (10 mg/day) resulted in significant reduction in the HOMA index. In addition, significant reductions in total and LDL cholesterol concentrations were observed in the atorvastatin group. It thus corroborates previous findings that though uncertain, statin therapy can affect insulin resistance syndrome. [6]Insulin Resistance refers to the reduction in insulin mediated glucose uptake in insulin sensitive tissues, specifically in the skeletal muscles. As a compensatory response, hyperinsulinemia ensures to maintain normal blood glucose levels. In epidemiological studies, fasting insulin level is commonly used as a surrogate marker of insulin resistance [7].

In normoglycemic subjects, fasting insulin correlated well with whole body glucose uptake. Although fasting insulin is a reasonable measure of insulin resistance, it is potentially confounded by variability in insulin secretion. Thus the indexes derived from fasting insulin and glucose, such as Homeostasis Model Assessment (HOMA), the Quantitative Insulin Sensitivity Check Index (QUICKI), and the Insulin Sensitivity Index (ISI) developed by Gutt and coworkers, have been more widely used to assess insulin resistance in clinical and population based studies [8].

Although the role of insulin resistance in the pathophysiology of type 2 diabetes mellitus is well accepted, the relationship between insulin resistance and blood pressure remains controversial. Nearly 40 years ago, Welborn and colleagues observed that non diabetic patients with essential hypertension had significantly higher plasma insulin concentrations than did normotensive individuals [9].Statins are the more effective LDL – cholesterol-lowering drugs by about 25% to 60%. In addition, they also increase HDL-cholesterol by about 5% to 10% and decrease triglycerides by about 10% to 30%. The effect on triglycerides is proportional to the decrease in LDL-cholesterol. Pre diabetes and type 2 diabetes are characterized with low grade inflammation.

Aggressive lowering of LDL-cholesterol by atorvastatin decreases hsCRP by 42% vs 9.6% with placebo. Several studies have proved that LDL-reduction by statins is associated with improved endothelial function due to enhance NO release. Besides these actions,the reduction in risk of development of diabetes is due to improved insulin sensitivity by statins [10]. Okajima et. Al [11] suggest that statins could have some impact on insulin action, and, to estimate the direct effects of statins on insulin secretion from pancreatic beta cells, MIN6 cells were treated with pravastatin, simvastatin or atorvastatin. Basal insulin secretion at low glucose concentration was unexpectedly increased at very high doses of simvastatin or atorvastatin after 24 and 48 hours of incubation, though insulin secretion was apparently decreased by these lipophilic statins.

Yoshitomi et al. assessed the relationship between IR and the changes of lipid profile in patients with hyperlipidaemia treated by atorvastatin. The IR did not affect the degree of reduction in cholesterol by atorvastatin in non-diabetic subjects. The IR may influence hypertriglyceridaemia greater than the effect of atorvastatin in non-diabetic subjects. [12]

It has been suggested that HMG Co-A reductase inhibitors (‘statins’) may reduce the risk of developing type 2 Diabetes mellitus. Yee et al. designed to evaluate whether use of statins would also delay progression to insulin therapy. After multivariate adjustment, however, statin use was associated with a 10-month delay before newly treated diabetic subjects needed to start insulin treatment. [13]

Poalisso G et al. observed that statins administration was associated with an improvement of insulin resistance and decline in plasma triglyceride concentrations.

This study suggests that statins increase insulin sensitivity even in normoglycemic patients.

## Conclusion

- Statins improve insulin sensitivity even in normoglycemics and prevent the progression of IGT to type 2 diabetes.
- Statins reduce levels of interleukin 6 and TNF through its anti-inflammatory activity. These cytokines inhibit lipoprotein lipase activity and to stimulate lipolysis in adipose tissue. Atorvastatin may therefore interrupt the progression from central obesity to insulin resistance mediated by the adipose tissue derived cytokines.
- Impaired endothelial function has been shown to correlate with insulin resistance. Atorvastatin by restoring endothelial function, may beneficially affect glucose and insulin transport.
- Since statins are used for the treatment of hypercholesterolemia in clinical practice, it is important to know their effect on insulin sensitivity. If further studies confirm the observation that statins improve insulin sensitivity and reduce the onset of type 2 diabetes, the perceived benefit of cardiovascular intervention in clinical trials could be greatly increased and the long term cost-benefit analysis of those interventions may be more positive than previous studies have estimated.

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