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ORIGINAL ARTICLE / RESEARCH

Role of Atorvastatin in Anti-diabetes Management

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ABSTRACT

The hyperinsulinaemic/insulin-resistant state is a metabolic condition linked to widespread and heterogeneous clinical syndromes 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. Data from National Health and Nutrition Examination Survey (NHANES) show 50 million Americans or more had hypertension. In world scenario, it approximates 1 billion individuals and 7.1 million deaths per year. India has 4% of adult population at risk of hypertension. India is facing a diabetic explosion also. 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 cause of the increase in prevalence of hyperinsulinaemic/insulin-resistant state is unknown, and both genetic and life style factors are being blamed. Beta-blockers (atenolol) and statins (atorvastatin) are widely used to combat hypertension and dyslipidaemia, particularly in obese patients who are also prone to diabetes and coronary artery disease. A 3-month study is done to compare the effects of atenolol with atenolol and atorvastatin in two groups of hypertensive volunteers. The study shows that statins improve the dyslipidaemic picture and also increases insulin sensitivity.

Introduction

The South Asian population is known to be at risk of atherosclerosis, even though the subject does not have the clinical evidence of coronary artery disease (CAD). Atorvastatin is known for its cholesterol lowering and cardioprotective effects. In India population is vast, and there is heterogenicity 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. In a study with 3000 patients, CAD occurred in 50% with cholesterol level of 152 mg% and in 5% even if cholesterol level was below 140 mg%. The significant finding was elevated triglycerides (>196 mg%) and low high-density lipoprotein cholesterol (HDLC) (<39 mg%). The lipid profile in Indians may appear benign, but the high triglycerides and low HDLC levels actually increase the rate of CAD. Persons with high low-density lipoprotein (LDL), high triglyceride and low high-density lipoprotein (HDL) have a three-fold higher rate of CAD [1]. Diabetes mellitus is defined as a syndrome characterised by chronic hyperglycaemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiencies in insulin secretion and/or insulin

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action [2]. The hyperinsulinaemic/insulin-resistant state is a metabolic condition linked to such widespread and heterogeneous clinical syndromes as hypertension, obesity, type 2 diabetes, etc. About 25% of the non-diabetic population show abnormalities of insulin sensitivity and compensatory hyperinsulinaemia. Considering the magnitude and severity of hyperinsulinaemic/insulin-resistant state, pharmaceutical measures are initiated early in an Indian and common drug to be used in hypertension and dyslipidaemia are beta-blockers and statins.

As hypertension is mainly asymptomatic, it acts as a silent killer. Even in advanced countries like U.S.A., 30% of individuals are unaware of their hypertension, other 40% do not like to be treated and 67% do not bother about the blood pressure (BP) values, which remains above 140/90 mmHg [3]. About 10–15% of Indian adult receive regular antihypertensive treatment [4]. Risk of hypertension, particularly systolic blood pressure (SBP), increases with advancing age, and about 50% of 60–69 years old are affected. The value becomes 75% in 70 years and above age range [3],[5]. Vasan et al. [6] reported that lifetime risk of hypertension is 90% for normotensive men and women at 55 or 65 years of age and who survives up to 80–85 years. Reduction of SBP, which continues throughout life, reduces total mortality, cardiovascular mortality, stroke and heart failure events. Diastolic blood pressure (DBP) is more potent cardiovascular risk factor than SBP before 50 years of age, and afterwards SBP is more important [7]. In the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) and controlled onset verapamil investigation of cardiovascular end points (CONVINCE) trial, it is found SBP control rate is less than DBP control rate [8],[9]. Physician's ignorance may be a factor in poor control of SBP.

While body mass index in Indians was not higher, they had a significantly higher waist–hip ratio, indicating that although Indians have no more general obesity than the others, they tend to put it on centrally or abdominally. They also had more hyperinsulinaemia, glucose intolerance and increased plasma activator inhibitor 1 (PAI-1). Regarding the antioxidants, Indians had a lower level of plasma vitamin C and selenium [10]. These factors could be due to food habits, especially prolonged cooking at higher temperatures, and cooking with omega-6 oils as the main oil medium with a myth to reduce cholesterol level [11] and a more vegetarian diet. Average Indian diabetic and CAD patients were younger [10].

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 [12]. The exact cause of the increase in prevalence of type 2 diabetes is unknown, and, both genetic and life style factors are being blamed, rural India is urbanising rapidly. A sample study of Medavakkam town near Chennai, which was a village a decade ago, showed that the prevalence of diabetes rose from 2.4% to 5% within 5 years of urbanisation. The Chennai Urban Population Study (CUPS) records in 1997 showed 12% prevalence of diabetes in the Chennai population, which was 70% higher, compared to what was reported 14 years ago [13]. The Chennai Urban Rural Epidemiology Study (CURES), which sampled 26,001 persons, recorded a prevalence of 16% diabetic [14]. This rising trend puts a significant health burden due to diabetes in India [15]. The urbanisation tendency of rural India puts the incidence of diabetes with all its complications and mortality on the rise [16],[17]. For every 1-percentage point drop in glycolated haemoglobin (A_1C), e.g. from 9% to 8%, there was a 35% reduction in the risk for diabetes-related complications and also a reduction in risk of fatal and nonfatal heart attacks by 18% [18].

Rural India lacks development in different sectors of health service infrastructures. Food-based control to different diseases can serve as an alternative, particularly if it is economically and socioculturally viable and acceptable [19]. Diet taken by rural people is diabetogenic in nature [20]. Urban diet composition varies with income [21]. Diet has a substantial role to play in dyslipidaemia, hypertension and type 2 diabetes [22]. Hence, a uniformity of dietary pattern is required in any study involving a cross-section of Indian population.

Present study deals with anti-diabetic effects of atorvastatin in a closed campus community of Indian Institute of Technology (IIT) at Kharagpur, which comes in rural Kharagpur location. In this study, 22 dyslipidaemic and hypertensive patients receiving atorvastatin 10 mg/day and atenolol 50 mg/day for more than 3 months at B.C. Roy Technology Hospital of IIT are chosen as volunteers and are compared with another group of 22 hypertensive patients receiving atenolol only. Uniform diet pattern is prescribed to all of them for the next 3 months.

Materials and Methods

Selection of volunteers

Sixty-four patients are screened for the study from a random population of 90 hypertensive patients receiving atenolol as anti-hypertensive measures from BC Roy Technology Hospital of IIT, Khargpur, by a random selection process, from which 44 patents are considered based on patient compliance, intelligence to understand dietary prescriptions and directions and whether free from any other disease on initial medical testing. Naturally, the volunteers are not receiving any drugs other than mentioned and not suffered from any diseases within the study period. Written consent for the study as per protocol and institute ethical clearance is obtained. The patients are divided into two groups, of 22 patients each, by a random selection process, the experimental group receiving atenolol and atorvastatin and the control group receiving atenolol only.

Duration of study

The study duration is for 3 months.

Anthropometrical, clinical and biochemical characters of volunteers

Anthropometrical, clinical and biochemical characters of volunteers are shown in [Table/Fig 1].

Table/Fig 1

	Experimental group (22)	Control group (22)
Age	**45 ± 4 years**	**43 ± 2 years**
Sex:		
Males	12	12
Females	10	10
Weight (kg)	79 ± 3 (beginning) 79 ± 3 (end)	79 ± 2 (beginning) 80 ± 2 (end)[a]
Body mass index (BMI)	27.3 ± 1.2 units	27.5 ± 2.1 units (beginning) 27.3 ± 1.9 units (end)[a]
Systolic blood pressure (mmHg)	154 ± 16	146 ± 24
Diastolic blood pressure (mmHg)	100 ± 12	94 ± 8
Total cholesterol (mg/dl)	282 ± 18	202 ± 12
Low-density lipoprotein cholesterol (mg/dl)	192 ± 19	139 ± 12
High-density lipoprotein cholesterol (mg/dl)	48 ± 5	42 ± 5
Very low-density lipoprotein cholesterol (mg/dl)	40 ± 6	20 ± 4
Triglycerides (mg/dl)	195 ± 11	105 ± 16
Fasting blood sugar (mg/dl)	105 ± 17	96 ± 5

[a]This variation may be non-identical conditions prevailing during measurements.

Anthropometrical, clinical and biochemical characters of volunteers (*n* = 44)

Clinically, both the groups show no abnormality, other than hypertension in both groups, along with dyslipidaemia in the experimental group. Different biochemical and clinical parameters like liver function tests (LFT), total leukocyte count (TLC), differential leukocyte count (DLC), Hb, urea, creatinine, total proteins, serum electrolytes, urine tests, electro-cardiograph (ECG), X-ray of chest, etc. are almost identical and within normal range in both the groups.

Collection of blood samples

Twelve hours fasting values are taken initially and at monthly intervals for 3 months. Measurement of total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), very low-density lipoprotein cholesterol (VLDLC), triglycerides (TG) and fasting blood sugar (FBS) is done by standard methods, as depicted by Boehringer Mannheim [23] and by reagents supplied to meet the standard quality at monthly intervals by an indwelling catheter placed in the anti-cubital vein. Serum insulin level is measured by radioimmunoassay by *Spandan Diagnostics*.

Statistical methods

For calculation of *t*-statistic and *p*-values, standard SPSS package is used. The statistical analysis is done based on paired *t*-test, and *p*-value is calculated using paired *t*-statistic. The normality of the parent population (from which the data have been collected) is not tested, but since the sample size is 44, which could be considered to be large, *t*-statistic is used, the validity of which is justified through central limit theorem.

Results

[Table/Fig 2] shows values of blood parameters of 22 volunteers who are receiving atenolol and atorvastatin, in comparison with 22 volunteers who are receiving atenolol. It is found that in the group receiving atenolol and atorvastatin (experimental group) TC is reduced from initial values of 282 ± 18 mg/dl to 271 ± 16 mg/dl ($p = 0.05$). HDLC increased from 48 ± 5 mg/dl to 50 ± 7 mg/dl ($p = 0.04$). LDLC reduced from 195 ± 11 mg/dl to 182 ± 21 mg/dl ($p = 0.05$). VLDLC, TG values remain almost same, and changes are statistically insignificant. FBS values changed from initial 105 ± 17 mg/dl to 100 ± 6 mg/dl ($p = 0.04$). [Table/Fig 2] also shows values of blood parameters of 22 volunteers who are receiving atenolol only (control group). It is observed that TC is from initial values of 202 ± 12 mg/dl to 200 ± 16 mg/dl. HDLC changes from 42 ± 5 mg/dl to 43 ± 7 mg/dl. LDLC changes from 139 ± 12 mg/dl to 140 ± 21 mg/dl. VLDLC, TG and FBS values remain almost same, and all the value changes are statistically insignificant. [Table/Fig 3] shows serum insulin and homeostasis model assessment of insulin resistance (HOMA 2-IR) values of different groups, in order to determine insulin sensitivity. It was observed that in the experimental group, serum insulin value initially is 32 ± 3 μU/ml and finally is 29 ± 3 μU/ml ($p = 0.03$), and in the control group, serum insulin value initially is 31 ± 2 μU/ml and finally is 31 ± 2 μU/ml. HOMA 2 values (insulin resistance or IR) of the two groups of patients show that in the experimental group it was 4.2 ± 0.5 initially to 3.7 ± 0.4 after 3 months, and in the control group it was 4.2 ± 0.3 initially and 4.2 ± 0.2 finally, showing increase in insulin sensitivity by atorvastatin.

Table/Fig 2

	Control group				Experimental group				*p*-value
	0 month	1 month	2 months	3 months	0 month	1 month	2 months	3 months	
Total cholesterol (mg/dl)	212 ± 18	208 ± 15	204 ± 17	202 ± 16	282 ± 18	278 ± 15	274 ± 17	271 ± 16	0.05
High-density lipoprotein cholesterol (mg/dl)	38 ± 5	39 ± 7	39 ±v6	40 ± 7	48 ± 5	49 ± 7	49 ± 6	50 ± 7	0.04
Low-density lipoprotein cholesterol (mg/dl)	142 ± 19	138 ± 17	132 ± 21	130 ± 21	195 ± 11	190 ± 17	184 ± 21	182 ± 21	0.05
Very low-density lipoprotein cholesterol (mg/dl)	28 ± 6	28 ± 4	28 ± 3	28 ± 5	40 ± 6	39 ± 4	39 ± 3	39 ± 5	Statistically insignificant
Triglyceride (mg/dl)	145 ± 11	143 ± 13	145 ± 17	145 ± 21	195 ± 11	193 ± 13	193 ± 17	192 ± 21	Statistically insignificant
Fasting blood sugar (mg/dl)	145 ± 11	142 ± 13	143 ± 11	144 ± 12	105 ± 17	103 ± 3	104 ± 7	104 ± 6	0.04

Values of blood parameters of 22 volunteers who are receiving atenolol and atorvastatin and values of blood parameters of 22 volunteers who are receiving atenolol

Table/Fig 3

	Serum insulin initial value	Serum insulin end value	Homeostasis model assessment of insulin resistance 2 initial value (insulin resistance)	Homeostasis model assessment of insulin resistance 2 end value (insulin resistance)
Experimental group	32 ± 2 µU/ml	29 ± 3 µU/ml (p = 0.03)	4.2 ± 0.5	3.7 ± 0.4
Control group	31 ± 2 µU/ml	31 ± 2 µU/ml	4.2 ± 0.3	4.2 ± 0.2

Showing serum insulin and homeostasis model assessment of insulin resistance 2 values of different groups

Discussion

The exact cause of increase in insulin sensitivity by atorvastatin is unknown. The study shows that atorvastatin increases insulin sensitivity in normal subjects. It thus corroborates the findings of Parhofer et al. [24], who found that, though uncertain, short-term statin therapy can affect insulin sensitivity in patients with insulin resistance syndrome. Compared with placebo, treatment with atorvastatin (10 mg/day) resulted in significant reductions in the HOMA index (–21%), fasting C-peptides (–18%) and glucose, as well as a borderline reduction of insulin. In addition, significant reductions in total and LDL cholesterol concentrations were observed in the atorvastatin group. Some subjects with a better

lipid profile and more normal baseline parameters respond less. Thus, the team concludes that patients with more pronounced metabolic syndrome would benefit more than those with less pronounced changes, and the present study thus is contrary to the studies of Parhofer et al. [24]. Okajima et al. [25] 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 at high glucose was not significantly changed, and, thus, net glucose-stimulated insulin secretion was apparently decreased by these lipophilic statins. Atorvastatin is frequently administered for the treatment of hypercholesterolemia associated with type 2 diabetes mellitus. However, a marked deterioration of glycaemic control has been reported in some patients treated with atorvastatin. Takano et al. [26] suggest a predisposition to a deterioration of glycaemic control in type 2 diabetic patients treated with atorvastatin and thus are against the evidence gained by the present study. Prasad et al. [27] hypothesised that statins influence the development of new-onset diabetes mellitus in renal transplant recipients. Yoshitomi et al. [28] 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. It has been suggested that HMG Co-A reductase inhibitors ('statins') may reduce the risk of developing type 2 diabetes mellitus. Yee et al. [29] 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. Whether this relationship exists for patients at high risk of developing diabetes should be examined in a randomised trial. In order to evaluate a hypothesised protective effect of the use of HMG Co-A reductase inhibitors (statins) on the development of type 2 diabetes, Jick and Bradbury [30] conducted a nested case–control study, based on data from the UK-based General Practice Research Database (GPRD). There was little evidence for a duration effect for simvastatin in these data, though there is a slight suggestion of a long-term protective effect with pravastatin. The study results are most consistent with the conclusion that there is little, if any, protective effect of statins on the development of type 2 diabetes. Ohmura et al. [31] report a patient in whom the administration of HMG CoA reductase inhibitors (statins) might have triggered the onset and worsening of diabetes and concluded that statin does not seem to have critical adverse effects on glucose tolerance, but it may uncommonly modify the natural course of the development of diabetes in certain patients. Our data suggest that statins have a generalised anti-diabetic role even in a section of normal patients.

Conclusion

Statins reduce the magnitude of hyperinsulinaemic/insulin-resistant state. Statins are believed to have an anti-infective role. The exact cause of hyperinsulinaemic/insulin-resistant state is unknown. Hyperinsulinaemic/insulin-resistant state is very common and is of explosive occurrence in India. Infective aetiology may play a role in the causation of the state, and statins reduce the infective conditions by its anti-infective role. The claim is controversial and several studies also refute the findings. Further, studies are needed in Indian context to find out a conclusive result.

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