Assessment of Atorvastatin Effectiveness on Serum PSA Level in Hypercholesterolemic Males

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Abstract- The previous large retrospective studies demonstrated that treatment with Statins reduces both the incidence of prostate cancer by 50% and serum Prostate Specific Antigen (PSA) level up to 40%. However the main problem in those studies was the absence of control groups of men with hypercholesterolemia without Statin treatment. We performed a small prospective controlled clinical trial to assess the influence of the treatment with Atorvastatin on serum PSA in men with hypercholesterolemia referred to our educational and treatment center from October 2007 to March 2008. In this study, among the newly diagnosed males with hypercholesterolemia (LDL > 130 mg/dl), 40 patients with LDL more than 190 mg/dl were selected as a case group and were treated with Atorvastatin (20 mg/day). Among the same population and in the same period, another 40 patients with LDL between 130 and 190 mg/dl were selected as first control group and were treated only with low fat diet. Another 40 patients with normal serum cholesterol and without any treatment were selected as second control group. The lipid profile and serum PSA level of patients of all groups were tested at the first and third months after the therapy. After completion of data, the mean serum lipids and PSA level were measured in both visits and compared with each other by paired t-test. Also the mean PSA change in two visits between three groups was compared by ANOVA and Tukey HSD test. There was not any significant difference in mean baseline PSA between hypercholesterolemic and normocholesterolemic patients (P=0.547). In case group, mean PSA and LDL was reduced by 14.1% (P=0.0001) and 30% (P=0.0001) respectively by second visit. In first control group, mean PSA was not changed significantly (P=0.337), whereas mean LDL in this group was reduced by 9.6% (P= 0.0001). Similarly in the second control group mean PSA was not changed significantly (P=0.309) by second visit. In addition, mean change of PSA in case group was compared with first and second control groups that was significantly different (P=0.0001) whereas mean change of PSA between two control groups was not significantly different (P=0.615). The results of this study showed that: 1) Short term treatment with Atorvastatin can reduce serum PSA level, and 2) This reduction is more likely to be due to direct effect and is not related to lowering serum cholesterol levels. Thus, if results of this study are confirmed by large prospective randomized clinical trials with longer follow up period, it will be possible that Atorvastatin could be used in long term as a safe chemoprophylactic agent against prostate cancer in high risk patients.
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Introduction

Prostate cancer is the fourth most common male malignant neoplasm worldwide that is an attractive and appropriate target for primary prevention because of its incidence, prevalence and disease related mortality. The goal of primary chemoprevention is to decrease the incidence of a given cancer, simultaneously reducing both treatment related side effects and mortality. Effective chemoprevention requires the use of nontoxic agents that inhibit specific molecular steps in the carcinogenic pathway (1).

Atorvastatin which is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) reductase (the primary enzyme in the process of cholesterol biosynthesis) is a cholesterol lowering drug with a

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relatively low price which is safe and well tolerated. Its side effects are minimal and the most common is gastrointestinal upset (4).

Statins have been reported to demonstrate strong chemopreventive potentials in cell lines (5,8). Furthermore reports indicate that Statins induce apoptosis in prostate cancer cell lines through some intracellular mechanisms that are not fully understood (9,10). Up to now, a few reports have been existed about the relationship between Statin treatment and decreasing serum Prostate Specific Antigen (PSA) level that all of those are retrospective (11). Also more retrospective reports have been existed about a link between current Statin usage and decreased prostate cancer risk especially in advanced prostate cancer. In some of those studies the risk of prostate cancer have reduced by 50% (12,14). To the best of our knowledge this is the first prospective study that shows a relationship between Atorvastatin treatment and a decrease in serum PSA level with time. The goal of this study is to assess Atorvastatin effectiveness in short term on serum PSA level (primary marker for prostate cancer risk) in hypercholstrolemic male patients.

Materials and Methods

In this study which is a nonrandomized controlled prospective clinical trial, among the newly diagnosed hypercholstrolemic males (LDL> 130 mg/dl) from Oct. 2007 to March 2008, 40 patients with LDL more than 190 mg/dl were selected as a case group and were treated with Atorvastatin (20 mg/day). Among the same population and in the same period, another 40 patients with LDL between 130 to 190 mg/dl were selected as first control group and were treated only with low fat diet. In the same period another 40 patients with normal serum cholesterol and without any treatment that were referred due to nonspecific complaints, were selected as second control group. Patients of all groups were assessed at baseline using medical history namely the diagnosis of hypercholesterolemia and history of treatment with Statins or any drug, and data of age, lipid profile including triglycerides (TG), total cholesterol, low density lipoprotein (LDL) and serum PSA level were recorded. The common inclusion criteria in all groups were males between 40 and 70 years, absence of any prostatic disease (benign prostatic hypertrophy, prostate cancer and prostatitis) and serum PSA level lower than 4 ng/ml for males between 50 and 70 years and lower than 2.5 ng/ml for males between 40 and 50 years. The common exclusion criteria in all groups were documented recent urinary tract infection (UTI) and

history of receiving Statins or any drug for more than a week. Patients of all groups were asked to visit three months later and same data of lipid profile (in case and first control group) and serum PSA level (in all groups) were recorded. Furthermore in case group, the liver enzymes (SGOT and SGPT) were tested six weeks after initiation of Atorvastatin to assess its side effect on the liver. All tests were performed in one laboratory. The diagnosis and treatment of hypercholesterolemia was based on the National Cholesterol Education Program (NCEP) guidelines (21). Age was defined as chronological age in years. We calculated the mean ± SD for age, lipid profile and serum PSA in patients of all groups. Since our data in all groups had a normal distribution, parametric analytic methods were used to compare the case group with control groups. This involved the use of paired t-test to compare group means between two visits. Also the mean PSA changes in two visits in all groups were compared with each other by ANOVA and Tukey HSD test. Then we calculated percent change in mean PSA in all groups by dividing the change in mean PSA between two visits by the baseline value and multiplied this by 100. In addition the mean baseline PSA in hypercholesterolemic (case + first control group) and normocholesterolemic (second control group) patients were calculated and compared with each other using t-test. All statistical analyses were done using SPSS software and P-value lower than 0.05 was considered statistically significant.

Results

Patients in case and control groups were of similar ages ($P=0.698$) (Table 1). Also, there was not any significant difference in mean baseline PSA between all groups ($P=0.653$, Table 1). Similarly, there was not any significant difference in mean baseline PSA between hypercholesterolemic and normocholesterolemic patients ($P=0.547$, Table 6). As was expected, the mean serum TG ($P=0.0001$), total cholesterol ($P=0.0001$) and LDL ($P=0.0001$) between case and first control group were different (Table 1). In case group, mean PSA was reduced by 14.1% by second visit ($P=0.0001$, Table 2). Also, mean LDL in this group was reduced by 30% ($P=0.0001$, Table 2). Furthermore mean TG and total cholesterol in this group was reduced by 9.1% ($P= 0.0001$, Table 2) and 13.7% ($P=0.0001$, Table 2) respectively. In contrast, mean high density lipoproteins (HDL) was increased by 8.9% ($P=0.0001$, Table 2). All patients in case group completed the course of treatment with Atorvastatin and no significant adverse effect was observed.

Table 1. The mean of demographic and laboratory varieties of all groups at baseline

Alternative	Group	Number	Mean	Standard Deviation	F	*P*-value
Age	Case	40	56.67	8.59	361	0.698
	1th control	40	55.82	8.40		
	2th control	40	57.42	8.28		
Triglyceride (mg/dl)	Case	40	198.82	24.17	90.21	0.0001
	1th control	40	176.77	26.42		
	2th control	40	125.85	24.09		
Total Cholesterol (mg/dl)	Case	40	261.87	21.02	157.456	0.0001
	1th control	40	228.75	19.88		
	2th control	40	182.70	19.16		
LDL (mg/dl)	Case	40	218.97	19.61	411.124	0.0001
	1th control	40	158.90	16.48		
	2th control	40	102.22	18.39		
HDL (mg/dl)	Case	40	32.45	5.71	69.441	0.0001
	1th control	40	37.35	8.03		
	2th control	40	56.02	13.04		
PSA (ng/ml)	Case	40	1.48	0.59	0.428	0.653
	1th control	40	1.4	0.52		
	2th control	40	1.37	0.64		

Table 2. The mean of laboratory varieties of case group (receiving Atorvastatin) by two visits

Alternative	Visit	Mean	Standard Deviation	*P*-value
Triglyceride (mg/dl)	First	198.82	24.17	0.0001
	Second	180.57	21.95	
Total Cholesterol (mg/dl)	First	261.87	21.02	0.0001
	second	225.77	18.14	
LDL (mg/dl)	First	218.97	19.61	0.0001
	second	153.25	65.12	
HDL (mg/dl)	First	32.45	5.71	0.0001
	second	35.37	6.62	
PSA (ng/ml)	First	1.48	0.59	0.0001
	second	1.27	0.42	

In first control group, mean PSA was not significantly changed by second visit (*P*=0.337, Table 3), but mean LDL in this group was reduced by 9.6% (*P*=0.0001, Table 3).

Table 3. The mean of laboratory varieties of first group (low fat diet) by two visits

Alternative	Visit	Mean	Standard Deviation	*P*-value
Triglyceride (mg/dl)	First	176.77	26.42	0.0001
	second	167.95	25.15	
Total Cholesterol (mg/dl)	First	228.75	19.88	0.0001
	second	215.57	18.15	
LDL (mg/dl)	First	158.9	16.48	0.0001
	second	143.57	7.51	
HDL (mg/dl)	First	37.35	8.03	0.0001
	second	35.85	7.65	
PSA (ng/ml)	First	1.40	0.52	0.337
	second	1.38	0.5	

Table 4. The mean PSA of second control group (Without Any treatment) by two visits

Alternative	Visit	Mean	Standard Deviation	*P*-value
PSA	First	1.37	0.64	0.309
(ng/ml)	second	1.38	0.66	

Table 5. The comparison of mean PSA change by two visits in all groups

Group	Number	Mean Changes of PSA (ng/ml)	Standard Deviation	*P*-value
case	40	↓0.21	0.2	
1th control	40	↓0.02	0.09	0.0001
2th control	40	↑0.01	0.09	

Table 6. The comparison of mean baseline PSA by hypercholesterolemic (case + 1th control groups) and normocholesterolemic (2th control group) patients

Group	Number	Mean PSA (ng/ml)	Standard Deviation	*P*-value
Case + 1th control	80	1.44	0.55	0.547
2th control	40	1.37	0.64	

Also, mean TG, total cholesterol and HDL in this group was reduced by 4.9% (*P*=0.0001, Table 3), 5.7% (*P*=0.0001, Table 3) and 4% (*P*=0.0001, Table 3) respectively. Similarly in second control group, mean PSA was not significantly changed by second visit (*P*=0.309, Table 4). Finally, mean change of PSA in case group was compared with first and second control groups that was significantly different (*P*=0.0001, Table 5), whereas mean change of PSA in two control groups was not significantly different (*P*=0.615, Table 5).

Discussion

We performed a small prospective controlled clinical trial to assess the influence of the treatment with Atorvastatin on serum PSA in men with hypercholesterolemia. In this study the mean PSA and LDL in case group after 3 month treatment with Atorvastatin was decreased by 14.1% and 30% respectively, whereas in first control group (low fat diet treatment) despite of 9.6% decrease in LDL, serum PSA levels were not significantly changed.

Similarly in the second control group (without any treatment) serum PSA was not significantly changed with time. Furthermore mean baseline PSA in hypercholesterolemic (case + first control groups) patients were compared with normacholesterolemic (second control group) patients that was not significantly different. Our results showed that: *a.* short term treatment with Atorvastatin, cause reduction in serum

PSA level, and *b.* this reduction is more likely due to direct drug effect and is not related to lowering serum cholesterol.

The effect of drug on serum PSA level is likely to be due to antiprolifrative and apoptotic effect of Statins on latent prostate cancer cell lines demonstrated in both *in vitro* and *in vivo* animal studies (5,8).

Furthermore reports indicate that Statins induce apoptosis (programmed cell death) in prostate cancer cell lines through some mechanisms (9,10). There are four possible mechanisms, including:

1) The inhibition of the biosynthesis of mevalonate (15), the produce of the enzymatic action of HMGCoA reductase, usually inhibited by Statins. Mevalonic acid is necessary not only for cholesterol biosynthesis, but also for isoprenoid synthesis (16). The activation of the small Ras-G protein, a major component of the signal transduction pathway, by isoprenylation is vital for cell survival (17) and isoprenylation inhibitors are reported also to induce apoptosis (18).

2) Inhibition of cdk2 activity by inhibiting the Thr-160 phosphorylation of cdk2 leads to the enhancement of P21, a step that is critical for the induction of apoptosis (7).

3) The transregulation and proteosomal degradation of E_2F-1, a cell cycle regulator that acts as an oncogene and as a tumor suppressor gene in tissue specific fashion, are thought to be critical regulation events in Statin induced apoptosis of prostate cancer cell lines (6).

4) Inhibition of the biosynthesis of precursors such as fanesyl pyrophosphate and geranyl pyrophosphate, which are responsible for the translation of Ras and Rho, respectively, to the cell membrane, is a step that is also necessary for the cell signaling that leads to cell proliferation and migration (19). The hypothesis of antiprolifrative and apoptotic effects of Statins on prostate cancer cell lines is buttressed by the fact that a significant proportion of men (30% in 1 series) have foci of malignancy in the prostate by the fifth decade of life, which increases to 70% by the eighth decade (20). Thus, we believe that the observed decrease in serum PSA in the case group was in part a result of the induction of apoptosis and the inhibition of proliferation in undetectable premalignant prostate cells. The previous retrospective studied demonstrated that Statin treatment reduces both the incidence of prostate cancer (specially the advanced type) by 50% (12,14) and serum PSA level up to 40% (11) that support the central hypothesis of our study. However those studies have several drawbacks including: 1) All of those studies were retrospective, 2) The use of serum PSA as an end point for prostate cancer is limited in that serum PSA is not always predictive of the risk of prostate cancer since increased PSA can be found in conditions such as BPH, prostatitis and following prostate manipulations, 3) The absence of control groups of men with hypercholesterolemia but no Statin treatment since decrease in serum PSA in the Statin users may have resulted indirectly ascribed to Statins *per se*. To the best of our knowledge, this is the first prospective controlled study to associate Atorvastatin treatment with a decrease in serum PSA with time and has solved most of the mentioned problems. However our study also has some drawbacks: 1) the use of serum PSA as an end point for prostate cancer, 2) the difference of LDL threshold for initiation of treatment in case and first control groups, 3) the normal lipid profile in second control group in contrast to case and first control groups. Thus, if results of this study are confirmed by large prospective randomized clinical trials with longer follow up period, it will be possible that Atorvastatin can be used in long term as a safe chemoprophylactic agent in patients at higher risk for prostate cancer (Black race, Familial history of prostate cancer and high grade PIN in prostate biopsy). In conclusion, the results of this study showed that: 1) Short term treatment with Atorvastatin can reduce serum PSA level, and 2) this reduction is more likely due to direct drug effect and is not related to lowering serum cholesterol levels. Thus, if results of this study are confirmed by large prospective randomized clinical

trials with longer follow up period, it may be possible that Atorvastatin could be used in long term as a safe chemoprophylactic agent against prostate cancer in high risk patients.

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