Urology Journal
UNRC/IUA

Vol. 2, No. 3, 153-156 Summer 2005
Printed in IRAN

The Effect of Garlic on Cyclosporine-A-Induced Hyperlipidemia in Male Rats

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ABSTRACT

Introduction: Cyclosporin A (CsA) is a potent immunosuppressive drug. However, it has adverse effects that include elevation of plasma low-density lipoprotein (LDL). This study was designed to determine the effect of garlic on CsA-induced hyperlipidemia in male rats.

Materials and Methods: Baseline serum blood samples from forty 10-month-old, male Wistar rats were obtained. They received intraperitoneal (IP) injection of CsA (25 mg/kg) for 28 days. Blood samples were again obtained after the 28-day treatment. Sixteen of 40 rats showed increased serum LDL levels. These 16 were divided into 2 groups of 8 rats each. In the first (experimental) group, 8 rats received garlic (tablets, 400 mg/d), CsA (25 mg/kg IP), and regular diet for 28 days. In the second (control) group, 8 rats received the same regimen without the garlic tablets. At the end of the experiment, blood samples were taken from animals in both groups, and LDL levels were assessed.

Results: The mean baseline LDL level in animals in the control group was 17.75 ± 4.1 mg/dL. This increased to 21.5 ± 1.6 mg/dL after 28 days of CsA administration. After 28 more days, the mean LDL level increased to 25.4 ± 4.9 mg/dL (P = .004). In animals in the experimental group, the baseline LDL level was 23.8 ± 3.7 mg/dL, which increased to 31.3 ± 1.6 mg/dL after the first 28 days (P < .001). After the second 28 days, it decreased to 26.0 ± 4.8 mg/dL (P = .06), and among 4 animals, the LDL level decreased more than 49%.

Conclusion: In a Wistar rat model, animals given cyclosporin A subsequently treated with garlic demonstrated reduced LDL levels compared with controls. This treatment may be useful in patients receiving organ transplantations.

KEY WORDS: cyclosporine, low-density lipoprotein, rat, garlic

Introduction

Cyclosporin A (CsA) is a fungous peptid that has strong suppressive effects on the human immune system. The drug preferably affects activation of helper T lymphocytes, which can weaken the immune system. Cyclosporin A is the most effective drug for preventing liver, heart, and kidney allograft rejection. Consequently, it has widespread application in controlling rejection in all types of organ transplantations, especially kidney allografts.(1) However, it has severe adverse effects including nephrotoxicity, hypertension, electrolyte imbalance, genitourinary tract upsets, neurotoxicity, hepatotoxicity, and hyperlipidemia, which results in atherosclerosis.(1) Currently, postoperative atherosclerosis is the main cause of mortality following transplantation. Obviously, preventing CsA-induced hyperlipidemia would mitigate the

Received May 2004
Accepted June 2005
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adverse effects of CsA in kidney transplant recipients.

Among herbal drugs used for medicine, garlic is particularly important for controlling hyperlipidemia and hyperglycemia. Garlic contains an alkaloid, *allicin*, as well as antioxidants (ie, vitamin C, germanium, and sulphuric materials).[2,3] Several studies of allicin have demonstrated its beneficial effects.[2-4] This study was designed to investigate the effectiveness of garlic on CsA-induced hyperlipidemia in male Wistar rats.

Materials and Methods

Forty 10-month-old male Wistar rats (250 ± 20 g) were obtained from the animal center of Urmia University of Medical Sciences. All experimental protocols were approved by our institution's animal research committee. They were kept under normal light and temperature conditions (ie, 25 ± 5°C; 12-hour light/dark cycle). Blood samples were obtained from the tails of all rats. Following centrifugation, samples were analyzed for serum LDL levels. Rats then received intraperitoneal (IP) injection of CsA (25 mg/kg, Sandoz, Basel, Switzerland) for 28 days. Subsequent blood samples were drawn, and serum LDL levels were measured. Rats with higher LDL levels in the second blood sampling were divided into 2 groups. Animals in the first (experimental) group were given garlic tablets (400 mg/d), food (regular diet), 12.5 g, and CsA (25 mg/kg IP). Rats in the second (control) group were treated as were the animals in the experimental group, except that animals in the control group did not receive garlic tablets. Animals in both groups were treated for a second period of 28 days.

Blood sampling was done again after 28 more days. Serum and blood cells were separated by centrifuge (10 000 rpm) and analyzed for LDL levels. Data were compared using the paired *t* test. The results are presented as means ± SEM, and the differences between the 2 groups were considered significant if the value for *P* was less than .05.

Results

Of 40 rats, 16 had elevated LDL levels after the second blood sampling, and these animals were randomly divided into 2 groups-experimental and control-of 8 rats each.

The mean baseline LDL level in animals in the control group was 17.75 ± 4.1 mg/dL. This increased to 21.5 ± 1.6 mg/dL after 28 days of CsA administration, which was not statistically significant (P = .30). But, when 2 rats with minimal increases in their LDL levels were excluded from the analysis, the increase was significant (P = .015). After the second 28 days, mean LDL levels reached 25.4 ± 4.9 mg/dL, which was significantly higher compared with their baseline LDL levels (P = .004). In 50% of the animals in this group, LDL levels increased markedly, reaching more than 50% of their baseline levels.

Figure 1 shows the LDL changes in animals in the control and experimental groups. In animals in the experimental group, the mean baseline LDL level was 23.8 ± 3.7 mg/dL, increasing to 31.3 ± 1.6 mg/dL after the first 28 days (P < .001). After the second 28 days (CsA and garlic administration), the mean LDL level decreased to 26.0 ± 4.8 mg/dL (P = .06). However, in more than 50% of these rats, the mean LDL level decreased by more than 49% (P = .023).

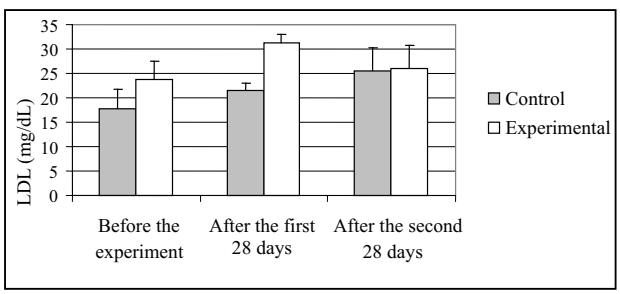

FIG. 1. Changes of serum LDL levels in garlic and control groups, before the exeperiment, after 28 days of cyclosporin administration, and after 28 days of cyclosporin and garlic administration in the experimantal group versus cyclosporin administration in controls

Discussion

This study demonstrates the beneficial effects of garlic in reducing the CsA-induced elevation in plasma LDL levels. LDL levels in rats in the control group increased during the second 28 days of this study and decreased in at least half of the rats in the experimental group. According to many investigations, hyperlipidemia is a severe CsA-induced adverse effect following transplantation.[5] Medical treatment is required to decrease or attenuate this phenomenon. Lipid-lowering drugs, used widely in human and animal models, have been shown to have adverse effects

including cancer.[6] Consequently, herbal drugs are strongly advocated.[7] Garlic is one of these drugs.[8] Garlic-containing drugs have been used to treat hypercholesterolemia, even though their efficacy has not been generally documented. Little is known about the mechanisms of action of the possible effects on cholesterol in humans.[9] Studies in experimental animal models, however, have shown that dietary garlic supplementation may suppress the hepatic lipogenic activities and attenuate the activities of enzymes such as malic (which synthesizes fatty acids) and enzymes like glucose-6 phosphate dehydrogenase and 3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase (which contribute to lipogenesis).[10]

It is likely that garlic-derived substances (which have sulphur-containing compounds) may effectively decrease cholesterol levels. This is probably the result of inhibition of hepatic cholesterol synthesis.[10] Meanwhile, garlic has some sulphur-containing materials such as S-allylcysteine, vitamin C, and selenium which are strong antioxidants.[11]

Several studies have indicated that the LDL decreasing effect of garlic results from its antioxidant compounds including vitamin C and germanium.[12-14] Garlic can play its role by scavenging free radicals, inhibition of the HMG-CoA and biosynthesis of cholesterol.[15,16] Another study by Qureshi and coworkers has shown that garlic extract can decrease the blood lipid level by suppressing lipogenic and cholesterogenic enzyme activities.[17]

Wei and Lau have reported that the S-allylcysteine of garlic can control reactive oxygen species and prevent lipid peroxidation and LDL oxidation adverse effects in endothelial cells.[18]

On the other hand, despite the numerous advantages of garlic, some studies have indicated that it does not produce any significant effect on decreasing blood lipid level. Berthold and colleagues[19] and Issacsohn and colleagues[20] have demonstrated that garlic has no significant effect on lipid profiles. However, our results are suggestive of an inhibitory effect on CsA-induced hypercholesterolemia, which could be the basis of establishing a new treatment in organ transplant patients who receive CsA.

Conclusion

Different effects of garlic on blood lipid levels have been reported. The exact mechanism of action of garlic in lowering blood lipid levels has not yet been established. As stated earlier, results from the present study indicate garlic's usefulness in decreasing blood LDL levels. This study differs somewhat from other studies in that we investigated the lipid-lowering effect of garlic in the presence of CsA (which increases lipid levels). It seems that to better elucidate garlic's effect on LDL levels, further studies on cellular and molecular levels are needed.

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