ORIGINAL ARTICLE

Novel Role of Irbesartan in Elevating Serum High Density Lipoprotein in Hypercholesterolemic Animal Model

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ABSTRACT

Objective: To explore the HDL cholesterol-raising capacity of Irbesartan (an antihypertensive drug) in rabbit's serum.

Study Design: Laboratory-based experimental study.

Place and Duration of Study: The study was carried out at the Animal House of the National Institute of Health (NIH) Islamabad, Pakistan from January 2023 to November 2023.

Methods: This study was conducted on 18 rabbits divided into three groups with six rabbits in each. Leaving one group as a normal control, two out of three groups were made hypercholesterolemic by a high-cholesterol diet. Irbesartan was given to one of the hypercholesteremic groups for 30 days. Blood samples were taken for serum analysis of HDL cholesterol.

Results: Results of blood serum levels of all three groups were compared and analyzed on three different occasions i.e., on day zero, day 120, and day 150 for HDL cholesterol. Their means were calculated using SPSS Version 20. The irbesartan-treated group showed obvious elevation in serum HDL cholesterol in comparison with the hypercholesteremic control group.

Conclusion: It is concluded that Irbesartan, an antihypertensive drug has an additional role of elevating serum high-density lipoproteins and can provide the supplementary benefit of improving the lipid profile in hypertension and Hypercholesterolemia.

Keywords: *HDL, Hypercholesterolemia, Irbesartan.*

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Introduction

Cardiovascular diseases have become one of the most important health concerns worldwide.[1,2] The co-existence of the two major risk factors hypertension and dyslipidemia have synergistic effects on the blood vessels, which results in enhanced atherosclerosis, and thereby leads to cardiovascular diseases and coronary heart disease.[3-6] However individuals with elevated plasma HDL levels are less susceptible to the development of atherosclerosis and endothelial dysfunction. High-density lipoproteins (HDLs) resist atherosclerosis directly, as they remove cholesterol from foam cells, inhibit the oxidation of LDLs, and also limit the inflammatory processes that underlie atherosclerosis. HDLs also have additional antithrombotic properties, benefiting cardiovascular diseases. In contrast, low HDL levels predict an increased incidence of myocardial infarction.[7]

Irbesartan, which belongs to an antihypertensive

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group of angiotensin receptor blockers (ARBs) is a medication used to treat high blood pressure, heart failure, and diabetic kidney disease. It is a reasonable initial treatment for high blood pressure. It is taken by mouth. The study was planned to explore the role of an antihypertensive drug, irbesartan, in improving lipid profile by raising serum high-density lipoprotein that may prove beneficial for the patients of CVD in the future.

Methods

The study was conducted in the Animal House of the National Institute of Health (NIH) Islamabad, Pakistan from January 2023 to November 2023 after getting approval from the Ethics Review Committee of Akhtar Saeed Medical College, Rawalpindi, Pakistan held on 05th January 2023 vide letter no: IRB-0504.

The adult, male rabbits were randomly apportioned into three groups (A, B, and C) of six animals (n=6) each. Group A was Normal Control, Group B was Hypercholesterolemic Control and Group C was Hypercholesterolemic and Treatment Group. Two out of three groups i.e., groups B and C were given a high cholesterol diet followed by Irbesartan (40mg/kg) which started on day 120, once daily to group C only. The study period comprised of a total of twenty weeks after one week for acclimatization by placing them in well well-ventilated rooms with proper light, temperature, food, and water. Blood samples were taken on three different occasions for biochemical analysis of serum HDL cholesterol that was carried out in pathology laboratory on a chemistry auto analyzer by enzymatic method.

1. Baseline samples were collected on day zero, before starting the high-cholesterol diet.
2. After 120 days of feeding on a high-cholesterol diet.
3. At the end of the study, on completing the treatment course for 30 days.

Data Analysis

The statistical analysis of all the values obtained was prepared on a computer applying SPSS version 20. The outcomes of serum analysis were set forth as means + standard error of the mean.[8] Afterwards one-way analysis of variance was performed using ANOVA followed by Post Hoc Tukey test to observe the differences among various means. The difference of less than 0.05 was taken as significant (P<0.04) and (P<0.006) as shown in Table-1.

Results

Group A was the normal control group. In this group, there was no change in values of serum HDL recorded on day 120 i.e. 0.31±1.1 mmol/L as compared to that recorded on day zero i.e., 0.31±0.7 mmol/L. In the same way, serum HDL values on day 150 were 0.32±0.2 mmol/L, which were also the same as that recorded on day zero i.e., 0.31±0.7 mmol/L, therefore p-value for serum HDL in the normal control group was not significant, p=NS (Not significant) i.e., P=0.10

In group B which was hypercholesterolemic control, values of serum HDL were raised on day 120 as compared to day zero, i.e. 0.73±0.2 mmol/L versus 0.18±1.1 mmol/L, p<0.03(4.2) and it remained almost unchanged on day 150 as compared to day 120, i.e. 0.72±0.5 mmol/L versus 0.73±0.2 mmol/L, p=NS. i.e., p=0.12

Group C which was the treatment group taking Irbesartan, showed significantly raised serum HDL levels when compared for day 120 and day zero, i.e. 0.78±0.5 mmol/L versus 0.27±0.3 mmol/L. p-value for group C (Irbesartan) was 0.0005 i.e., significant.

When group A was compared with group B, the mean of serum HDL showed by group B (hypercholesterolemic control) on day 150 was significantly greater than that shown by group A (normal control), i.e. 0.32±0.2 mmol/L versus 0.72±0.5 mmol/L, p<0.04 (significant).

The irbesartan-treated group showed obvious elevation in serum HDL cholesterol in comparison with the hypercholesteremic control group.

When the values of group C were compared with group B (hypercholesterolemic control) for serum HDL levels on day 150, the results indicated a significant rise for group C (Irbesartan), i.e. 0.81±0.2 mmol/L versus 0.72±0.5 mmol/L, P < 0.006 (significant).

Discussion

The widely held of studies about HDL high-density lipoprotein (HDL) have for years orbited around the possible contribution of HDL in atherosclerosis prevention and its therapeutic potential towards cardiovascular diseases.

In our study, we found a highly significant increase in

Table-1: Serum HDL TEST (mmol/L)

Groups		Day 0	Day 120	Day 150	*P*-Value
Group A	[1]*n=6 mean*	0.317	0.31	0.322	*(A&B on day 150)*
	[1]*n=6 ± SEM*	±0.12	±0.12	±0.13	*P*<0.04
Group B	[1]*n=6 mean*	0.18	0.732	0.725	
	[1]*n=6 ± SEM*	±0.075	±0.1	±0.1	*(B&C on day 150)*
Group C	[1]*n=6 mean*	0.273	0.785	0.812	*P*<0.006
	[1]*n=6 ± SEM*	±0.11	±0.32	±0.33	

[1]*n=6, Results are expressed as mean ± SEM (Standard Error of Mean)*

serum HDL cholesterol with irbesartan (*P*<0.006). This favors the dual role of irbesartan, i.e. an antihypertensive drug serving as an antihyperlipidemic drug as HDL absorbs cholesterol and carries it back to the liver.[6,7] Our study's effects concerning serum HDL cholesterol strongly support the previous study performed on cholesterol-fed rabbits by Sanz et al. In their study, they reported the lipid-lowering effect of irbesartan and losartan.[8-9] They also evidenced a significant elevation in the plasma HDL levels by this drug.

Irbesartan increased the levels of serum HDL after 30 days of augmentation and this could have contributed to a consequent reduction in serum total cholesterol. This was also proved by Kintscher et al. (2007) after conducting prospective observational, two-armed studies on 14,200 patients.[10] They reported that monotherapy with irbesartan is associated with a significant improvement in plasma HDL levels compared to baseline values. In light of these findings, it is evident by our study that irbesartan can raise plasma HDL-C.

After conducting this experimental study on eighteen rabbits and assessing the results statistically, we concluded that Irbesartan which is an efficient antihypertensive drug, has the ability to raise the serum HDL cholesterol to levels that are good enough for a healthy life. Keeping these two properties in view, as assessed by serum analysis of rabbits, this varied drug with dual actions of lowering blood pressure and improving serum HDL can be used effectively for the prevention and treatment of cardiovascular diseases. This conclusion is also supported by two important reflections, one of which is that all the other antihypertensive drugs (beta-blockers, diuretics, and calcium channel blockers) when used in cardiovascular diseases, have no known role in elevating serum HDL levels. Secondly, by using conventional antihyperlipidemic agents (statins) in cardiovascular diseases for a long time, one has to suffer from the adverse effects of myopathy which may progress to fatal or nonfatal rhabdomyolysis and there may be liver damage with elevated liver enzymes. It is worth mentioning here that in a study by some coworkers, cerivastatin was withdrawn from clinical use for the same adverse effect, and this reminds us that treatment safety in statins is the issue of utmost importance.[11] Apart from these, all the statins produce adverse drug reactions of arthralgia and arthropathy and with simvastatin, the incidence is higher than with other statins.[12] As cholesterol is the main precursor for steroid hormone, vitamin D metabolites, and bile acids, so blocking the early step of the mevalonate pathway leads to disturbances in many structural and functional components of the cell besides the adverse reactions related to antihypertensive drugs used in cardiovascular problems.[13,14] Statins only work for people who have already had heart attacks to prevent further heart attacks and deaths. So when one has to deal with the risk factors, irbesartan exhibiting both antihypertensive properties and HDL-raising action, with least or no side effects can serve humanity by treating initial hypertension as well as minimizing the risks for the development of cardiovascular diseases.[15]

A study by Onishi also reflects the effects of Irbesartan on serum HDL with a little disparity in his

study the HDL levels were insignificantly raised in comparison to our study where serum HDL levels are raised significantly. [16]

However, in another advanced study by Wang H and his companions, the results are very much consistent with our study results i.e., a significant elevation in the levels of HDL was seen. [17]

Our study is also consistent with the comparative study of Lee CJ and his colleagues who conducted a comparison of angiotensin receptor blockers' effect on lipid profile with a lipid-lowering drug and an antihypertensive drug of another class. their results showed a significant increase in serum HDL levels by Angiotensin receptor blocker, as was observed in our study.[18]

Keeping our results in view and by making comparisons with other related studies, our inference is that irbesartan increased the serum HDL-C in high-cholesterol diet-fed rabbits.

Irbesartan administration can help decrease the risk of developing cardiovascular diseases. Besides its antihypertensive property, irbesartan has an additional subsidy of elevating serum HDL cholesterol which is evident from this study.

However, our study does not focus on the mechanism of irbesartan's effect on HDL boost, so studies can also be undertaken to explore the mechanism of elevation of serum HDL by irbesartan. Furthermore, in our study we used Irbesartan in low doses i.e., 40mg, studies can be done using a regular antihypertensive dose of irbesartan (150-300mg) to observe its HDL-raising capacity. Irbesartan might be considered a novel drug for hyperlipidemia treatment.

Conclusion

Irbesartan provides the supplementary benefit of improving the lipid profile with a much better elevation of serum HDL and the least unwanted reactions, as compared to conventional antihyperlipidemic. As medication safety is a recognized indicator of quality of care, irbesartan can be considered to treat life-threatening cardiovascular problems safely for a long duration serving at the same time correcting both hypertension and hyperlipidemia by raising serum HDL levels.

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Authors Contribution

SS: Idea conception, study designing, data collection, data analysis, results and interpretation, manuscript writing, and proofreading
ZRC: Study designing
MA: Data analysis, results and interpretation
RSA: Study designing
ERC: Study designing
SRC: Data analysis, results and interpretation