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Analysis of Simvastatin Usage in Hypertension Patients in Kediri City Health Center

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ABSTRACT

Hypertension is a chronic condition characterized by increased blood pressure on the walls of the arteries. The use of simvastatin in hypertensive patients has proven to be useful in primary and secondary prevention of cardiovascular disease. The increase in blood sugar levels in long-term simvastatin users is caused by increased gluconeogenesis with increased gene expression of an enzyme that plays a role in increasing glucose production in the liver, namely phosphoenolpyruvate carboxykinase (PEPCK). The objective to analyze additional simvastatin therapy on a random plasma glucosa (GDA) Lipid levels in outpatient hypertensive patients at the Kediri City health center. This research method is analytical observational. The sampling technique for this research was using accidental sampling and time limited sampling. The patients obtained were 30, 3.3% women, 84% aged 46-59 years, 5, 10 mg amlodipine monotherapy, captropril 25 mg and 2 patients received polytherapy, namely amlodipine 10 mg + HCT 25 mg + lisinopril 10 mg ; captopril 25 mg + HCT 25 mg Based on the average levels of GDA pre 198.47 ± 10.3 mg/dl, GDA post 211.63 ± 12.62 mg/dl, LDL pre 88.43 ± 4,535 mg/dl and LDL post 79.60 ± 4,197 mg/dl. Shapiro Wilk Normality Test results of sig >0.05 indicate that the data is normal except trigliserida test. Conclusion: Based on the sig value of 0.00 in the inter-subject aspect test using SPPS 24 paired test and wilcoxon, it can be concluded that the use of simvastatin has a statistically significant effect on GDA, lipid levels in research subject.

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ABSTRAK

Hipertensi adalah suatu keadaan kronis yang ditandai dengan meningkatnya tekanan darah pada dinding pembuluh darah arteri. Peningkatan kadar gula darah pada pengguna simvastatin jangka Panjang disebabkan oleh peningkatan *gluconeogenesis* dengan peningkatan ekspresi gen dari enzim yang berperan dalam peningkatan produksi glukosa di hepar, yaitu *phosphoenolpyruvate carboxykinase* (PEPCK). Tujuan untuk menganalisis terapi tambahan simvastatin terhadap kadar Gula darah acak (GDA), , Low Density Lipoprotein (LDL) pada pasien hipertensi rawat jalan di puskesmas Kota Kediri. Metode penelitian ini adalah observasional analitik. Teknik sampling penelitian ini yaitu menggunakan *accidental sampling* dan *time limited sampling.* Pasien yang didapatkan adalah 30 pasien, perempuan 73,3% , rentang usia 46-59 tahun sebanyak 25 pasien (84%), Terapi monoterapi amlodipine 5 mg (13 pasien), amlodipine 10 mg (14 pasien), captopril 25 mg + HCT 25 mg (1 pasien). Berdasarkan rata-rata kadar GDA pre 198.47±10,3 mg/dl, GDA post 211.63±12,62 mg/dl, LDL pre 88,43 ±4,535 mg/dl dan LDL post 79,60±4,197 mg/dl. Hasil Uji Normalitas Shapiro-Wilk sig >0,05 menunjukkan data normal. Berdasarkan nilai sig 0,00 pada uji aspek antar-subjek menggunakan SPPS 24 *Paired t test and Wilcoxon.* disimpulkan bahwa penggunaan simvastatin memiliki pengaruh yang signifikan secara statistik terhadap kadar GDA dan Kadar Lipid pada subjek penelitian

Kata Kunci: Efektivitas; Efek Samping; Simvastatin; Hipertensi

1. Introduction

Hypertension is an increase in blood pressure after 3 measurements taken on the patient, where the patient is said to be hypertensive if the systolic blood pressure is ≥ 140 mmHg and the diastolic pressure is ≥ 90 mmHg. Blood pressure measurements are taken on adult patients aged ≥ 18 years. Over half of patients with hypertension also have other cardiovascular risk factors. Diabetes (15–20%) and lipid abnormalities (higher triglycerides and low-density lipoprotein cholesterol [LDL-C]) are the most prevalent extra risk factors. [30%], overweight-obesity (40%) metabolic syndrome (40%) hyperuricemia (25%) and smoking (for example, excessive alcohol intake, sedentary lifestyle, and heavy alcohol consumption) [1] Management of all these comorbidities is very important to prevent cardiovascular events and minimize kidney damage. Non-optimal control can increase the severity of kidney damage leading to CKD [2].

With some common mechanisms of action and pathophysiology, the relationship between hypertension and other modifiable risk factors is intricate and interconnected. Blood pressure is influenced by a number of mechanisms, including the sympathetic nervous system, the renin-angiotensin-aldosterone system, endothelial dysfunction, and the suppression of the cardiac natriuretic peptide system [3]. The detrimental metabolic effects of hypertension treatment have been proven by the ALLHAT study (The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) which examined the use of hypertension medication, and one of the results was that the use of commonly prescribed diuretics had reported side effects, namely presence of hypokalemia; Fasting glucose was elevated (>126 mg/dL) in nearly 12% of nondiabetic participants prior to 2 years, and total cholesterol was significantly higher in the group receiving diuretics [4].

Guidelines for the use of hypertension drugs provide statins as an effort to prevent atherosclerosis, which is a risk factor for cardiovascular disease. Based on the ACC/AHA Pooled Cohort Equations research conducted in America on hypertensive patients aged 40-79 years, it shows that without statins the risk of cardiovascular disease increases when the age is over 79 years [1]. In hypertensive patients with type 2 diabetes

mellitus or Metabolic syndrome often has atherogenic dyslipidemia characterized by increased triglycerides and LDL. Administration of statin drugs improves long-term outcomes in this group of patients and their use is guided by estimates of the cardiovascular risk profile according to SCORE calculations [5].

The use of Statins, namely atorvastatin 40 mg for 10 weeks in 76 patients without any indication of cardiovascular disease or Type 2 Diabetes Mellitus who had the same baseline glucose levels, showed that there was a decrease in LDL Cholesterol but there was an increase in both fasting blood sugar and intermittent blood sugar [6]. The test results using the correlation coefficient test showed that the significance value was 0.000 ($p < 0.05$), meaning that there was a significant relationship between the use of simvastatin and an increase in the patient's GDP (Fasting Blood Glucose) levels. So it can be concluded that the use of simvastatin has an effect on increasing patient GDP levels [7]. The use of statins was also linked to the development of diabetes, as evidenced by retrospective cohort studies. This association included an increased risk of developing diabetes, significant hyperglycemia, acute glycemic complications, and an increased number of prescriptions for this class of glucose-lowering drugs. The metabolic consequences of statin treatment in diabetic individuals must be included in the risk-benefit ratio [8].

The most common treatment for cardiovascular disease, the world's leading cause of death, is the use of statins for both primary and secondary prevention. Clinical trials, meta-analyses, and observational studies all point to a higher risk of new-onset type 2 diabetes mellitus (T2DM) following long-term statin medication, despite the relative safety and tolerability of statins. It has been demonstrated that statins can raise insulin resistance in peripheral tissues and impair pancreatic β cells' ability to secrete insulin and sensitivity. Adipocytes' downregulation of GLUT-4, reduced Ca 2+ signaling in pancreatic β cells, and impaired insulin signaling are a few of the mechanisms underlying this process. Furthermore, it has been reported that statin-induced type 2 diabetes may potentially be influenced by the effects of statins on epigenetics through variable microRNA expression. The evidence and processes linking statin medication to the development of type 2 diabetes are the main focus of current research. And this clarifies the confluence of multiple processes that probably play a role in statins' diabetogenic effects [9]

Based on the research and review of the material above, the researchers concluded that the use of statins in hypertensive patients can reduce lipid levels, namely total cholesterol and LDL cholesterol, but can also increase the patient's blood sugar. Clinically, these findings should encourage physicians to consider diabetes monitoring in patients receiving statin therapy to ensure early diagnosis and appropriate management.

2. Methodology

Tools

Blood Sugar checking tools use the Easy Touch brand and Blood Sugar Sticks. The tool for checking LDL, HDL, Total Cholesterol and Triglyseride levels uses Nesco brand sticks and capillary pipettes for blood collection. The analytical tool used is SPSS 24.

Research Method

A prospective technique was employed to collect data for this investigation. Research that looks forward is called prospective. In this study, time-limited sampling techniques and incidental sampling were employed as sample techniques. Any patient who happens to meet a researcher by coincidence might be utilized as a sample if it is determined that the individual they happen to meet is eligible as a data source. This practice is known as accidental sampling. There are two categories of criteria used in sample selection: inclusion and exclusion. Sampling from all patients who satisfy the research inclusion requirements is known as time-limited sampling. The inclusion criteria in this study are; Adult patients (over 18 years) outpatient with a diagnosis of hypertension, Hypertensive patients receiving simvastatin 10 mg therapy, Patients who are willing to be research subjects and Patients who died during treatment.

Data Analysis

In this study, using SPSS 24, it started by testing normality between the use of simvastatin with pre data when the researchers took data, which included GDA, LDL, Total Cholesterol, HDL, and Triglycerides and post data, namely after the patient took 10 mg simvastatin for 6 weeks. Then the normality data uses . Shapiro Wilk between the use of simvastatin 10 mg and pre-post levels were normal data for GDA, LDL, Cholesterol Total and HDL levels with a p value > 0.05, whereas for the use of simvastatin 10 mg and Triglysiride levels the pre –post value was < 0, 05 then the normality test results are not normal. Then proceed by using paired t test and wilcoxon analysis, and obtaining a p value with sig < 0.05

3. Result and Discussion

Based on data obtained from 30 patients, there were 22 female patients and 8 male patients. The largest percentage who used additional simvastatin therapy were female patients, namely 73.3%. Based on these results, it shows that there are more female patients than male patients. This is in line with data from the Kediri City SPM Health Office [10]which shows that the total number of hypertensive patient visits at the Kediri City Health Center is more women with a total of 48,284 patients (62.7%), while only 28,717 patients (37.3%) are men [10]. According to Kusumawaty et al [11]ⁱIn actuality, hypertension affects women at the same rate as it does men. Essentially, though, women are shielded from cardiovascular illness prior to menopause by the hormone estrogen, which contributes to elevated levels of HDL (high-density lipoprotein). Elevated levels of HDL cholesterol can eliminate atherosclerosis [11]

The hormone estrogen acts as an antioxidant, and also has a role as a vasodilator of the heart's blood vessels so that blood flow becomes smooth and the heart gets an adequate supply of oxygen. A decrease in estrogen levels is closely related to cardiovascular disease because an increase in cholesterol occurs simultaneously with an increase in renin angiotensin activity causing vasoconstriction and endothelial diffusion [12] .Premenopausal female immunity is assumed to be explained by the protective impact of estrogen. Blood arteries are protected from damage by the hormone estrogen, which women going through menopause progressively start to lose. The amount of estrogen hormone naturally varies with a woman's age, and this process is ongoing. This often begins in women between 46 and 59 years old, and before they reach old age, the amount increases by 5 to 19%. And it will increase 3.19 times if you are 60 years of age or older. Menopausal women should be more prone to hypertension in order to [13].

Table 1. Characteristic Profile of Hypertension Patient

Gender		**Jumlah**	**Presentase (%)**
Male		8	26,7
Female		22	73,3
Age (Year)			
31-45		3	10
46-59		28	90
History of Simvastatin Use			
Never Use		12	40
To Have Use	1-3 month	6	20
	4-6 month	1	3,3
	10-16 month	1	3,3
	>1 year	10	33,4
Therapy Received			
Monotherapy	Amlodipin 5 mg	13	43,4
	Amlodipin 10 mg	14	46,7
	Captopril 25 mg	1	3,3
Polytherapy	Amlodipin 10 mg Hidroklorotiazid 25 mg Lisinopril 10 mg	1	3,3
	Captopril 25 mg Hidroklorotiazid 25 mg	1	3,3

Adult patients' ages served as the inclusion criterion for this investigation. where patients are separated into two age groups: late adulthood, which is defined as 31–45 years, and pre-elderly, which is defined as 46–59 years. The largest age percentage of patients in this study was ninety-seven percent, who were all between the ages of 46 and 59. The aforementioned data provide credence to the hypothesis that aging-related physiological alterations lead to increased pulse pressure, mean arterial pressure, systolic blood pressure, and decreased sensitivity to sudden variations in hemodynamics. Aging is associated with alterations in the heart, autonomic nervous system, and vascular system. As we get older, the arteries change, becoming wider and stiffer.

This reduced elasticity causes the area affected by systolic pressure to narrow, causing blood pressure to increase. So as we age, the ability of LDL receptors also decreases, so that LDL levels in the blood will increase, which has an impact on blockage of coronary arteries [14]. Based on the results of this study, it shows that the older you get, the greater the risk of increasing LDL levels and blood pressure.

The highest history of using simvastatin therapy was in patients who had never received simvastatin therapy, namely 12 patients (40%). In patients who had previously received simvastatin therapy, the highest duration of simvastatin use was ≥1 year, namely 10 patients (33.4%). Usually taken over the long term to avoid the recurrence of increased cholesterol levels, simvastatin is an effective medication, particularly in decreasing LDL cholesterol. Statins are beneficial for both primary and secondary prevention of cardiovascular disease in terms of mortality and morbidity. (Hariadini et al, 2020).

The relationship between the duration of simvastatin use and LDL levels shows higher LDL levels in the group of patients who have previously used simvastatin therapy, especially in patients who have used simvastatin for ≥1 year. This could happen because the samples from patients with a duration of simvastatin use of ≤1 year were patients who had recently been diagnosed with hypertension with dyslipidemia, so the increase in cholesterol levels was not too high. Meanwhile, patients who have been using simvastatin for a long time have experienced hypertension with dyslipidemia disorders. This triggers an increased risk of cardiovascular disease. Thus, reducing cholesterol levels from an early age can reduce the risk of coronary disease, even in patients at high risk of developing cardiovascular disease [15].

Teti Sutriati Tuloli's research from 2021 indicates that amlodipine, which belongs to the class of calcium channel blocker medications and is used in the first line of hypertension therapy, is the most commonly utilized antihypertensive medication (53%) [16]. Amlodipine belongs to the calcium antagonist class of antihypertensive medications. It can be used alone or in conjunction with other drug classes such beta blockers, ACE inhibitors, diuretics, or ARA II to control hypertensionIn addition, the findings of study reveal that amlodipine is the most commonly prescribed antihypertensive (32.78%) due to its affordability for the general population and its vasculoselective properties, which prevent abrupt drops in blood pressure by having a long half-life, slow absorption, and relatively low oral bioavailability [17].

At the lowest statin dosage of 10 mg, rosuvastatin reduced LDL-C by 49%, atorvastatin by 39%, simvastatin by 30%, and pravastatin by 21%. [18]. It has also been reported, based on additional studies, that simvastatin administered at doses of 5, 10, 20, 40, or 80 mg daily can lower LDL-C levels. After starting statin therapy, a new steady state will be reached in around two weeks because the half-life of LDL-C is known to be three to four days. Therefore, with consistent administration, statins have their maximal effect after 4-6 weeks [19].This research used a normality test with the Shapiro-Wilk method because the samples used were <50 samples. Based on the results obtained from the normality test in this study using the Shapiro-Wilk method, the data obtained a p value > 0.05 except for the initial and final triglyceride data, so it can be concluded that the triglyceride data is not normally distributed. Meanwhile, the other data were normally distributed, followed by a difference test using the paired t test to test GDA, LDL, Total Cholesterol and HDL levels, and Triglycerides using the Wilcoxon test. From the SPSS results it was found that the p value of all of them was > 0.05 so it could be said that there were differences in the data on GDA, LDL, HDL, Total Cholesterol and triglyceride levels.

Table 2. Analysis of simvastatin use on initial and final levels of GDA, LDL, Total Cholesterol, HDL and Triglycerides.

SPSS test	Variabel	P (value)
Wilcoxon	Trigleserida pre-post	0,00
Paired-T test	GDA,LDL, HDL Total Kholesterol prre-post	0,00

This study obtained results that were in accordance with previous research conducted by Jianwei Wan and Min Chen (2023) with the title "Effects of statins on hypertension patients: A systematic review and meta-analysis" which stated that giving additional statin therapy to hypertensive patients clinically effective in reducing the patient's LDL levels [20]. And also in accordance with previous research by Aghasizadeh, M. et al (2021) with the title "Evaluation of LDL Goal Achievement in

Statin Consumption, South East of Iran" also showed that patients with cardiovascular risk who were given statin therapy (high/medium intensity/ low) succeeded in reducing the LDL-C levels of one third of the population studied (43.4%)[21]. Apart from that, it is also in accordance with research conducted by Welty, F. K. et al (2016) entitled "A Comparison of Statin Therapies in Hypercholesterolemia in Women: A Subgroup Analysis of the STELLAR Study" which states that the use of low dose simvastatin therapy 10 mg can reduce LDL levels by 30% [18].

Apart from lowering LDL, statins have also been shown to have significant mortality and morbidity benefits for primary and secondary prevention of cardiovascular disease [15]. So in recent years, a cardiovascular protective effect of statins has been proposed, namely that statins are also useful in lowering blood pressure, thereby reducing the risk of hypertension [22]. Because simvastatin has pleiotropic effects—improving endothelial function, modulating the inflammatory response, stabilizing plaque, and lowering the risk of blood clots—its treatment in hypertensive patients also helps to lower blood pressure. By inhibiting reactive oxygen species, statins can lower blood pressure by vasodilating blood vessels. Alternatively, statins might reduce arterial stiffness by restoring endothelial function and downregulating angiotensin II type-1 receptors. Also statins given alone or together with antihypertensive drugs that act through the RAAS can lower arterial blood pressure. Therefore, the use of statin therapy in hypertensive patients can be useful for controlling hypertension and, as a result, also contribute to reducing the risk of cardiovascular events. In addition, it was able to show an increase in survival and reduce mortality from CVD-related diseases [23].

The longest duration of simvastatin use was for new patients, namely 12 patients (40%). In old patients, the highest percentage was use ≥1 year, as many as 10 patients (33.4%). Simvastatin is an effective drug, especially in lowering cholesterol, which is usually used long term to prevent the increase in cholesterol levels again. The relationship between the duration of statin use and GDA levels is that in patients who used simvastatin long term (>6 months), it was found that statins could increase GDA levels, thereby increasing the incidence of DM by 9%. In addition, the FDA (2012) issued a warning that statins can affect glycemic control which can cause an increase in GDA levels .

The increase in blood sugar levels in long-term simvastatin users is caused by increased gluconeogenesis with increased gene expression of an enzyme that plays a role in increasing glucose production in the liver, namely phosphoenolpyruvate carboxykinase (PEPCK) [13]. According to Thakker, simvastatin causes an increase in blood sugar levels, especially when used intensively, as stated in the results of a meta-analysis of 29 studies covering 163,039 respondents, that the use of simvastatin has indeed significantly increased blood sugar levels [24].

4. Conclusion

Based on the sig value of 0.00 in the inter-subject aspect test using SPPS 24 paired test and wilcoxon, it can be concluded that the use of simvastatin has a statistically significant effect on GDA, LDL, Cholesterol Total, HDL and Triglyceride levels in research subject

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