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Genetic Variants In the Slco1b1 Gene and Their Effect on Statin-Associated Myopathy Risk: A Population-Based Overview

Dr. Ilaria Ventresca[1], Dr. Omar Halim[2]
[1] Department of Molecular Pharmacology and Genomics, University of Milan, Milan, Italy
[2] Faculty of Clinical Pharmacy and Therapeutics, Cairo University, Cairo, Egypt
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Abstract
There is an association of SLCO1B1 gene polymorphism, especially the c.521T>C variant, with abnormal hepatic uptake of statins, which is associated with an elevated risk of statin-induced myopathy (SIM). This paper set out to assess the frequency of the SLCO1B1 c.521T>C variant use and its relationship to SIM amongst 300 hyperlipidemic people on statin treatment. PCR-RFLP techniques were used to conduct genotyping and clinical data such as levels of creatine kinase, perceptive muscle symptoms, and type of statin was obtained. The allele SLCO1B1 c.521T>C was present in 23.7 percent of the entire population, and the risk of myopathy occurrence in carriers of homozygous variants was increased 4.6 times (p < 0.001). Such association was stronger in patients receiving simvastatin, as carriers of a variant had higher chances of lowering the dose or discontinuing the drug. It was found that, on the basis of them, it is possible to state that such a strategy as clinical recommendation algorithm can be offered that selective applications of the genotype based guidelines in terms of statin choice and dose adjustments are acceptable in high-risk patients. These findings highlight the need to screen SLCO1B1 to reduce adverse drug reaction and the need to support the personalization of statin treatment in a population at risk.

Keywords: ***polymorphism SLCO1B1, myopathy statin-related, genetic scanning, pharmacogenetics, statins simvastatin, individualized medicine, hyperlipemia, Statin treatment, dose adjustment, cardiovascular pharmacology.***

1. Introduction

1.1 Background Information about Statins and the Extensive Use of Statins in Cardiovascular Problems

Statins or HMG-CoA reductase inhibitors are drugs that are widely prescribed to treat hyperlipidemia, thereby decreasing heart attacks and strokes. These drugs exert their effect through the inhibition of an enzyme known as HMG-CoA reductase that is found in the liver and is responsible in cholesterol production. Statins have the ability of reducing the risk of developing atherosclerosis because of lowering cholesterol levels of low-density lipoprotein (LDL) that helps in reducing the accumulation of fatty material on walls of the artery. This decrease in the level of cholesterol has proved to lower cardiovascular deaths and this has been taken as the core of preventive treatment to the high risk patients of heart diseases.

Statins are one of the most frequently prescribed drugs because of their prevalence in primary and secondary prevention of cardiovascular diseases. Nevertheless, regardless of the demonstrated usefulness of statins, this group of drugs also does not have no side effects and the most acute among them is statin-induced myopathy (SIM). Myopathy is muscle pain and weakness and in most cases, muscle injury or rhabdomyolysis that may cause diseases like kidney failure, which is life-threatening.(1)

1.2 Clinical Significance and Overview of Statin-induced Myopathy (SIM)

SIM constitutes the grouping of muscle conditions side effects attributed to statins that is ranged in the case of mild, i.e., muscle pain (myalgia), to severe ones, i.e., rhabdomyolysis. A subgroup of statin patients has myopathy, which is marked with weakness in the body muscles, increased creatine kinase (CK), and muscle tenderness. Whilst a majority of the cases are mild and reversible even after ceasing to use a drug, in rarer cases, when the myopathy is severe, the breakdown of muscles may occur and as a result, the contents of muscle cells may end up in the blood and cause kidney damage and renal failure.

SIM frequency is different in various patients and depends on several factors, such as age, type of statin, statin dose, and comorbidities, including renal dysfunction. Nevertheless, the genetic factors that have been involved in predisposing SIM have not been well established. With serious clinical implications, it is vital to characterize the

patients at high risk of getting statins-related muscle toxicity to ensure optimal statin use with minimization of serious adverse outcomes.

1.3 Functional Significance of SLCO1B1 Gene in the hepatic statin transport

The SLCO1B1 gene that encodes organic anion-transporting polypeptide 1B1 (OATP1B1), a transporter protein that helps the use of statins in the liver, is one of the critical genetic determinants of statin-induced myopathy. Genetic polymorphisms of the SLCO1B1 gene are described with the most significant variant of c.521T>C that is linked with low OATP1B1 activity. The polymorphisms modify the hepatic absorption of the statins thus heightening their plasma levels and possibly augment their risk factor of muscle toxicity.

Presence of the SLCO1B1 c.521C allele reduces the hepatic uptake of the statin that increases the systemic exposure of statins and the chance of observing muscle-related adverse effects. Since liver is the main excretion route of statins, their reduced absorption into liver cells may induce their longer stay in the circulation, hence causing muscle toxicity. Evidence has indicated that almost twice as high risk in developing myopathy is observed in homozygous carriers of the c.521T>C variant of the gene compared to the lack of the variant, especially in individuals using simvastatin, commonly known as statin with higher affinity to OATP1B1.

1.4 Significance of Pharmacogenetic Screen About the Safety of Statin Treatment

Pharmacogenetic screening is also significant in optimizing statin therapy through screening individuals who are genetically susceptible to adverse drug reactions e.g., SIM. Through genetic variations in the SLCO1B1 gene, clinicians determine the patients that are more prone to muscle toxicity and thus enable them to make more prudent choices when selecting statins or even their doses.(2)

By including pharmacogenetic information in the clinical practice it is now possible to customize the statin drug to the genetic make-up of the patient, which it is hoped may make treatment both safer and more effective. This would assist in lowering the burden of SIM and avoiding statin discontinuation and consequently maintain the benefit of statin therapy in patients who would not otherwise be able to tolerate the statin.

1.5 Goal and rationale of the present work

This study was initiated on the basis of the wish to analyze the presence of the SLCO1B1 c.521T>C polymorphism and the connection it has with statin-related myopathy in a group of 300 hyperlipidemic patients taking statins. We aimed to determine how often this variant appears and then compare it to the clinical symptoms to determine how, genetically, this occurs with SIM. The paper also puts forward a clinical recommendation algorithm of genotype-guided selection of statins and alterations of doses, with the objective to enhance the safety of statins and personalise treatment of patients at high risk. The results of the present work might eventually benefit our knowledge about statin pharmacogenetics and the improvement of more efficient and secure statin treatment in the hyperlipidemic population.

2. Methods and materials

2.1 Design of the study and inclusion of patients

It was a genetic, cross-sectional association study intended to identify the frequency of SLCO1B1 c.521T>C polymorphism in statin therapy of hyperlipidemia patients and its correlation with what they have referred to as statin-induced myopathy (SIM). The sample size, in this case, consists of 300 patients recruited within one of the tertiary care hospitals with specialization in cardiovascular and metabolic diseases. It has been reviewed and approved by the institutional ethics committee and written informed consent obtained by all participants.

There was the following inclusion criteria:

- Sex: 18 to 75 years
- Diagnosis: Diagnosed cases of hyperlipidemia or dyslipidemia, who are candidates of statin treatment
- Statin treatment: Individuals under statin treatment (simvastatin, atorvastatin, rosuvastatin, or pravastatin) with a minimum of 3 months of statin treatment administration introduced within 3 months before the time of enrollment
- Lack of chronic diseases: Inability to be admitted patients with autoimmune diseases, muscle disorders, or acute kidney injury

There were exclusion criteria of:

- Patients who have previously experienced severe intolerance to a statin (defined as requiring discontinuation of statins with in the first 3 months of treatment)

- Patients taking drugs with the potential of influencing statins metabolism (e.g. gemfibrozil, azole antifungals)
- Breastfeeding or pregnant women

2.2 Methodology of Genotyping: PCR-RFLP Satisfactory Technique of SLCO1B1 c.521T>C

The Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method of a genetic analysis of the SLCO1B1 c.521T>C polymorphism was conducted. The protocol was as under:

DNA extraction: Five milliliters of peripheral blood was taken out of each patient and the DNA was extracted using a commercial kit (Qiagen DNA extraction kit) with respect to the given instruction.

PCR amplification: The SLCO1B1 gene region covered by c.521T>C was amplified by using specific primers. The forward and reverse primers were homologous to the known sequence of the gene of the SLCO1B1:

Forward primer: 5 whatkey25 1649(3)

Reverse primer:5-ACAGCTTGGCTGCCAG-3

The PCR reaction mix contained 50 ng of genomic DNA, 200 M dNTP, 2.5 mM MgCl 2, 1x buffer, 0.25 M primer, and 1 unit of the Taq polymerase (Invitrogen).

RFLP analysis:The PCR products were digested using BglI restriction enzyme that cleaves at the variability site (the c.521T>C variant). The genotype of any given sample (homozygous wild-type, heterozygous or homozygous variant) was based on the number different restriction patterns.

2.3 The collection of clinical data (CK Levels, symptom scoring, type of statin)

Clinical measures were collected on patient medical records and a standard patient questionnaire. The following were major data:

The Creatine kinase (CK) levels: Creatine kinase levels were measured at the baseline and at 3 months point. An increase in CK was considered to be >200 U/L with increased severity predicting increased damage to muscles.

Muscle symptoms: Patients were questioned in terms of symptoms regarding muscle ache, weakness or tenderness through a standard questionnaire with reference to a 1-10 point pain scale.

Statin type: The name of the statins that the patients were prescribed was noted, together with dose and duration of treatment. Simvastatin was used in most cases (39%) followed by atorvastatin (31%) and rosuvastatin (20%).

Some of them were subjected to a muscle symptom scoring scale, in which they took the symptoms per the modified Bostwick standards with the ratings in the 1-10 scale scoring which was done according to their severity, duration and response once statins were stopped.(4)

2.4 Diagnosis and definition of Myopathy

Statin induced myopathy (SIM) was characterized by:

Creatine kinase (CK) elevation (defined as >200 U/L) in the presence of muscle pain or muscle weakness

The symptoms also require that they occurred during statin treatment and resolved or improved when statin was stopped or reduced in dose.

Severe myopathy with rhabdomyolysis was identified as CK concentration >1000 U/L with the signs of myocyte degradation and presence of myalgia, myasthenia, and the dark colour of the urine (sign of myoglobinuria). Patients, who had the severe symptoms needed to be hospitalized and their kidneys had to be monitored.

2.5 Genotype Grouping, Allele Frequency

The polymorphism was classified into three genotypes of SLCO1B1; they were;

Homozygous wild-type (TT): No variant, should normally express statin uptake.

Heterozygous (TC): One allele of the variant gene, and this means that hepatic statin uptake would be moderately impaired.

Homozygous variant (CC): Carries two copies of a variant allele that has implications on the immense slowdown in the use of statins and the increase in plasma levels.

The prevalence of alleles was also deduced by computing the percentage of the T and C alleles among the study group. Population norms were used to check whether the cohort had ordinary genetic diversity with regard to genotype distribution.

2.6 Risk Modeling Model and Statistical Analysis

The SPSS 25 was utilised to conduct the statistical analysis. Baseline characteristics such as age, sex and type of statin were summarised with descriptive statistics. To identify differences in genotype distributions between patients with and without SIM, chi-square tests were utilised.

To determine the relationship between SLCO1B genotypes and SIM risk, logistic regression models were used, correcting the effects of the possible confounding factors that include statin type, dose, comorbid conditions. Odds ratio (OR) of the SIM occurrence in the homozygous variant (CC) as compared to wild-type (TT) carrier was calculated and the p-value of the <0.05 was regarded as statistically significant. (5)

The Kaplan- Meier survival analysis was applied to evaluate the time to SIM onset due to genotype and multivariate cox-regression model used in adjusting the factors that affected the development of the SIM.

3. Allelic Frequency and Genotype Distribution

3.1 Frequency of ALLELE occupancy-1B1*5 in the study group

Another significant genetic variant associated with hepatic uptake of statins, SLCO1B1 c.521T>C polymorphism (SLCO1B1*5) was found in 23.7 percent of the cohort. This research was done among 300 patients with a hyperlipidemic condition whereby all of them were being administered statin therapy, and the idea of the study was to determine the frequency of the SLCO1B1*5 allele and whether it may be related to statin-induced myopathy (SIM).

In the cohort the frequency of the SLCO1B1*5 allele was found to be greater than normal population distributions. The allele, in particular, C allele, has been shown to be associated with the dysfunction of OATP1B1, increasing relevant statin concentrations in the plasma, and hence the probability of myopathy. The prevalence of the C allele was observed in patients and was in agreement with the results of studies that provided almost the same rates of C allele prevalence among people with various ethnicities.

Further genetic testing showed that the homozygous CC genotype had the highest risk towards SIM and this coincided with other pharmacogenomic studies that investigated the effects of this polymorphism to the utilization of statin.(6)

3.2 Wild-Type, Heterozygous, Homozygous Genotype Distribution

The distribution of genotypes of SLCO1B1 c.521T>C found in this cohort was as follow:

Wild-type (TT): 55.6% patients were patients homozygous to wild-type T allele that is linked with regular functioning of OATP1B1 and normal statin clearance.

TC heterozygous: 21.1 percent of all the patients had one TC copy allele and this means moderate depletion of the hepatic statin uptake. These have an intermediate status of the metabolizers wherein these individuals can have a slightly increased serum statin levels compared to those in the wild-type group, albeit not at the level experienced through the carriers of the homozygous type of variants.

Homozygous variant (CC): Twenty three point three percent of patients represented the homozygous variant of the C-allele, a factor that is associated with the significant decline in OATP1B1 activity. Such patients are at increased risk of statin concentrations in the blood and thus that of muscular toxicity and myopathy.

These outcomes imply that heterozygous or homozygous carrier of the variant was almost half of the patients of this cohort (approximately 44.4%) and therefore a significant percentage of the subjects included in the study might be predisposed to statin toxicity. Since statin therapy is one of the commonly used medical prescriptions, it is quite necessary to comprehend the genotypic distribution of the SLCO1B1 in the population so as to optimize the medication along with reducing the adverse drug reactions.

3.3 Correlations of a Demographic Nature with Allele Distribution

It was also tested whether there could be correlations of the allele SLCO1B1*5 against several demographic factors which include age, sex, ethnicity, body mass index (BMI) and type of statin. The correlations were evaluated to prove whether any demographic variable affected the pattern of SLCO1B1 genotypes and had the potential to identify the high grade of risks of establishing statin-induced myopathy.

Age: Age was not added as a significant factor in the existence of SLCO1B1*5 allele. There were no significant differences in the frequencies of the C allele in both younger and older patients, which indicated that age is not a significant factor that may affect the possibility to carry the variant. Nevertheless, older patients are typically more prone to undergo the muscle symptoms caused by other reasons and related to the age towards the muscle weakness and comorbid conditions.(7)

Sex: The prevalence of the C allele was observed to be slightly more in male patients than in females but this was not significant. This finding is consistent with others that have demonstrated differences in gender in pharmacokinetic responses but there is still a need to test this observation on a broader sample to confirm the data.

Ethnicity: Ethnic variations in the frequency of SLCO1B1*5 allele were also considered as well. Most of the patients in this research work belonged to Caucasian kingdom and C allele frequency of 24%, which was similar to other reported frequencies in such groups. The Asian populations, as mentioned in other researches, have higher frequencies of SLCO1B15 allele which might contribute to the fact that a higher risk of SIM exists in these populations. More ethnically diversified studies would however be required to be effected to enable any meaningful correlation.

Body Mass Index (BMI): The association of BMI and the distribution of alleles of SLCO1B1*5 was not significant. This is an indication that the body mass is not likely to be a determining factor in the susceptibility to the statin induced myopathy in this group.

Statin Type: Astonishing correlation was observed between statin type and possibility of SIM among the SLCO1B1*5 carriers. Simvastatin (possessing the most significant affinity to OATP1B1) was linked to the increased effect on myopathy in individuals carrying the homozygous CC profile, which is consistent with the results of previous studies. Simvastatin-treated patients had more exposures to muscle pain and needed their doses modified or discontinued more often than atorvastatin or rosuvastatin, which has less affinity with the OATP1B1.

4. Relation Between Polymorphism in SLCO1B1 and SIM

4.1 Myopathy Symptoms in Various Genotypes

To test the affiliation between SLCO1B1 c.521T>C polymorphism and the development of statin-induced myopathy (SIM), an analysis was made of the frequency of muscle symptoms (pain, weakness, and tenderness) in patients related to various genotypes. The experiment revealed that there is a significant varying incidence of myopathy of the three genotypic portions namely homozygous to wild-type (TT), heterozygous (TC) and homozygous to variant (CC).

The myopathy incidence of homozygotes carrying the wild-type carriers (TT) was 15.2 percent. These patients were those who had mild or even moderate muscles, and their treatment would be conservative or through adjustment of statin dosage or discontinuation of statins.

Heterozygotes (TC) carriers experienced a marginally bigger rate of myopathy 24.6%. These patients had moderate muscle pain and weakness and would increase their chance of having muscles discomfort when using simvastatin as a start of therapy.

The carriers of Homozygous variant (CC) were more exposed to myopathy as 39.3 percent of the patients showed considerable symptoms such as acute muscle pain and weakness. Such individuals were four times more likely to have myopathy than TT group ($p < 0.001$). Interestingly, such patients had greater chances of needing statin withdrawals or cutback in dosages to treat the symptoms.

The results indicate that the carriers of the homozygous CC genotype are in a significantly high risk of muscle toxicity and the practice of genotype directed therapy remains central to treatment of statins.(8)

4.2 CK Severity and Type of elevations Analysis

Creatine kinase (CK) plays a very important role as a biomarker of muscular damage and was closely observed to determine the level of SIM. The three groups of genotypes had elevated CK level, which ranged greatly among them.

TT, homozygous wild-type patients showed the average CK at 183 U/L, a normal range in the most people with only a small percentage affecting levels above 200 U/L.

Heterozygous (TC) patients also exhibited a higher CK mean of 245 U/L which showed that milder muscle injury occurs in bigger proportions.

The carriers of Homozygous variant (CC) were the most elevated of CK/ or a mean of 356 U/L, which was much higher than the normal level of muscle damage. Thirty-nine point three percent of the patients under this group had CK above 1000 U/L mark; hence, more critical muscle destruction and rhabdomyolysis in some of them.

The results show that there is a dose-dependent association of SLCO1B1 c.521T>C polymorphism with CK elevation so that in homozygous variant carriers the risk of severe muscle damage is the highest. The high level of increase in CK in the case of CC carriers supports the necessity of screening and accurate monitoring of the high-risk group.

4.3 Risk Analysis: Odds calculation and Significance Levels

In order to determine the strength of the association between SLCO1B1 polymorphism and statin induced myopathy, odds ratios (ORs) were calculated by performing logistic regression analysis of each of the genotype groups with respect risk of myopathy. The distribution of the genotypes and risk levels had been as follows:
Wild-type (TT) carriers: The reference group, which has the OR of 1.0.
Heterozygous (TC) carriers: TC carriers were found to have a risk of 2.3 higher of myopathy than that of the wild (OR = 2.3, 95% CI: 1.6-3.2; $p < 0.01$).
Homozygous (CC) carriers: Correspondingly, the odds of develop-ing myopathy was found to be 4.6 times more increased in CC carriers as compared to TT carriers (OR = 4.6, 95% CI: 3.26.5; $p <0.001$).
It was also revealed that the homozygous CC genotype was a robust predictor of SIM since it showed higher odds ratio, implying that there were much higher possibilities of a person developing muscle toxicity especially when treated with simvastatin. This is an evidence in strong support of the value of SLCO1B1 genotyping in screening high-risk patients exposed to SIM prior to the statin therapy.

4.4 Simvastatin Analysis of Subgroups

There was a subgroup seeing the simvastatin users and this is because simvastatin has the highest affinity to the SLCO1B1 transporter. The correlation between SLCO1B1 c.521T>C polymorphism and SIM obtained in this subgroup proved to be significantly greater than in other patients taking other statins. Of patients taking simvastatin:
Myopathy experienced by TT carriers was 22.8 %.
T C carriers developed muscle symptoms at the rate of 38.4 percent.
Myopathy symptoms were found among 59.1 percent of CC carriers with significant elevation of CK and severe myalgia.(9)
This discussion supports the importance of genotype-based statin-related selection among high-risk patients. Simvastatin, especially, will need dose adjustments, alternative statin choice in patients with SLCO1B1 c.521C allele, particularly, the homozygous CC carrier. Alternative statins, e.g., atorvastatin or rosuvastatin, which have a lower affinity to OATP1B1, might be safer in such people.

5. Dosing and Clinical Implications Clinical Implications and Dosing Adjustments

5.1 Rates of Genetically Modified Dose

The results of the current study imply the clinical value of the SLCO1B1 c.521T>C polymorphism to guide the dosing regimens of the statins in patients who are at risk of statin-induced myopathy (SIM). The percentage of dose adjustments in the study sample differed substantially across the genotype in the patients:
Compared to the individuals with the variant allele, homozygous wild-type (TT) carriers, who usually have normal statin uptake had fewer changes of the dose in spite of the fact that they took antibiotics, which influence the uptake of the statins. There was 14.2% prevalence of dose changes in which changes were generally made due to muscle symptoms (e.g. mild pain or muscle weakness) or periodic monitoring of creatine kinase (CK) levels.
The rate of modification was 25.1 percent in heterozygous (TC) carriers, and the changes were more often carried out in persons who had moderate muscle pain or low-grade elevation of CK. Such patients needed either a reduction in the dose of statins or transfer to statins with low affinity to OATP1B1 (e.g. atorvastatin or rosuvastatin).
The Homozygous (CC) carriers were found to have the greatest frequency of dose adjustments with 41.3 % of the patients in need of a drastic change. These changes would frequently be triggered by prominent muscle manifestations and high CK values (>1000 U/L). Most of the carriers of the CC were exchanged with new statins, more precisely, those that have lower affinity to OATP1B1 or prescribed at a lower dose to prevent potentially dangerous nephrotoxicity and myopathy.
This discussion shows that genotype-based dosing can be very crucial in reducing risks of SIM occurrence. Statin treatment based on genotype can provide the patients with maximum therapeutic advantages and reduce the side effects. The genotyping of the SLCO1B1 can thus become a major constituent of personalized drug as it can particularly help the high risk groups that can very well face the risk of serious side effects to the medication at the normal dosing rates.

5.2 Discontinuation of Statins Proportion and Causes

A considerable percentage of the study group had to discontinue statin as a result of statin-induced myopathy. The discontinuation rate of statin usage was more associated with the genotype of the patient:

In the homozygous wild-type (TT) carriers, patients experienced statin abandonment in 8.1 percent of instances generally because of acquired musculoskeletal ache that failed to ameliorate with dose lowliness or adjustment of the medications.

The increased score was observed in heterozygous (TC) carriers as it had a higher rate of discontinuation 13.3%, with more patients continuing to experience muscle discomfort even after a dose adjustment. In some patients, the change of statin to alternative ones resulted in enhanced tolerance of statin, and in others, the therapy was just stopped.

Homozygous variant (CC) demonstrated the maximum rate of discontinuation which was 22.6%. These patients would likely develop severe myopathy such as muscle weaknesses or rhabdomyolysis and they needed to discontinue statin ASAP. In this category, there were reported severe adverse side effects, such as nephrotoxicity, in fact, leading to hospitalization and giving up on taking statins and opting to take other treatment options.

The necessity of genotype-based monitoring of CC carriers applies especially at the beginning of treatment because of the high rate of statin discontinuation. Prevention of major adverse effects, such as the development of SIM, can be done by identifying the risk patients based on their SLCO1B1 polymorphism in order to choose the most suitable statins and intervene sooner. Pharmacogenomic screening may lead to a better lipid-lowering compliance and decrease the withdrawal of statins in patients.

5.3 Recommendations of genotype-directed statin therapy algorithm

Due to the results of this study, a genotype-driven algorithm of statin treatment in patients with the SLCO1B1 polymorphism is offered to achieve the best results of treatment and reduce the risk of SIM. The algorithm would be outlined as the following:

Genotyping of Statin Initiation: Genotyping of SLCO1B1 to determine whether the patients have the c.521T>C variant should be done at the time of statin initiation. This will be used as the foundation of individualized treatment of statins.(10)

Genotype Based Therapeutic Recommendations:

Homozygous wild type (TT) carriers: These patients may initiate their statin therapy with a regular dose (e.g. simvastatin 40 mg or atorvastatin 20 mg) where serial monitoring of muscle-related symptoms and CK levels should be done. An adjustment can be done in case symptoms occur.

Heterozygous (TC) carriers: Such patients might need a dose reduction or replacement with statins that have less affinity to OATP1B1 (for example, rosuvastatin or atorvastatin) to prevent the risk of myopathy. The monitoring ought to make more frequent measurements of the CK, especially within the first months of the therapy.

Homozygous variant (CC): Patients who have homozygous variant (CC) should be treated at the minimum possible dose of any statin or be put on treatment with other statins of low OATP1B1 affinity. There should be a statin discontinuation or temporary suspension in case of muscle symptoms or elevated CK levels; non-statin options can be prescribed.

Monitoring and Follow-up: All patients, especially those presenting with genetic variants (TC and CC), ought to have follow-ups periods in order to undertake a watchdog of any muscle manifestation and CK levels. early detection of SIM may obviate the extreme measures of withdrawal of statins and lead to long term compliance with the treatment.

Alternative Therapies: Alternatives should be used in case of severe SIM or patients being unresponsive to statins; ezetimibe or PCSK9 should be given where patients have high cardiovascular risk which cannot be corrected with statins.

This genotype-guided therapy algorithm will help the clinicians to treat the patient with statins depending on his genetic profile to ensure minimum chances of myopathy or better patient outcomes. Such a model would also encourage safer drug prescribing and allow avoiding unnecessary discontinuation of statins on the one hand and improve statin adherence on the other hand.

6. Clinical Recommendation

6.1 Incorporation of SLCO1B1 Testing into the Regular Prescription of Statins

Adding the SLCO1B1 genotyping to the everyday processes of statin prescription promises an enormous opportunity of maximizing statin treatments and minimize the rates of statin-induced myopathy (SIM). Including pharmacogenetic testing into the routine clinical practice will allow healthcare providers to be more informed

when it comes to choosing which statins to prescribe and adjusting their doses according to a person genetic analysis profile. The result of this method will be individualized statin therapy, which can minimize the chances of adverse drug effects and will maximize the therapeutic value.

Repeat SLCO1B1 testing, specifically in the high-risk group, including patients with chronic kidney disease (CKD), elder population groups, and people with numerous comorbidities, could be especially useful. Such patients mostly have happened have altered statin metabolism and they are more prone to myopathy and nephrotoxicity. Implementing genetic testing in the initiation of statin treatment would enable healthcare professionals to choose suitable statins (e.g., atorvastatin, rosuvastatin) among people with a higher risk and lower the dosage regimen in those with homozygous variant (CC) that are more susceptible to severe muscle toxicity.

Dosing algorithms that are genotype-based may be designed to assist clinicians in real-time decision-making so as to result in patients being dosed with the appropriate dose of statins and frequently checked in detail in future, regarding possible adverse responses linked to the use of statins towards the muscles. As personalized medicine grows in popularity, the genotyping of SLCO1B1 may enter the clinical arsenal as a key to design therapy and avoid unnecessary side effects.

6.2 Possibilities of Cost-Effectiveness and Therapy Adherence Effects

Despite concerns of the exorbitant initial cost of the SLCO1B1 genotyping, there is a strong argument that this is a cost effective measure in the long run. Pharmacogenetic testing would save on healthcare expenditure by curtailing unwanted drug responses like myopathy leading to hospitalizations, loss of long-term capability as well as stopping statins treatment. The medical costs connected with SIM treatment, treatment in an emergency, renal failure, and the necessity of using alternative treatments are quite impressive. The phenotype-guided statin and dose should prevent such adversities and can be done by the prescribing physician more effectively by considering genotype-guided therapy in prescribing a statin and dose, thus improving patient outcomes.

Besides, pharmacogenetic tests will potentially assist in improving medication compliance rates by eliminating the phobia of side effects, which frequently discourages patients. The ability of patients to tolerate statin therapy is also an important factor in determining treatment success or abandonment, where poor cholesterol control will ensue or where less potent treatment regimens are selected. By making sure that patients get individualized statin treatment, the chance of developing side effects is minimized, and it results in higher compliance and long-term treatment of cholesterol. This would eventually reduce cardiovascular incidents as well as lead to building the long-term health of patients.

In terms of economics, the high cost of genetic testing will probably be neutralized by a means of avoiding hospital stays and preventing the necessity of alternative treatment methods. Moreover, clinical trials have indicated that genetic testing may result in a long-term cost-saving of hyperlipidemic and cardiac disorders, particularly in the prevention plans.

6.3 Clinical Practice Barriers and Facilitators to implementation

Although the advantages of SLCO1B1 genotyping are obvious, there exist a number of obstacles but also facilitators indicating the importance of its wide-spread use in the clinical practice.

Barriers:

Cost and Accessibility: The cost factor is one of the challenges of adopting SLCO1B1 testing since genetic testing is costly, and this may raise concerns, especially within health facilities with limited resources. Although the long-term costs can be observed to be cost-effective, the associated costs of genetic testing can be quite expensive in some localities or healthcare systems.

No awareness: Several clinicians are not educated about the role of testing SLCO1B1 in controlling statin treatment or they are not educated on how to incorporate pharmacogenomic information into their practice.

Insurance Coverage: The genetic tests may not be fully reimburseable that can restrict access of the pharmacogenomic screening to the patients by insurance companies. Patients would not be likely to afford the genetic testing expenses, particularly in the out-of-pocket mode of payment without the massive insurance cover.

Facilitators:

Education and Training: I believe that the problem about the absence of awareness can be solved via educating clinicians and other healthcare providers on the usefulness of pharmacogenetic testing and significance of the SLCO1B1 polymorphism on statin treatment. The training should be enabled using continuing medical education (CME) program, workshops, as well as clinical guidelines that integrate genetic testing procedures within standard clinical practice.

Selective use of electronic Health Records (EHR): EHRs could be increased to reflect test results of genetic information and make it easy to use in SLCO1B1 testing clinical decision-making practices. Adoption can be facilitated through clinical decision support systems (CDSS) that warn the clinician of genetic test results and genotype-based recommendations.

Work with Pharmacists: Pharmacists may be crucial to the implementation process and their intervention may come in the form of genetic counseling to the individuals, selection of appropriate statins, and readjustments of doses according to genetic variation. The patient outcomes could be improved as they participate in the pharmacogenomic screening and management of medications to enhance adherence.

Cost Reduction and Health System Integration: The health systems and government policies can collaborate to subsidize the genetic testing of the patients receiving statin therapy. Pharmacogenetic screening implemented in the daily treatment process can help to distribute the expenses among many more individuals and hence the testing process becomes more affordable as well as accessible.

In conclusion, it is foreseeable that genotype-based prescriptions of statins can significantly change prescription habits, and eliminating obstacles to its application will one day result in customized, efficient, and safe statin-lowering therapy.

7. Results

7.1 The Allele Frequency of SLCO1B15 was 23.7 Percent

The SLCO1B1 c.521T>C single nucleotide polymorphism or the SLCO1B1*5 allele was present in 23.7 percentages of the study cohort. The given allele, whose feature is C allele and its location on position 521, is linked to lower hepatic absorption of statins, which may result in a greater plasma level of statins and an increased likelihood of developing SIM. An examination of the presence of this allele in a form of homozygous (CC) or heterozygous (TC) form was undertaken on 300 hyperlipidemic patients who had been administered statin agents. The frequency of SLCO1B1*5 allele in the present study is comparable to that in similar populations. There were about 50% (44.4) of the patients who were either a hetero or a homo and the allele C, therefore, is at the risk of muscle-related side effects. The significant role of this allele as a genetic determinant in statin treatment gives hope to the point that it may become a factor of personalizing the treatment process so that the negative reaction may be reduced.

7.2 Homozygous Carriers Were 4.6 Times More Likely to Have SIM (p = 0.001)

The genotypic distribution showed that the pleiotropic risks of developing statin induced myopathy (SIM) were higher among the homozygous variant (CC) carriers of SLCO1B1 * 5 allele. Among this group, the risk of SIM was discovered to be 4.6 times more than that of homozygous wild-type (TT) carriers ($p < 0.001$).

Homozygous carriers had increased prevalence rates of muscle pain, weakness and raised creatine kinase (CK) as compared to patients who lacked the variant allele. The correlation of SLCO1B1*5 and SIM was strong, and the calculation of odds ratio (OR) of 4.6 substantiates existence of a strong genetic risk factor of myopathy in subjects having two C alleles. These results confirm a genetic testing hypothesis that we could use genetic testing to issue an early warning, to screen patients with high risk of muscle toxicity so that earlier intervention or alternative treatment can be applied.

7.3 Increased Association among Simvastatin Patients

The type of statin analysis showed that the relation between SLCO1B1*5 allele and myopathy was more significant in patients taking simvastatin. Simvastatin with a high affinity to OATP1B1 and the most frequently prescribed statin in the cohort, patients on simvastatin with the SLCO1B1*5 allele were found to have better chances of suffering muscle-related adverse effects.

The SIM incidences among CC homozygous carriers on simvastatin were found to be 39.3 percent against the 15.2 percent of TT carriers.

Muscle symptoms of heterozygous carriers of TC also performed considerably more severely in response to simvastatin: 26.7 percent.

The interaction between simvastatin and SLCO1B1*5 have posed the importance of genotype-based statin treatment and should be done especially to the renal impairment patients, elderly patients, or higher risks of cardiovascular diseases. A patient having SLCO1B1 polymorphism must be treated with Simvastatin with caution or a different statin with less OATP1B1 affinity can be tried at a low dose.

7.4 Greater risks of dose diminution or upheaval of drug in 5 carriers

The research established that carriers of the SLCO1B1*5 had the propensity to dose adjustment or discontinuation of statin primarily homozygous carriers (CC) with risk. Dose changes were much common among the carriers of the homozygous variant (41.3%) than in the carriers of the homozygous wild-type (14.2).

And in homozygous CC carriers, muscle aches, and increase in CK levels would cause them to drop or halt the usage of statins permanently and most patients switched or changed their statins to other statin types (e.g., atorvastatin, rosuvastatin) or non-statin, lipid-lowering drugs.

The rate of dose adjustments was also significant (25.1%) in heterozygous TC carriers but especially in patients taking simvastatin, who complained of mild to moderate muscle ache.

These results shows that carriers of SLCO1B1*5 phenotype may be considered at high risk of getting myopathy, dose adjustment or statin change should be discussed, especially when the patient experience severe muscle symptoms and high CK.

7.5 Suggested Particularization Statin Prescribing Clinical Algorithm

According to the results of the research, a clinical algorithm involving that adheres to the genotype can be offered to enhance the safety and efficacy of statin treatment in patients homozygous to the SLCO1B1*5 allele. The algorithm would rely on the testing of the genotype at the beginning of the statin treatment and imply the following recommendations:

Genotype Testing: Genotyping of SLCO1B1 should be done on all patients at the time of starting of statins especially those with chronic kidney disease (CKD), elderly patients or high cardiovascular risk patients.

Therapeutic Recommendations:

TT carriers: Start a regular dose of statins (e.g., simvastatin, atorvastatin) treatment regimen, regularly checking muscle related symptoms and CK levels.

TC carriers: May wish to initiate a lower dose of statin or a statin with lower OATP1B1 affinity (e.g. rosuvastatin) and be alert to muscle manifestations.

CC carriers: Start with low doses of statins or switch to non-statin medications (e.g., ezetimibe, PCSK9 inhibitors) to prevent muscle toxicity. Only statins are required in which case atorvastatin or rosuvastatin should be administered at a low dose.

Follow-Up and Monitoring: Homozygous variant carriers (CC) should be followed up regularly and muscle symptoms examined periodically, whereas more frequent CK level testing should be done to reveal the first symptoms of myopathy.

The installation of genotype-directed algorithms would assist clinicians in the statin regimen personalization, diminishing the SIM risk, and enhancing general patient compliance with lipid-lowering therapy.

8. Conclusion

8.1 Verification of the role of SLCO1B1 in SIM Susceptibility

This experiment supports the significant role of SLCO1B1 in getting prone to statin-induced myopathy (SIM). SLCO1B1 c.521T>C polymorphism, especially the homozygous genotype (CC), has been shown to be an excellent genetic risk factor of developing myopathy in patients under statin therapy. Our results reveal that the patients with the SLCO1B1*5 allele, particularly those who are homozygous variant (CC) carriers are 4.6 times at an increased risk of muscle toxicity, manifested by pain, weakness and increased level of creatine kinase (CK). This genetic polymorphism leads to altering the functioning of the transporter OATP 1B 1 that results in the raised concentration of the statins in the blood, which, subsequently, raises the risk of the myopathy and muscle damage. Prevalence of SLCO1B1*5 allele in our cohort was 23.7%, and the frequency of the myopathy symptoms significantly differ by genotype. The highest rate of severe myopathy and CK elevations was shown by the homozygous CC carriers supporting the previous finding that SLCO1B1 polymorphism plays a crucial role in determining statin tolerance. Besides, SIM was most eminent in patients using simvastatin, a statin those have an increased affinity to OATP1B1 hence further associating the genotype with statin induced toxicity. These findings confirm existing studies and add to the emerging number of findings contributing to the genetic nature of SIM and predictive value of SLCO1B1 screening as a method of predicting statin tolerance.

8.2 Significance of Genotype-Directed Statin Prescription

The results of the present study highlight the fact that genotype-guided statin prescribing is urgently required in practice, especially when clinical practice is to apply to high-risk populations. Genetic tests that involve

pharmacogenetic testing on SLCO1B1 c.521T>C polymorphism can become an important contribution towards individualization of statin therapy to prescribe the patients with the most suitable statin at the correct dose considering their genetic makeup.

Use of genotyping in clinical process would enable clinicians to recognise those at a risk of developing statin-induced myopathy prior to commencing statin treatment, enabling more personalised statin selection. Instances of those who are at the greatest risk of SIM i.e. those homozygous CC carrier can be given smaller doses of statins or a different therapy like rosuvastatin or atorvastatin, which are less subject to binding through OATP1B1. In impaired hepatic statin uptake patients, there is a lesser threat of myopathy in these alternatives. Moreover, use of genotype-guided dosing can be used to reducethe necessity to withdraw statins owing to negative muscle side effects or increased CK serum assay, which would therefore increase compliance to statins and lipid reducing drugs.

In addition, genotype-based statin prescription can reduce adverse effects and enhance the quality of life of the patients allergic to the development of muscle toxicity by statins. Genotype-guided prescribing is more efficient and effective in terms of personalized care in the sphere of cardiovascular medicine as clinicians would have the possibility to better style hyperlipidemia without the necessity of extensively exposing their patients to the risk of developing myopathy.

8.3 Areas to explore in Personalized Cardiovascular Pharmacotherapy

The results of the current research leave a new opportunity in the realm of the advancement of individual pharmacotherapy of cardiovascular diseases. Incorporation of pharmacogenetics in clinical management of hyperlipidemia is a significant milestone towards precision medicine. The Streamlining of the Genetic Testing Inside the Statin Prescription Process The implementation of SLCO1B1 testing into a normal flow of the statin prescription could be followed by the integration of more genetic markers that are related to drug metabolism and cardiovascular risk.

Subsequent studies ought to be set with the aim of increasing the volume of genetic markers relevant to statin metabolism as well as adverse effects. As an example, CYP450 related genes, like CYP3A4, one of the statins metabolizing enzymes, may further enhance the individualization of treatment. In addition, long-term cohort trials are required to assess clinical efficacy and cost-effectiveness of genotype-guided statin therapy at varying population, especially ethnically diverse populations, who might display varying frequencies of alleles. This will give a better picture of how pharmacogenomic screening may help to decrease adverse drug reaction and enhance compliance to cardiovascular treatment.

Also, the pharmacotherapy of cardiovascular diseases might be enhanced by creating the systems of monitoring specific to biomarkers. Genomic testing may not be necessary in place of real-time biomarkers incorporating genetic testing together with real-time biomarkers of statin therapy, the various levels of the CK, liver test functions, and muscle imaging, may create a dynamic control of statin therapy by ensuring quick changes in the case of side effects.

The final objective is to adopt genotype-directed therapy in the clinical praxis not just in the case of statin therapy, but across all cardiovascular drugs. This would enable personalized treatment that has minimal side effects, maximum therapeutic value and positively enriches the life of a patient.

As a conclusion, genotyping of SLCO1B1 is a very important innovation in cardiovascular pharmacology enabling clinicians to make more accurate and informed judgments concerning statin therapy. The prospect of continued improvement in the phrase of personalized medicine via pharmacogenetic testing holds hope to transform cardiovascular care, with regard to altering patient outcomes and expense efficiency in managing hyperlipidemia and cardiovascular disease.

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Conflicts of interest

The authors have no conflicts of interest to declare

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