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ANALYSIS OF EFFECT OF STATINS ON BLOOD GLUCOSE LEVELS AND LIPID PROFILE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Introduction: Statins, by inhibiting cholesterol synthesis, may cause an accumulation of acetyl-CoA in hepatocytes, leading to its diversion towards ketogenesis. Ketone bodies can serve as an alternative energy source, potentially sparing blood glucose and contributing to hyperglycemia. This study aimed to evaluate the impact of Atorvastatin therapy on blood ketone levels, glycemic control and lipd profile in patients with Type 2 Diabetes Mellitus (T2DM).

Methods: The study included 45 individuals with T2DM who had not previously used statins. They were prescribed Atorvastatin tablets at a daily dose of 10 mg before bedtime, while their ongoing anti-diabetic medications remained unchanged. Measurements of blood ketones, urine ketones, fasting plasma glucose (FPG), post-prandial plasma glucose (PPG), glycated hemoglobin (HbA1c), and lipid parameters were conducted at baseline and after three months of Atorvastatin therapy.

Results: After three months of Atorvastatin therapy, there was a moderate yet significant increase in blood ketones, FPG, and PPG. Concurrently, there was a significant reduction in serum total cholesterol and low-density lipoprotein cholesterol levels.

Conclusion: A three-month therapy with Atorvastatin at a dose of 10 mg daily at bedtime among patients with T2DM led to a moderate increase in blood ketone levels, FPG, and PPG, alongside improvements in lipid parameters.

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Keywords: Statins, Glycated hemoglobin (HbA1c), Lipid profile. Ketone bodies.

INTRODUCTION

Dyslipidemia represents a significant cardiovascular risk factor among individuals with type 2 diabetes mellitus (T2DM). The alterations in lipid parameters in T2DM stem from elevated plasma levels of free fatty acids primarily resulting from insulin resistance. Statins stand as the most commonly prescribed drugs for lowering lipids in T2DM patients. Various clinical trials have substantiated the effectiveness and safety of statins in mitigating fatal and non-fatal coronary heart disease incidents. Nevertheless, statins have been associated with an increased risk of diabetes development and exacerbation of glycemic control in existing diabetes cases. The mechanisms behind statin-induced hyperglycemia involve increased insulin resistance or impaired insulin secretion [1-5]. However, the precise mechanism driving statin-induced dysglycemia remains unclear.

Statins structurally resemble 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) and function as competitive inhibitors of HMG-CoA reductase, a key enzyme in the early cholesterol biosynthetic pathway [6]. Inhibiting HMG-CoA reductase results in the accumulation of precursor substrates like acetyl coenzyme A (acetyl-CoA), which could be redirected for ketone body synthesis. Our hypothesis posits that statin therapy enhances ketogenesis within hepatocyte mitochondria. These ketones may serve as an energy source, thereby preserving blood glucose levels and leading to hyperglycemia. Acetoacetate and β-hydroxybutyrate are the primary circulating ketone bodies, with acetone being the least abundant. Typically, ketone body levels are low during an overnight fast (approximately 0.1–0.5 mmol/L). However, in hyperglycemic crises such as diabetic ketoacidosis, ketone body levels are markedly elevated (usually exceeding 3 mmol/L) [7,8].

The impact of statin therapy on blood ketone levels holds clinical significance, especially since T2DM patients commonly receive statins for managing dyslipidemia. This study aims to evaluate the effects of Atorvastatin on blood ketone levels, glycemic control and lipid profile in T2DM patients.

MATERIALS AND METHODS

The study was conducted in India at a tertiary care medical college and hospital. The study enrolled 45 patients aged between 30 and 80 years with T2DM who were not using statins. Patients requiring changes in anti-diabetic medications, pregnant individuals, and those using corticosteroids or immunosuppressive drugs were excluded.

The patients were prescribed Atorvastatin tablets at a daily dose of 10 mg at bedtime for a duration of three months. These patients were deemed appropriate for statin therapy as per the guidelines of the American Diabetes Association [9]. Biochemical assessments were conducted

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twice during the study: at the initiation of statin therapy and at the end of three months of Atorvastatin treatment. These assessments included blood and urine ketone levels, fasting plasma glucose (FPG), 2-hour postprandial plasma glucose (PPG), glycated hemoglobin (HbA1c), serum total cholesterol, serum triglycerides, serum low-density lipoprotein cholesterol (LDL-C), and serum high-density lipoprotein cholesterol (HDL-C). Samples for these tests were collected after an overnight fast, and there were no changes made to the anti-diabetic medications throughout the study period. Patient compliance was monitored through telephonic conversations.

Biochemical analyses were conducted using standard methods in laboratory. Blood ketones were measured using the ketometer. Urinary ketones were qualitatively assessed manually using Rothera's method [10]. FPG, PPG, HbA1c, and lipid parameters were analyzed using appropriate methods on automated analyzers. Data management and statistical analysis were performed using IBM SPSS 21, with paired sample t-tests used to compare parameters at baseline and after three months of Atorvastatin therapy, considering p-values less than 0.05 as significant.

RESULTS

The research involved 45 participants who met the specified criteria, comprising 26 males and 19 females, with a mean age of 54.89 ± 12.26 years. The body mass index (BMI) of these participants was 23.56 ± 3.65 kg/m2, and 58.3% (14 subjects) were classified as overweight-obese (BMI ≥ 23.0 kg/m2) using the World Health Organization's Asia-specific thresholds [11]. Tables 1-3 provide details on the baseline and 3-month biochemical parameters of the participants after initiating Atorvastatin.

Following three months of Atorvastatin therapy, there was a notable increase in fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG). While the mean glycated hemoglobin (HbA1c) was higher at three months compared to baseline, this difference was not statistically significant.

Serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) exhibited significant reductions at the three-month mark. However, there were no significant changes observed in serum high-density lipoprotein cholesterol (HDL-C) or serum triglyceride levels with Atorvastatin therapy.

Blood ketone levels notably increased from baseline to three months after commencing Atorvastatin therapy. Both males and females showed a comparable rise in blood ketones during this period, although the increase was modest. Importantly, none of the patients experienced hyperketonemia, defined as blood ketone levels exceeding 1 mmol/L [12]. Furthermore, all urine samples tested negative for urinary ketones both at baseline and after three months of Atorvastatin therapy.

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Table 1: Effect of Atorvastatin on blood glucose levels

Parameter	At Baseline	3 months after Atorvastatin	p-value
FPG (mg/dL)	131.2 ±16.72	145.8 ±20.65	<0.05
2-h PPG (mg/dL)	190.2 ±34.87	213.2 ±46.63	<0.05
HbA1c (%)	7.1 ±0.91	7.5 ±1.01	0.47
HbA1c (IFCC mmol/mol)	55.8 ±9.93	57.2 ±10.97	0.86

Table 2: Effect of Atorvastatin on serum lipid parameters

Serum Parameter	At Baseline	3 months after Atorvastatin	p-value
TC (mg/dL)	203.5 ±24.37	160.4 ±40.65	<0.05
TG (mg/dL)	216.2 ±181.59	179.5 ±143.68	0.10
HDL-C (mg/dL)	46.5 ±10.23	42.59 ±7.81	0.12
LDL-C (mg/dL)	121.9 ±18.65	86.2 ±23.79	<0.05

Table 1: Effect of Atorvastatin on ketone levels

Parameter	At Baseline	3 months after Atorvastatin	p-value
Blood ketones (mmol/L)	0.14 ±0.07	0.28 ±0.06	<0.05

DISCUSSION

Statins are frequently prescribed to lower cardiovascular risk in patients with T2DM. However, research has also revealed the potential for statin therapy to induce hyperglycemia [1,2,4]. Statins work by inhibiting the enzyme HMG-CoA reductase in the cholesterol synthesis pathway, leading to the accumulation of precursor molecules before this step. Our hypothesis suggests that this accumulation of precursors may trigger increased ketone synthesis. These ketones could serve as an alternative energy source for cells, sparing blood glucose and resulting in hyperglycemia.

Our study involved 45 statin-naïve patients with T2DM who were prescribed Atorvastatin at a dose of 10 mg once daily at bedtime for three months. We observed a significant increase in blood ketone levels compared to baseline after three months of Atorvastatin therapy. This finding contrasts with previous studies by Wurtz P et al. [13] and Sliz E et al. [14], which measured serum acetoacetate and beta-hydroxybutyrate in statin users compared to non-users, primarily without diabetes. However, these studies did not find a significant difference in serum ketones between the two groups.

We propose an explanation for the rise in blood ketones with Atorvastatin based on the drug's mechanism of action. Statins reduce cholesterol synthesis in the liver by inhibiting HMG-CoA reductase, leading to the accumulation of HMG-CoA and other precursor intermediates, including acetyl-CoA, in the cytoplasm. This excess acetyl-CoA may interfere with its

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movement from mitochondria to the cytoplasm, crucial for cholesterol biosynthesis. Additionally, in mitochondria, reduced utilization of acetyl-CoA through the tricarboxylic acid (TCA) cycle may occur due to lower oxaloacetate (OAA) levels in diabetes. This can lead to excess acetyl-CoA being diverted toward ketone body synthesis [15].

Interestingly, the increase in blood ketones observed in our study was modest, and none of the patients developed significant hyperketonemia (>1 mmol/L) [12]. The use of a low dose of Atorvastatin (10 mg once daily) and the fair glycemic control at baseline may have contributed to this modest rise. Higher doses of statins, particularly in patients with poorer glycemic control, may have a more substantial impact on blood ketones.

Our study also showed a significant increase in fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG) after three months of statin therapy. This rise may be explained by the glucose-sparing effects of blood ketones, which can serve as an alternative fuel for tissues, including the brain and skeletal muscles. The association between higher serum ketones and hyperglycemia has been demonstrated in other studies and may result from impaired insulin secretion and altered gluconeogenesis pathways [16–20]. Although there was a modest increase in HbA1c after three months of statin therapy in our study, it was not statistically significant, possibly due to the small sample size. Additionally, serum total cholesterol and LDL-cholesterol significantly decreased with statin therapy, consistent with expected outcomes.

Limitations of our study include the small sample size, lack of a control group, and limited information on diet and anti-diabetic agents used by patients. Future research with larger sample sizes and exploration of higher statin doses commonly used in T2DM patients with coronary artery disease could provide further insights into the effects of statins on blood ketones and glycemic control. Variations in fasting duration, diet composition, exercise habits, and medication usage, such as sodium glucose co-transporter-2 inhibitors (SGLT2 inhibitors), should also be considered in future studies to better understand their impact on blood ketone levels.

CONCLUSION

In patients with T2DM, statins are frequently prescribed to mitigate cardiovascular risks. This study investigated the impact of low-dose Atorvastatin on blood ketone levels in individuals with T2DM. Following three months of statin therapy, there was a modest yet notable increase in blood ketone levels, accompanied by a rise in blood glucose levels. We propose that the glucose-sparing effects resulting from increased blood ketones could potentially contribute to the hyperglycemia induced by statin therapy.

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