

The Effect of Statins on Type II Diabetes Mellitus



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Abstract

Although cholesterol is a significant compound produced by the body, its presence is elevated due to the availability of foods containing high levels of saturated fats and an over-consumption of carbohydrates. In addition to this lack of control, the probability of suffering from a cardiovascular disease due to genetic inheritance is a prominent factor. As a result, there is an increased risk to cardiovascular diseases due to atherosclerosis. Subsequently, the use of prescribed statins has become a commonality.

Several researchers highlighted the effects of statins such as pravastatin, fluvastatin and atorvastatin on the effect of insulin production from Beta cells as well as the reducing glucose tolerance statins have, therefore resulting in the onset of pre-diabetes or diabetic patients. It is not confirmed that the presence of cardiovascular disease and the use of statins automatically results in diabetes, but a comparative review is attempted based on studies conducted to denote the effect statin use has on the probability of developing diabetes.

Keywords: Diabetes mellitus; Statins; Cardiovascular diseases; Insulin levels; Glucose tolerance

Background

Statins function by controlling the metabolic pathway at the level of HMG CoA reductase in producing cholesterol. Hence, it is referred to as a rate controlling enzyme. However, the Mevalonate pathway in which this enzyme exist, is the sole contributor to the production of cholesterol and therefore acts as a rate limiting step. As a result, it is the target for pharmacokinetics to utilize inhibitors to reduce the production of cholesterol while increasing the expression of Low Density Lipids (LDL) receptors [1].

Based on previously done research it has been established that statins have been shown to be effective in improving the lifespan and quality of patients suffering from cardiovascular diseases. It must be noted, that within the endocrine functioning there is an AMP- activated protein kinase. This pathway functions in cellular energy homeostasis. Consequently, in the presence of high blood glucose levels, HMG-CoA reductase is active, but its functionality is decreased through the homeostatic abilities of the AMP- activated protein kinase pathway occurring naturally [2].

The missing link was the effect of statin use had over the production of insulin, which could relate statins to the risk or resistance of diabetes. Thus, observing the correlation between

those suffering from cardiovascular disease to the susceptibility to type-2 diabetes mellitus (T2DM) [3].

Review

In studies conducted by Cumaoglu et al. [4], Wistar rats were induced with diabetes using 55mg/kg Streptozotocin while fluvastatin was administered 2mg/kg for 6 months. From the research it appeared that the statin reduced oxidative stresses and damages incurred to a diabetic pancreas [4]. Contrastingly, in non-diabetic induced rats, there was an increase in 3-nitrotyrosine levels. This chemical is an indicator of cell damage and inflammation [5]. Therefore, the findings stated that fluvastatin, a cholesterol reducing drug, has a negative effect on non-diabetic pancreas compared to diabetes-induced. This effect is deemed specific to the pancreas but the biochemical reasoning behind this is unclear.

The limitation found in this study was that very low insulin produced, due to the large dosage of Streptozotocin, resulted in very high fasting blood glucose indices, which is not relatable to a human model. In addition to this, considering the dosage of statin was not alternated in the experiment, the study shows some restriction and lacks insight to the unknown effect of the statin on the pancreas of the non-diabetic patients and

limits the ability to decipher if there are toxic effects on the liver. Furthermore, studies conducted on rodents and rabbits concluded with varying results to those found in this study, thus making the relation of the rat to human comparison unconfirmed. Further studies are required.

Before the above research, studies by Yamakawa et al. [3] focused on the effect of three statins on the glucose tolerance for those already diagnosed with T2DM. Their results showed for those using atorvastatin there was a reduction of metabolites, including isoprenoid which is used for the uptake of glucose to reduce adipocyte maturation, as a result glucose tolerance was impaired. Consequently, the effect of atorvastatin was a significant increase in blood glucose levels. Comparative to pitavastatin and pravastatin had no effect on Haemoglobin A1c (HbA1c) levels [3].

Based on a comparative study between the three mentioned statins, pravastatin has been seen to have the most positive effects for cardiovascular treatment with insignificant effects on glucose levels, contrary to the studies conducted on atorvastatin. This was not only confirmed in the results of the above article but in other experiments conducted by Yokoyama et al. [6]. However, research by Yamakawa et al. [6] was limiting as they failed to consider the age group of their sample size, smokers or non-smokers in the sample, dosage and the severity or number of years patients were suffering from T2DM or cardiovascular diseases. Considering, an increase in the severity of cardiovascular health can result in a larger prescribed dosage of statins and therefore adverse effects on the pancreas and by extension insulin production and risk of diabetes, that were not prevalent at lower doses, the study requires further research.

Contrasting to the studies by Yokoyama et al. [6], a study conducted by Ishikawa et al. [7] determine the effect of atorvastatin and pravastatin on non-diabetic patients with cardiovascular conditions. It was observed that those treated with atorvastatin showed a significant increase in blood glucose levels and HbA1c values, similarly to the results obtained in Yamakawa et al. [3] results. Meanwhile, no effect of blood glucose levels on the non-diabetic patients to pravastatin. Both statins however, were able to reduce LDL levels while increasing High Density Lipids (HDL) levels, hence proven effective. Again, research is leaning towards the use of pravastatin over atorvastatin for the effect of blood glucose, pancreatic and prediabetic patients [8].

Not only did this study utilize male and female patients, with recorded, varying dosages of statins in human approved models but compared their research to those carried out by Anglo-Scandinavian Cardiac Outcomes, Trial Lipid Lowering Arm (ASCOT-LLA) which confirmed patients with a great risk of cardiovascular diseases treated with atorvastatin became newly diabetic to those treated with a placebo statin [9]. Considerable research determines that the effect of statins on HbA1c and overall blood glucose levels differ from statin to statin.

The review has covered research on the effect of statins on the pancreas function and blood glucose, HbA1c levels on diabetic and non-diabetic patients suffering from cardiovascular diseases. Focus on diabetic patients suffering from nephropathy with prescribed statins in their regime is observed in research carried out by Shen et al. [10]. It's known that renal failure is because of progressively worsening diabetes [11]. The effect of statins on renal failure is observed through the presence of albumin in the urine, albuminuria. It was seen that with the use of statins, inflammation, macrophage infiltration, fibrosis of the kidney was reduced with greater antioxidant effects [12]. Thus, reducing the effect of albuminuria and diabetic nephropathy.

This study not only had enough sample size and reference to original research but considered the Caucasian and Asian ethnicities in their study, with extended years of treatment before concluding the research with a large sample size and carrying degrees of renal diseases in diabetic patients. Lastly, effect of statins on the liver of diabetic patients will be explored. Liver diseases have been prevalent in both diabetic and cardiovascular disease sufferers. With a statistic of 40-70% of these diseases resulting in liver abnormalities [13]. In the research carried out, statins did not have any effect on the fibrosis or worsening of a healthy to infected liver. This statement was confirmed when patients suffering from advanced liver disease were treated with statins and resulting in no negative effects. Studies were conducted on the widely known atorvastatin and rosuvastatin medications [14].

In this research, the statin users were of older male populations. Although there were no toxic effects on the liver, there was an increase in the glycaemic control of these patients. However, based on findings in this review, with the use of atorvastatin in the research and the history of this statin increasing glucose levels, the effect may be linked to this statin. Unfortunately, this was not explored further in the study conducted.

Conclusion

The effect of statins on diabetes were explored. Indicating the effect on the pancreas, liver and diabetic versus non-diabetic patients' blood glucose and HbA1c control. It can be concluded that statins do not have a direct effect on the onset of diabetes. However, specific statins such as atorvastatin have adverse effects on glucose levels at higher dosages, which will contribute to the onset of diabetes with continued use over a prolong period. Meanwhile, statins such as pravastatin, have no adverse effects, even at varying dosages, on glucose levels while reducing LDL and increasing HDL levels. Hence, it can be noted that the patient history and statin use differentiate between its effect on, or onset of type II diabetes mellitus.

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