

# Diabetes & dyslipidaemia goals in management of diabetes

## Abstract

Diabetes Type I and Type II are at increased risk for early atherosclerotic CVD i.e CHD and PAD<sup>1</sup> and we know that Glucose control improves TG Level and Cholesterol lowering have favourable effects on CVD outcomes in T1DM & T2 DM.

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Hypercholesterolemia is the main cause of atherosclerosis, The incidence of coronary heart disease is usually low where population cholesterol concentrations are low, Many studies have shown that after the introduction of statins resulted in reducing the hypercholesterolemia is an important means of decreasing coronary risk.<sup>2</sup> Old studies on CV Mortality in T1DM shows that risk goes up with progression of nephropathy which is directly related to dyslipidaemia and blood pressure elevation.<sup>3</sup> This is important that in Type I Diabetes Proteinuria increases the risk 37 times compared to Relative risk of 4.3 in without proteinuria<sup>4</sup> and we can change the risk to 3 for women and 2.3 for men after risk factors control.<sup>5</sup>

In type II Diabetes conditions are little bit different because CVD risk start almost 10 years before the Diagnosis or onset of biochemical hyperglycaemia and other conditions like obesity, insulin resistance, hypertension, dyslipidaemia often called metabolic syndrome exist.<sup>6</sup> Therefore in UKPDS study with T2DM it was shown that one sixth patients who were recently diagnosed T2 DM had history of silent MI.<sup>7</sup>

Dyslipidaemia is one of the top problems in diabetes Type I & Type II patients and elevated level of TG and Cholesterol is related to atherosclerotic changes. Risk reduction is more with hypertriglyceridemia and Cholesterol reduction therapy<sup>8</sup> It has been shown that improved blood glucose has favourable effect on Triglyceride and LDL cholesterol which is due to decreased in VLDL & increased LDL catabolism through LDL receptor<sup>9</sup> and effects of benefits in CVD is actually through lipoprotein metabolism and not through directly glucose lowering.<sup>10</sup>

Who are Predisposed: Hypercholesterolemia usually results from such as obesity and a diet high in saturated fats and underlying polygenic predisposition. There is overproduction of LDL and its genetic component is unlikely to be monogenic. Hypercholesterolemia

which have an entirely genetic cause. A common example of this is monogenic familial hypercholesterolemia, an autosomal dominant disorder in which the LDL cholesterol is raised from birth, It is characterised by a dominant pattern of inheritance of premature coronary disease with or without tendon xanthomata.<sup>11</sup>

How to investigate the patient with hypercholesterolemia, when we plan to treat for hypercholesterolemia a history, clinical examination, and baseline laboratory tests are needed to discover causes of secondary hypercholesterolemia. Family history of smoking, alcohol intake, and dietary intake will help to indicate the extent to which these factors contribute to hypercholesterolemia and risk of cardiovascular disease and desire to change lifestyle. The physical examination should include blood pressure, body weight, height, waist circumference, and look for xanthomata.

Laboratory for hypercholesterolemia done preferable at fasting Triglyceride to avoid post prandial lipaemia . If plasma triglycerides do not exceed 4.5 mmol/l, the LDL cholesterol concentration can be calculated by the Friedewald formula : Low density lipoprotein cholesterol = total serum cholesterol - (HDL cholesterol + serum triglycerides/2.2) mmol/L

Non-HDL cholesterol = total cholesterol - HDL cholesterol(mmol/L)

If low density lipoprotein cholesterol cannot be measured owing to hypertriglyceridemia, then non-HDL cholesterol can be used as a target for statin treatment.

The National Institute for Health and Clinical Excellence<sup>12</sup> on lipid Guidelines suggest on secondary prevention targets but do not say any targets for primary prevention. The recommendation advice to decide to prescribe a statin for primary prevention and should be given 40

mg of simvastatin without monitoring of lipids, The JBS2 and NICE guidelines both suggest concentration of total cholesterol of 5mmol/L or an LDL cholesterol concentration of 3mmol/L as a minimum for good degree of care in high risk individuals.

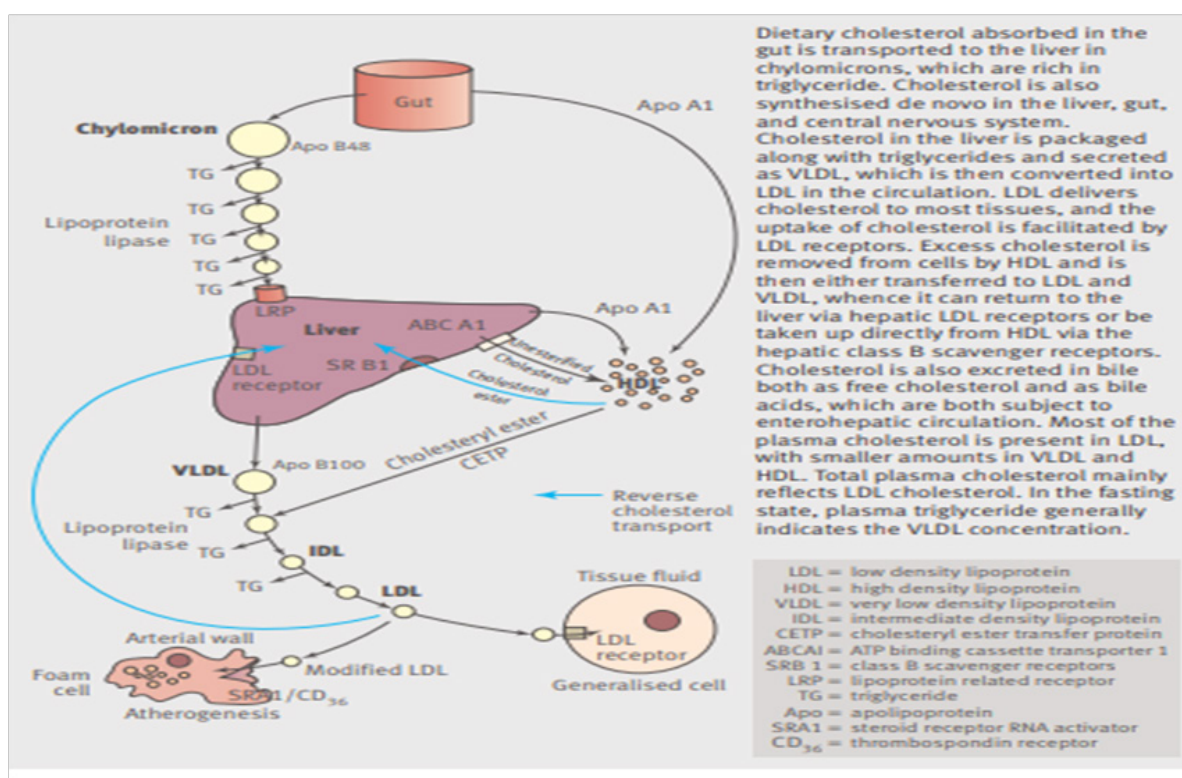
### Starting statin treatment without formal estimation of cardiovascular risk

Statin treatment should be considered in the following people without formal estimation of cardiovascular risk.<sup>13</sup>

1) Those with atherosclerotic cardiovascular disease including

coronary heart disease, stroke, transient cerebral ischaemia, peripheral arterial disease

- 2) Those with type 1 and type 2 diabetes mellitus who are aged  $\geq 40$  years (or younger if additional cardiovascular risk factors are present)
- 3) Those with renal dysfunction including diabetic nephropathy.
- 4) Those with familial hypercholesterolaemia, familial combined hyperlipidaemia, or other genetic dyslipidaemias.
- 5) Ratio of total cholesterol: HDL cholesterol  $\geq 6.0$  (Figure 1).



**Figure 1** The role of cholesterol in the metabolism of lipoprotein.<sup>29</sup>

These changes of High TG and low HDL are observed many years before the Clinical diabetes onset,<sup>6</sup> recently its was found that HDL is independent marker for Diabetes and CVD disease,<sup>14</sup> and small dense LDL particles & VLDL contribute more to atherosclerosis even before the formal diabetes.<sup>15</sup> In case of Type I Diabetes HDL may be normal until nephropathy or poor glycemia set in.<sup>16</sup>

In Diabetes low HDL and high Triglyceride is common condition, First and foremost the Lifestyle Changes with focus on Weight reduction, Trans fats and saturated fats, and reduction in cholesterol from outside is very crucial in Management of dyslipaemia. Increase in Omega 3 fatty acids, plants stanols/sterols and fibers have shown to improves dyslidemia in diabetes patients,<sup>17</sup> level of evidence A. Lipid-associated risk for CVD events is gradual and continuous, Target LDL cholesterol levels for adults with diabetes are  $< 100$  mg/dl (low Risk Diabetes); HDL cholesterol levels are  $> 40$  mg/dl for man and  $50$  mg/dl for women; and triglyceride levels are  $< 150$  mg/dl.<sup>18</sup>

Second is the Glycemic control and lifestyle therapy helps in reduction of triglyceride beyond  $150$  mg/dl and low HDL  $40$  mg/dl for men and  $50$  mg/dl for women which have weak evidence,<sup>17</sup> Its helps specially in High TG level. Lifestyle measures Lifestyle measures such as stopping smoking, decreasing excess alcohol consumption, increasing physical activity, losing weight, and following a low fat saturated diet will all decrease the risk of cardiovascular disease.

However, dietary advice given by health professionals often produces inadequate lowering of cholesterol, typically by about 3%, although reductions of 10% or more have been seen in studies carried out in controlled conditions on hospital ward,<sup>19</sup> So many factors are responsible for lipid metabolic abnormality in diabetes through insulin resistance, insulin dysfunction, adipocytokines and high blood sugars.<sup>20</sup>

Hypertriglyceridemia is a well understood phenomena in diabetes, it stimulate the intracellular hormone sensitive lipase which gives

rises to NEFA form adipose tissue,<sup>21</sup> high level of NEFA induce more production of TG from liver and insulin inhibitory role on hepatic apoB production and TG secretion in VLDL is lost and VLDL is more TG rich and at the same time VLDL catabolism is inhibited.<sup>20</sup>

Endothelial lipoprotein lipase removes the TG from the circulation and this is inhibited due to insulin deficiency and resistance and this is contributed by high level of post prandial lipemia.<sup>22</sup> Almost all the Patients with Diabetes are at high risk for Atherosclerotic CVD and most of the clinical trials have demonstrated good outcomes with statin in patients with or without CHD in diabetes.<sup>23</sup>

In the large Meta-analysis of 14 trials with statin therapy shown the 9% relative reduction in all cause mortality and 13% reduction in CV mortality with mean 39 mg/dl reduction in LDL cholesterol.<sup>24</sup> High dose statin is recommended in case of Diabetes with established ASCVD as reduction in non fatal CV events were less compare to moderate doses of statin<sup>8</sup> In the past years there had been number of trial adding non statin to statin for further lowering LDL in high risk for CVD in diabetes, three non statin agents added were ezetimibe<sup>25</sup> with relative reduction of 13% in combination of simvastatin with ezetimibe compare to simvastatin alone. similarly PCK9 inhibitors and CETP, cholesteryles-ter transfer protein inhibitors and in all three trial it was found reduction till 70 mg/dl of LDL resulted in more better CVD outcomes.

High TG level individual with diabetes should refrain from alcohol<sup>26</sup> and severe TG 1000 mg/dl should need therapy as fibric acids compound or high dose fish oil to reduce acute pancreatitis. So therapy can be initiated to reduce acute pancreatitis if the TG level >500 mg/dl in diabetes. Diabetes is more commonly associated with Low HDL and high TG, combination with fenofibrate did not reduced all CVD outcomes significantly,<sup>27</sup> instead liver enzymes very raised. Therefore combination of statin with Fibrate not recommended as no improvement in ASCVD in diabetes.

Similarly Two trial HIGH-AIM and HPS2-THRIVE have failed to improve CVD outcome with Simvastatin and niacin,<sup>28</sup> no significant difference in the rate of CV death, stroke, and coronary revascularization on simvastatin with the addition of niacin versus placebo (13.2% vs. 13.7%, P 5 0.29) High intensity statin should be used in high risk CVD patients with Diabetes and Moderate intensity statin should be used in other diabetes patients.<sup>29</sup>

High intensity statin decreases 50% LDL where target of less than 70 mg/dl LDL is needed and Moderate intensity statin decreases LDL by 30%-50%, low intensity statin is not useful in diabetes CVD reduction significantly.<sup>17</sup>

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## Conflicts of interest

The author declares there are no conflicts of interest.

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