Summary & Conclusion
SUMMARY OF RESULTS

1. Significantly higher post prandial hypertriglyceridemia was observed in high sucrose diet fed rats which started from 2\textsuperscript{nd} week and persisted throughout. This suggests that post prandial hypertriglyceridemia is an early phenomenon in high sucrose diet fed model of type 2 diabetes.

2. The post prandial hypertriglyceridemia induced by high sucrose diet was significantly blunted both by atorvastatin and pioglitazone. But was earlier, greater and more complete with atorvastatin.

3. High sucrose diet fed rats showed significant blunting of LPL activity from week 2-16 as compared to other three study groups suggesting that blunted LPL activity could be an underlying factor that is associated with higher post prandial triglyceride responses to fat challenge.

4. LPL activity reduced from 18\textsuperscript{th} week in all the four groups after which there was no significant difference in LPL activity between all the four groups. The observation that post prandial hypertriglyceridemia continued to be higher in high sucrose diet fed rats compared to controls even during the period of 18\textsuperscript{th} - 48\textsuperscript{th} week despite similar LPL activity suggest that at this stage post prandial triglyceride responses to fat challenge were independent of plasma LPL activity. Since plasma LPL activity mainly reflects endothelial lipoprotein lipase. It is possible that adipose tissue LPL activity and/or hepatic lipase activity may be more important.

5. Glucose area under the curves were significantly higher in high sucrose diet fed rats compared to controls only after 12\textsuperscript{th} week and remained so till 26\textsuperscript{th} week when streptozotocin was administered. Since post prandial lipaemia occurs as early as 2\textsuperscript{nd} week but glucose intolerance manifests only after 12\textsuperscript{th} week, it would
be logical to conclude that post prandial lipaemia leads to glucose intolerance and not vice-versa.

6. Atorvastatin treated rats in whom post prandial triglyceride responses were effectively and completely blunted to control levels also had blunted glucose area under the curves similar to controls despite being fed on high sucrose diet. Pioglitazone treated rats with intermediate post prandial triglyceride responses also showed intermediate glucose area under the curves subsequently. Taken together, these findings clearly indicate that it is post prandial hypertriglyceridemia which determines future hyperglycemia and glucose intolerance during the development of diet induced diabetes.

7. Diabetes developed in 43.47% of rats in high sucrose diet fed group and 17.39% in pioglitazone treated group compared to 8.69% in controls as well as atorvastatin group.

8. 82.6% (19/23) of high sucrose diet fed rats and 79.1% – 70.8% (19/24 and 17/24) of pioglitazone treated rats with intermediate post prandial triglyceride responses had impaired glucose tolerance. In contrast, only 37.5% (9/24) at 24th week and 4.2% (1/24) of rats at week 26 in control group showed impaired glucose tolerance. Similarly, only 37.5% (11/24) at week 24 and 12.5% (3/24) at week 26 in atorvastatin treated group with post prandial triglyceride responses similar to controls had impaired glucose tolerance.

8.1 STZ treated rats

8.1.1 100% in high sucrose diet fed rats and 58.33% in pioglitazone treated rats had impaired glucose tolerance. In contrast only 9% rats in control group and 16.66% rats at in
atorvastatin treated group had impaired glucose tolerance at 26th week.

8.1.2 At week 30 i.e., 4 weeks after streptozotocin injection, 81.81% of rats in high sucrose diet group developed diabetes as compared to 18.18% in controls. Atorvastatin treated rats also developed diabetes in 16.16% of rats at this stage which was similar to controls, while pioglitazone treated group had an intermediate figure of 33.33%.

8.1.3 The cumulative incidence of diabetes was 100% in high sucrose diet group by week 48 as well as at week 72. This was far higher than all the three other groups at both time points.

8.2 In non STZ treated rats, at week 30, 8.33% of rats in high sucrose diet group developed diabetes while no rat developed diabetes in control group. The cumulative incidence of diabetes increased further in high sucrose diet group to 16.66% and 25% at week 48 and 72 respectively as compared to 0% in control as well as atorvastatin treated group at both time points.

9. Rats in high sucrose diet fed group had significantly higher body weight compared to controls and atorvastatin treated rats throughout the study follow up. While visceral fat content was significantly higher in all the three high sucrose diet fed groups compared to controls indicating that high sucrose diet leads to greater visceral fat deposition and predisposes them to insulin resistance.

10. Insulin resistance as indicated by HOMA IR was significantly higher in all the three high sucrose diet groups compared to controls till week 26. However, there was an
improvement in insulin resistance in atorvastatin treated rats reaching levels similar to controls.

11. HOMA $\beta$ was found to be higher in atorvastatin treated group followed by high sucrose diet group and pioglitazone treated rats respectively when compared to controls. However, after week 18, HOMA $\beta$ decreased significantly in all the three study groups fed on high sucrose diet and was found to be even lower than controls at most time points.

It would appear that high sucrose diet and resultant postprandial lipaemia are important underlying factors in the development of subsequent visceral adiposity and insulin resistant.

12. Serum leptin levels were significantly higher in all the three groups receiving high sucrose diet with/without pioglitazone/atorvastatin treatment throughout the study at all time points compared to controls reaching at peak by week 18.

Uniformly elevated serum leptin levels in rats receiving high sucrose diet regardless of drug treatment suggests that hyperleptinemia could be an important link between high sucrose diet, postprandial hypertriglyceridemia and insulin resistance. Hyperleptinemia, which is also believed to be secondary to leptin resistant state, has also been postulated to be an important factor in the development of insulin resistance.

13. Serum adiponectin levels were significantly higher in all the three study groups fed on high sucrose diet compared to controls at most time points till week 48.

The uniformly high levels of serum adiponectin in high sucrose diet fed groups seems to be a consequence of increased adipose tissue mass which is also evident by high visceral fat content in these rats.
14. There was no significant difference in HsCRP levels between any of the four groups at any time point.

15. However, higher ICAM 1 levels were seen in high sucrose diet fed group compared to controls, pioglitazone treated group and atorvastatin treated group after week 48 and remained significantly higher even at week 72.

16. Similar trend was also observed in VACM 1 levels in high sucrose diet group versus other three groups at week 72. These findings with respect to endothelial function biomarkers suggest a higher risk of atherosclerosis in them.

17. Leptin/Adiponectin ratio, which is a good marker of atherosclerosis and has also been labeled as atherogenic index by some authors, was significantly higher in high sucrose diet fed rats as compared to controls at week 48 and 72. Leptin/Adiponectin ratio was also high in pioglitazone treated group and atorvastatin treated group compared to controls reaching statistical significance at some time points.

18. There was an increase in thickness of aorta. Also, collagen fibers between two elastic lamina were increased.

19. There is disruption in elastic lamina with focal disruption of intima

Taken together, these findings along with a positive correlation of triglyceride area under the curve with leptin to adiponectin ratio in high sucrose diet group suggests that there is a greater endothelial dysfunction and atherosclerosis risk in high sucrose diet fed rats who displayed the higher post prandial triglyceride responses.
Conclusion

In conclusion, the present study provides for the first time, unequivocal evidence that post prandial hypertriglyceridemia leads to the development of insulin resistance, glucose intolerance and type 2 diabetes mellitus in a rat model of type 2 diabetes mellitus. In addition, post prandial hypertriglyceridemia associated with high sucrose feeding, also leads to greater endothelial dysfunction and atherosclerosis risk.