Triglyceride and high density lipoprotein metabolism in diabetes

Abstract
Atherosclerosis is a major complication of diabetes. The dyslipidaemia of diabetes appears to play an important part in the atherosclerotic process mainly through the disturbance in triglyceride metabolism and the resulting low HDL cholesterol. The article discusses abnormalities in fat metabolism as observed in both chylomicron and the intestine and very low density lipoprotein (VLDL) in the liver. The impact of disturbed triglyceride metabolism on the atherogenicity is briefly described. Low HDL is a recognised marker of cardiovascular risk. The article describes the relationship between the disturbed triglyceride-rich lipoprotein metabolism found in diabetes and HDL. The effect of diabetes on HDL function is also explored.

Keywords: triglycerides; chylomicron; type 2 diabetes; high density lipoprotein; Apolipoprotein A-5; bariatric surgery; Angiopoietin-like protein 3

Introduction
Atherosclerosis is a major complication of diabetes. Hyperglycaemia, hypertension and dyslipidaemia are the major risk factors found in diabetes. This article reviews the metabolic disturbance which occurs in diabetes that leads to hypertriglyceridaemia and low high density lipoproteins (HDL) and discuss why this profile is atherogenic. Diabetes is a condition in which there is a deficiency of insulin. Absolute deficiency occurs when the beta cells in the pancreas have entirely lost their insulin secreting capacity but most patients with diabetes have some residual function and it is insulin resistance that tips the balance into diabetes when the insulin resistance cannot be overcome by a sufficient increase in insulin production.

Chylomicron and VLDL formation
Triglycerides are particles consisting of 3 fatty acids attached to glycerol. They are broken down in the intestine into monoacylglycerol and fatty acids, absorbed in the enterocytes and re-esterified primarily through the monoacylglycerol pathway, prior to incorporation into the chylomicron. Another pathway, the glycerol 3 phosphate transfer pathway (GPATH3) has recently been shown to be involved in intestinal lipid metabolism. The chylomicron is assembled in the intestine from triglyceride, cholesterol, phospholipid and Apolipoprotein (Apo) B 48, a truncated version of Apo B 100, under the influence of microsomal triglyceride transfer protein (MTP).

The chylomicron is taken up from the intestinal wall via the lymphatic system and the triglyceride is transferred to the liver for circulation or stored in adipose tissue. Fatty acids are released from the liver in the fasting state, converted to triglycerides through 2 steps, diacylglycerol transferase 1 (DGAT 1) to diacylglycerol and DGAT 2 to triglyceride and assembled with the addition of cholesterol and Apo B100, by MTP for transport as very low density lipoprotein (VLDL) or to a lesser extent as low density lipoprotein (LDL). In the intestine DGAT is predominantly involved with the synthesis of triglyceride and dietary fatty acids. In the postprandial state esterified lipids generated by intestinal DGAT1 are incorporated into chylomicron particles. Loss of DGAT1, specifically in the intestine, leads to a loss of postprandial triglyceride.

Sachdev et al. have shown that deficiency/ inhibition of DGAT1 reduces chylomicron size and increases transintestinal cholesterol excretion. Hung et al. have shown that DGAT 1 and 2 regulate enterocytes triacylglycerol distribution into distinct subcellular pools.
Apo B48, the solubilising protein, in the intestine and Apo B 100 in the liver with cholesterol, triglyceride and phospholipid. This process is in part regulated by insulin and in diabetes intestinal MTP mRNA is increased with an increase in postprandial Apo B48. Improvement in blood sugar control reduces post prandial Apo B48.

Chylomicron and atherosclerosis

Interestingly, inhibition of intestinal MTP reduced fat preference in rats, and increased HDL-C. A rare condition causing malabsorption of fatty acids is abetalipoproteinemia caused by a genetic defect in MTP. This results in fat accumulation in the intestinal mucosa with resulting malabsorption of vitamins and cholesterol, and low serum triglycerides, cholesterol, Apo B48 and Apo B 100.

Since the chylomicron particle is mostly a post prandial particle, usually being rapidly cleared by the liver. It is of interest that Irawati et al., examined in normal subjects the distribution of Apo B48 chylomicron particles after a meal. They divided them up into 3 sizes. The smallest particles with the greatest triglyceride delipidation had a Svedberg flotation rate of < 20. They found that chylomicronaemia principally consisted of the smallest particles and thus most the atherogenic fraction. It is suggested that the large particles have a more difficult in gaining access to atherosclerotic plaques. However 40% of subjects demonstrated exaggerated postprandial lipoaemia specifically in response to a saturated fatty acid rich meal with a transient shift to more buoyant larger particles. The authors point out that their study suggests the importance in examining the post prandial state when looking at atherogenic triglyceride rich Apo B 48 lipoproteins. In another post prandial study of triglyceride lipolysis in patients with a history of multi factorial chylomicronaemia, the authors found that some patients had a defect in lipolyisability and/or hepatic clearance that could be picked up by examining post heparin lipoloysis at 60 min rather than at the more usual 10 minutes, again demonstrating the importance of the post prandial measurements if looking for chylomicron potential atherogenicity. This on the premise that the smaller particles have greater access to arterial subendothelial space and therefore greater ability to accelerate the atherosclerotic process.

Dyslipidaemia and the beta cell in diabetes

The relationship between diabetes and alterations in normal lipid metabolism presumes that insulin deficiency/insensitivity is central. More recently it has emerged that altered lipoproteins and in particular LDL may play a role in damaging the beta cell and so promote further beta cell damage in a vicious circle. LDL receptors are found on the beta cell and an increase in oxidized LDL has been found in diabetes. Masuda found that after a fat meal, as in the fasted state, the chylomicrons in the blood mostly consisted of the smallest particles and thus most the atherogenic. A recent paper by Natali et al., investigated whether serum lipids are associated with alterations in insulin secretion or clearance in non diabetic subjects. This was a cross sectional and observational prospective study. Surprisingly LDL cholesterol did not show independent associations with fasting or stimulated insulin secretion or clearance. However, triglycerides showed positive independent associations and HDL cholesterol a negative independent associations with insulin secretion, fasting or after glucose stimulation. The authors conclude that high triglycerides and low HDL cholesterol might contribute to sustain the abnormalities in insulin secretion that characterise the pre diabetic state.

Apolipoprotein A-V diabetes and triglycerides

Apo A–V is involved in the lipoprotein lipase hydrolysis of triglyceride. There is a strong correlation between single nucleotide polymorphisms in Apo A-V and elevated plasma triglyceride. Apo A 5 modulates triglyceride levels and has a predictive role in CVD events. Sharma et al., have recently reported that in patients with Type 2 diabetes, low levels of Apo A-V are associated with hypertriglyceridaemia and oxidative stress was increased in these patients. Glycation of LDL, is a well known risk factor for CHD as glycated LDL is taken up by the macrophage in an unregulated way and it is more easily oxidised and therefore more atherogenic. Glycated HDL has been shown to trigger oxidative stress and promote the proliferation and migration of vascular smooth muscle cells, another reason why high HDL in diabetic patients may not be cardioprotective.

Apo A-V is synthesised in the liver and is present in bile. The secretion of Apo A5 is increased by dietary lipid at least in rats. The authors suggest that the secretion of Apo A-V into the intestinal lumen constitutes a physiological mechanism to regulate the intestinal formation and secretion of chylomicrons.

Weight loss, triglycerides and reversal of diabetes

The liver X receptors are hormone receptors that regulate cholesterol absorption through their effect on ABC G5/8, and in the intestine are involved in the pace of lipid transport. Since triglyceride in the chylomicron is dependent on diet, it is interesting to examine the changes that occur in starvation. Many studies over the past years have studied short term and long term effects of weight reduction on triglyceride metabolism. Impetus to revive interest has come from effective measures to sustain weight loss in obese patients with and without diabetes through bariatric surgery and more recently through initial low calorie liquid diets and then slow introduction of a more normal diet with supervision. This produced very impressive results at the end of one year in a real world situation as the study was carried out in a variety of general practices. Remission of diabetes varied with weight loss. Thirty four % of patients who lost 5-10 kg and 86% of those who lost 15 kg or more reversed their diabetes. Of the 150 patients who commenced the dietary intervention only 32 withdrew demonstrating that in a real world situation, very important benefits can be gained by a structured weight loss program. Serum triglycerides fell by 0.31 mmol/l - a 20% drop. Recently Perry et al have shown in a rat model of Type 2 diabetes, 3 days of semi-starvation leads to reduction of hepatic triglyceride and diacylglycerol content and protein kinase C (PKC) theta translocation associated with improved insulin sensitivity. Previously in human studies Taylor’s group, had shown that in Type 2 diabetes a negative energy diet reduced liver and pancreas triglyceride within 7 days and restored B cell function with normalisation of fasting glucose and even improvement of first phase insulin release.

Life style and dietary intervention

Lifestyle modification programmes have been shown to reduce cardiovascular risk. Boyer et al., have shown that at one year after introduction of a lifestyle modification programme in men with abdominal obesity and dyslipidaemia, HDL function and quantity improved.

There has been recognition recently that dietary advice from various national august bodies has been flawed in relation to dietary recommendation and advice about eating eggs and excess cholesterol intake. In the prospective Framingham offspring study Lin et al., examined dietary cholesterol intake in 993 adults with prevalent impaired glucose tolerance or Type 2 Diabetes. They found that there was no evidence of an adverse association between dietary cholesterol and serum lipid levels or atherosclerotic cardiovascular disease risk.
This result is perhaps not surprising given the very strong regulation of cholesterol absorption and the feedback mechanisms that up-regulate cholesterol synthesis if cholesterol absorption is decreased. A good review of dietary cholesterol and the lack of evidence for cardiovascular disease has recently been published.51

**Bariatric Surgery**

Bariatric surgery is a well accepted, effective treatment for obesity resulting in very important weight loss and in type 2 diabetes leads to a high remission rate. Adams et al.,52 reported weight and metabolic outcomes 12 years after gastric bypass. They had 3 groups of patients with severe obesity. Those who sought and underwent Roux-en-Y gastric bypass surgery, a second group were those who sought, but did not undergo, surgery and the third group who did not seek surgery. The patients who had surgery were 45.0 kg lighter after 12 years. Fifty one percent of these patients with diabetes before the operation had normalised their blood sugars and their diabetes had not reappeared. Triglycerides had fallen from 185mg/dl (2.0mmol/l) to 103.3 mg/dl (1.16mmol/l) a drop of more than 44%. HDL had risen from 46.6 mg/dl (0.52 mmol/l) to 61.5 mg/dl (0.69mmol/l) a rise of 25%. In the patients who did not have diabetes pre-operation only 3% developed diabetes at 12 years whereas 26% of the non-surgery group had diabetes at 12 years. With such a significant drop in triglycerides one would expect a reduction in atherosclerosis and this indeed was found.53,54 Ikramuddin et al.,55 examined lifestyle intervention and medical management with/without Roux-en-Y gastric bypass and hemoglobin A1c (HbA1c), LDL cholesterol, and systolic blood pressure at 5 years in the Diabetes Surgery Study. Adding gastric bypass compared with lifestyle and intensive management along, was significantly better. Ota et al.,56 reported very long term results have also shown a reduction in cardiovascular risk factors and events For example Jakobsen et al.,57 found after a median of 6.5 years that bariatric surgery as compared to medical treatment resulted in more remission and less new onset hypertension and greater likelihood of diabetes remission at the expense of more depression and treatment with opioids.

**Are triglycerides rich particles atherogenic particles?**

The extent to which effects of body mass index (BMI) on coronary heart disease (CHD) are mediated by glycaemia and lipid risk factors have recently been examined using a two sample Mendelian randomisation method in a very large sample.58 The authors conclude that increased triacylglycerol levels and poor glycaemic control appear to mediate much of the effect of BMI on CHD.

Pharmacological reduction in small cholesterol enriched, triglyceride depleted, VLDL has been shown to be associated with a reduction in atherosclerotic cardiovascular disease in the JUPITER trial.59 Increased triglycerides have been shown to predict brain beta-amyloid and tau pathology 20 years later.60

The triglyceride rich particles generate pro-atherogenic LDL and are associated with low HDL, hence hard to tease out the individual risk of the various particles. Treatment to reduce the triglyceride rich particles results in changes to LDL composition and levels as well as increasing HDL.61 In the treating to new targets trial (TNT) a post hoc analysis has shown cardiovascular risk was increased in patients who had high triglyceride-rich cholesterol and lowering triglyceride rich cholesterol lipoproteins with atorvastatin yielded benefit over and above lowering LDL cholesterol.62

**HDL and reverse cholesterol transport**

The examination of large populations investigating the role of genes known to affect serum triglyceride levels have helped to define cardiovascular risk.63 Elevated triglyceride-rich lipoproteins represent causal risk factors for low-grade inflammation, atherosclerotic cardiovascular disease, and all-cause mortality. However almost all other studies have failed to distinguish the role of trigly cerides from the inverse relationship with HDL.64–66 HDLs are circulating complexes of protein and lipid. The particles vary in size, protein, lipid composition and charge.67 this explains the many functions attributed to HDL, which include reverse cholesterol transport, inhibition of oxidation, reduction in vascular cell mediated inflammation, and many other functions.68–70

Attention is mostly focussed on the ability of HDL to scavenge cholesterol from the periphery through ABCA1 and deliver it to the liver via the scavenger receptor (SR) B1. Mechanisms are being actively investigated in the hope that HDL therapies may become useful therapies in the treatment/prevention of atherosclerosis. Recently a novel new regulator of ABCA1 expression has been described.71 the authors describe trafficking protein kinesin binding 2 (TRAK2) to be a novel regulator of liver X receptor (LXR)-mediated ABCA1 expression, cholesterol efflux and HDL biogenesis.

An alternative pathway has been the uptake of cholesterol by cholesteryl ester transfer protein (CETP) in a two way process, transferring cholesterol from HDL to Apo B-containing lipoproteins while accepting triglyceride from these lipoproteins. The major proteins on HDL are Apo A1 and A2. Apo A1 is synthesised both in the liver and intestine and carried into the circulation on triglyceride-rich lipoproteins where it is shed and together with phospholipid forms nascent HDL.72 Trigueros-Motos et al.,73 have shown that ABC A8 facilitates cholesterol efflux and modulates HDL by interacting with Apolipoprotein A1 and potentiates the adenosine triphosphate binding cassette transporter A1-mediated cholesterol efflux.

Through the various roles of HDL, including reverse cholesterol transport, anti-inflammatory, antithrombotic and anti oxidative functions, many studies have shown HDL to be an independent negative risk factor for atherosclerosis.74 Apo A1 has been shown in patients with type 2 diabetes to have a stronger effect on preventing cardiovascular disease than HDL.75 Borja et al.,76 have shown that HDL Apo-A1 exchange, a measures of HDL function, is impaired in the metabolic syndrome and this may be a reason why Apo A1 may not be a better marker for CVD risk as compared to HDL-C. The role of Apo A2 in prevention is less clear, but a recent paper has demonstrated that Apo A2 enhances ABCA1 mediated efflux of cholesterol. The authors suggested that Apo A2 induces a structural change in Apo A1 and this is one mechanism to improve cholesterol acceptance.77

Feng et al.,78 in a cross sectional study of patients with impaired glucose tolerance, found an inverse association between Apo A1 and insulin resistance in these patients. Many studies have shown HDL to be low in type 2 diabetic patients but not type 1. Apo A1 has been independently demonstrated to promote insulin secretion and glucose uptake and to be negatively correlated with insulin resistance.79 Understanding the function of HDL requires detailed knowledge of the primary protein Apo A1. This until now has been very difficult however Pournousa et al.,80 have recently reported results which they suggest provide a framework for understanding HDL maturation and revise all previous models of nascent HDL.

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Obesity is associated with lower HDL-mediated cholesterol efflux from macrophages and a higher cholesterol ester transfer protein. Talbot et al., have surprisingly shown that these parameters of cardiovascular risk are not changed by diet-induced weight loss.

**Factors effecting HDL function**

Since HDL contains so many proteins and has such diverse functions it is not surprising that quantity of HDL may not reflect its antiatherogenic function and quality may be more important. This has been demonstrated clearly by the lack of therapeutic benefit with the CETP inhibitors which very successfully rise HDL levels. However the recent results from a trial of Anacetrapib has shown an increase of HDL by 43% and a reduction in non HDL cholesterol 18%. This was associated with a 1% difference in primary outcome events specified as first major coronary event or composite of coronary death, myocardial infarction or coronary revascularisation. The modest effect in benefit may have been due to the reduction in LDL. The manufacturing company Merc Pharmaceuticals have decided not to take the drug forward for licensing.

The failure of CETP inhibitors to show meaningful benefit in cardiovascular prevention terms even though very successful in raising HDL, focused attention on whether it was correct to think of HDL in terms of 'good cholesterol'. Apo A 1 is the major protein associated with HDL and like HDL has also been inversely associated with cardiovascular risk. Apo A1 has also has also been shown to have anti oxidant anti inflammatory anti thrombotic and nitric oxide promoting properties. The association between HDL cholesterol vs Apo A1 with risk of coronary heart disease has been examined in three prospective studies (The Cancer-Norfolk Study, The Atherosclerosis Risk in Communities Study and the Womans Health Study). The study found that ApoA1 levels do not offer predictive information over and above HDL-C. Surprisingly, in some quartiles of HDL-C, ApoA1 was associated with higher risk of CHD events! Interestingly Sun Y et al., have shown that older people with diabetes who have higher serum HDL-C had better executive function. The authors followed 152 subjects with normal cognitive function and 119 who had impaired function and re-examined them after 27 months.

There are many reasons why LDL cholesterol in diabetic patients with hyperglycaemia, may be atherogenic, such as increased glycation and increased oxidation. It is less clear that glycation of Apo A1 alters HDL function. Domingo-Espin et al., have recently shown that glycation of ApoA1 led to loss of lipid binding capability and a reduced ability to catalyse cholesterol efflux from macrophages. Modification of Apo A1 also affected in vivo glucose clearance.

Serum amyloid A (SAA) is an inflammatory protein that associates with HDL and causes HDL to become dysfunctional. It has been suggested that solubilisation of membranes by SAA provides a first line of defence in clearing debris from injured sites. SAA has also been shown to increase vascular smooth muscle cell proliferation. It has been suggested that the contractile vascular smooth muscle phenotype de-differentiates following injury leading to vascular lesions. Zhang X et al., have shown that SAA induced vascular smooth muscle cell phenotype switch, thus potentially promoting atherosclerotic lesions. Griffiths et al., have shown in young female type 2 diabetic patients an increase in SAA concentrations and dysfunctional HDL features with lower paraoxinase-1 activity.

Apo C 111, which is an important protein attached to triglyceride-rich lipoproteins and inhibits lipoprotein lipase and uptake by the Apo B receptor, is also found on HDL particles and has been shown to effect HDL mediated cholesterol efflux. They showed Apo C111 attached to HDL to be a strong predictor of cardiovascular risk whereas HDL without Apo C111 was inversely associated with diabetes cardiovascular risk.

**Angiopoietin-like protein 3 and 4**

Angiopoietin-like protein 3 and 4 are glycoproteins involved in angiogenic regulation. It is an important regulator of lipoprotein metabolism. The n-terminal region mediates the inhibition of lipoprotein lipase whereas the C-terminal region is involved in cell adhesion and migration. There is an inverse correlation between angiopoietin like protein-4 and HDL cholesterol. Plasma levels of angiopoietin-like protein4 are increased in type 2 diabetes. Angiopoietin-like protein4 is present in HDL. Yang et al., have shown that angiopoietin-like protein 4 on HDL protected HDL from hydrolysis. In type 2 diabetes angiopoietin-like protein4 levels are increased but the inhibitory effect on endothelial lipoprotein lipase was diminished with a compromised inhibitory effect on endothelial lipase leading to increased HDL hydrolysis and dysfunction.

The authors suggest that improved glycaemic control would result in a lowering of angiopoietin-like protein4 and improvement in HDL function and therefore reduce cardiovascular risk. Angiopoietin-like protein3 is an endogenous inhibitor of lipoprotein lipase that is related to angiopoietin-like protein4. Rare loss of function variants are associated with decreased triglyceride levels and lower LDL and HDL. Deletion of angiopoietin-like protein3 has been shown to reduce the development of atherosclerosis in Apo E deficient mice.

Dewey et al., examined the relationship between angiopoietin-like protein 3 loss of function variants and coronary artery disease and found that the loss of function variants had significantly lower triglyceride, HDL cholesterol and LDL cholesterol. Loss of function variants were found in 0.33% of case variant patients as compared to 0.45% of controls P=0.004. In dyslipidaemic mice, inhibition of angiopoietin-like protein3 resulted in a greater area of atherosclerotic lesion and necrotic lesion area. In another study Graham et al., using an antisense oligonucleotide targeting angiopoietin3 mRNA, triglycerides fell by 33-63%, LDL cholesterol by 1.3 -34%, VLDL reduced by 28 -60% and Apolipoprotein C111 by 19-59%. In treated mice similar lipid reductions occurred with reductions in liver triglyceride content and progression to atherosclerosis. There was also an improvement in insulin sensitivity. These studies represent a fresh frontier in the treatment of atherosclerosis and coronary artery disease.

Interestingly HDL levels also fell. Angiopoietin-like protein3 inhibits in vitro endothelial lipase, an enzyme involved in HDL catabolism and has been shown to be positively correlated to plasma HDL cholesterol and phospholipid levels, high triglycerides, low HDL and cardiovascular risk.

**High triglycerides, low HDL and diabetes**

The metabolic syndrome is associated with insulin resistance obesity and diabetes. Low HDL and high triglycerides are a common feature in the syndrome and impairment in the functionality of HDL. A life style weight reduction intervention programme was examined in patients with the metabolic syndrome. The antioxidant capacity of HDL was significantly improved but only in patients who had normal LDL cholesterol. The improvement in function was associated with improvement in Apo A1 content and core lipid composition. A surprising result but only 33 patients and only a 12 week study. High triglycerides and low HDL predicted the development of incident
coronary heart disease and stroke particularly in those with diabetes.\textsuperscript{113} High triglycerides and low HDL were found in a retrospective study of 47000 patients attending Italian diabetes centres to predict the development of diabetic kidney disease.\textsuperscript{114}

Pre-beta1 HDL is a major acceptor of free cholesterol from cells. Shiu et al.,\textsuperscript{115} have recently shown that pre-beta1 HDL was significantly decreased in Type 2 diabetic patients without cardiovascular disease compared to controls and was associated with decreased cholesterol efflux in cultured cells mediated by ABCA1. The authors suggest that impairment of cholesterol efflux in Type 2 diabetic patients may be a cause for the increased risk of atherosclerosis that these patients carry.

**Conclusion**

One way to examine the cardiovascular risk of high triglycerides and low HDL is to examine whether variants in genes that determine the levels of HDL and triglycerides are associated with vascular events. Voigl et al.,\textsuperscript{116} examined 14 common single nucleotide polymorphisms (SNP) that exclusively associate with HDL cholesterol and one SNP in the endothelial lipase gene. They found that some genetic mechanisms that raise HDL cholesterol do not seem to lower risk of myocardial infarction.

In a recent excellent review Dron and Hegely,\textsuperscript{117,118} state that definitive evidence for a direct causal role of triglycerides in cardiovascular disease still eludes our grasp. However, there seems to us to be too much evidence already available to suggest definite risk that it would be unwise to ignore the dangers of high triglycerides. Treatment of hypertriglyceridaemia over and above treating LDL to target, in 2018 would seem to be the wise option. HDL and Apo A1 are useful markers of cardiovascular disease risk but treatment to improve function rather than to increase HDL levels seems the new goal of treatment to prevent cardiovascular disease.\textsuperscript{119}

**Summary**

The article discusses new research into the relationship between the brain and the liver. The role of insulin in lipid metabolism is discussed with particular reference the disturbances that occur in chylomicron metabolism in diabetes. Apo A5 and lipoprotein lipase hydrolysis of triglyceride is discussed. The chylomicron is dependent on dietary intake. New insights from bariatric surgery and starvation diets are presented. The interdependence between triglyceride-rich lipoproteins and HDL is explored. HDL function in diabetes is discussed including the role of Apo C111 and the angiopoietin-like lipoproteins attached to HDL. Cardiovascular disease is prominent in diabetes. Triglyceride metabolism is a major disturbance in lipid metabolism generating a cascade of atherogenic particles eventually leading to dysfunctional HDL. There is a great deal of evidence to suggest that triglyceride-rich lipoproteins are atherogenic. The interdependence of these lipoproteins with HDL and LDL have in the past obscured the atherogenic role of atherogenic triglyceride-rich lipoproteins. The lipoprotein cascade starts with dietary cholesterol and triglyceride via the chylomicron. Most of the time now days we are in a postprandial phase, with an increase in grazing. It is likely that lipoprotein patterns have changed over the past number of years and may at least in part be responsible for the increase in diabetes, obesity and atherosclerosis.

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None.

**Conflict of interests**

The author declares there is no conflict of interest.

**Reference**


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