Lipid disorders in type 1 diabetes

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Abstract

Patients with type 1 diabetes (T1D) also present with lipid disorders. Quantitative abnormalities of lipoproteins are observed in T1D patients with poor glycaemic control (increased plasma triglycerides and low-density lipoprotein [LDL] cholesterol) or nephropathy (increased triglycerides and LDL cholesterol, low level of high density lipoprotein [HDL] cholesterol). In cases of T1D with optimal glycaemic control, plasma triglycerides and LDL cholesterol are normal or slightly decreased, while HDL cholesterol is normal or slightly increased. Several qualitative abnormalities of lipoproteins, which are potentially atherogenic, are observed in patients with T1D, even in those with good metabolic control. These abnormalities include increased cholesterol-to-triglyceride ratios within very low-density lipoprotein (VLDLs), increased triglycerides in LDLs and HDLs, compositional changes in the peripheral layer of lipoproteins, glycation of apolipoproteins, increased oxidation of LDLs and an increase in small, dense LDL particles. These qualitative changes in lipoproteins are likely to impair their function. In vitro, VLDLs and LDLs from patients with T1D induced abnormal responses in the cellular cholesterol metabolism of human macrophages. HDLs from patients with T1D are thought to be less effective in promoting cholesterol efflux from cells, and have been shown to have reduced antioxidative and vasorelaxant properties. These qualitative abnormalities are not fully explained by hyperglycaemia and may be partly due to peripheral hyperinsulinaemia associated with subcutaneous insulin administration. However, the precise consequences of these qualitative lipid changes on the development of cardiovascular disease in T1D are, as yet, unknown.

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Résumé

Anomalies lipidiques au cours du diabète de type 1.

Les patients diabétiques de type 1 présentent des anomalies lipidiques, qualitatives, parfois quantitatives. Les anomalies quantitatives sont observées en cas de diabète de type 1 mal contrôlé (augmentation des triglycérides et du low-density lipoprotein [LDL]-cholestérol) ou de néphropathie associée (augmentation des triglycérides et du LDL-cholestérol, diminution du high density lipoprotein [HDL]-cholestérol). Lorsque l’équilibre glycémique du diabète est satisfaisant, les triglycérides et le LDL-cholestérol sont normaux ou légèrement diminués et le HDL-cholestérol normal ou discrètement augmenté. Les patients diabétiques de type 1 présentent des anomalies qualitatives, potentiellement athérogènes, même en cas de bon contrôle glycémique. Ces modifications qualitatives comprennent une augmentation du rapport cholestérol/triglycérides au sein des very low-density lipoprotein (VLDL), un enrichissement en triglycérides des LDL et HDL, des changements de la composition de la couche lipidique périphérique des lipoprotéines, une glycation des apolipoprotéines, une augmentation de l’oxydation des LDL ainsi qu’un accroissement du nombre des particules LDL petites et denses. Ces modifications qualitatives des lipoprotéines sont susceptibles d’avoir des conséquences fonctionnelles. Les VLDL et LDL des patients diabétiques de type 1 induisent une accumulation anormale de cholestérol au sein des macrophages. Les HDL des sujets diabétiques de type 1 présentent une réduction de leurs propriétés anti-oxydantes et vasorelaxantes. Ces anomalies qualitatives ne sont totalement secondaires à l’hyperglycémie et semblent, en partie, être la conséquence de l’hyperinsulinémie périphérique lié à l’administration sous-cutanée de l’insuline. Les répercussions exactes de ces anomalies lipidiques qualitatives sur le développement des complications cardiovasculaires, au cours du diabète de type 1, sont encore inconnues.

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Mots clés : Diabète ; Type 1 ; Insuline ; Lipides ; Lipoprotéines
Patients with type 1 diabetes (T1D) present with lipid disorders — mostly qualitative abnormalities of lipoproteins — that can promote atherogenesis. The pathophysiology of these lipid abnormalities has not been completely elucidated, but hyperglycaemia and peripheral hyperinsulinaemia, as the result of subcutaneous insulin administration, are likely to play a role. This is a brief review of lipoprotein metabolism, including the role of insulin in lipid metabolism, and the quantitative and qualitative abnormalities of lipoproteins seen in T1D.

1. Lipoprotein metabolism in brief

Lipoproteins, which transport non-water-soluble cholesterol and triglycerides in plasma, are spherical particles composed of a central core of non-polar lipids (cholesterol esters, triglycerides) and a surface monolayer of phospholipids, free cholesterol and apolipoproteins. Lipoproteins are generally classified according to their density as chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). An overview of lipoprotein metabolism is shown in Fig. 1.

1.1. Chylomicrons

Chylomicrons, the largest of the lipoprotein particles, are responsible for the transport of dietary triglycerides and cholesterol. They are composed of triglycerides (85–90%), cholesterol esters, phospholipids and apolipoproteins (mainly apoB48, but also apoA-I and apoA-IV). The formation of chylomicrons takes place in enterocytes, and the process that links the lipid components (triglycerides, cholesterol esters, phospholipids) and apoB48 is carried out by microsomal transfer protein (MTP). Chylomicrons are secreted into the lymphatic circulation before entering the bloodstream. In plasma, the triglycerides of chylomicrons are hydrolyzed by lipoprotein lipase, leading to the formation of smaller, triglyceride-poorer particles known as “chylomicron remnants”. Chylomicron remnants are cleared by the liver through the LDL B/E receptor or LDL receptor-related protein (LRP) receptor.

1.2. VLDLs and IDLs

VLDL particles, secreted by the liver, consist of endogenous triglycerides (55–65%), cholesterol, phospholipids and apolipoproteins (apoB100, as well as apoCs and apoE). In the hepatocyte, the formation of VLDL occurs in two major steps. In the first step, which takes place in the rough endoplasmic reticulum, apoB is co-translationally and post-translationally lipidated by MTP. MTP transfers lipids (mainly triglycerides, but also cholesterol esters and phospholipids) to apoB. This first step leads to the formation of pre-VLDL.[1] In the second step, pre-VLDL is converted to VLDL in the smooth-membrane compartment. This step is driven by ADP ribosylation factor-1 (ARF-1) and its activation of phospholipase D, needed for the formation of VLDL from pre-VLDL.[1]

In plasma, the VLDL triglycerides are hydrolyzed by lipoprotein lipase. As VLDL becomes progressively triglyceride-depleted, a portion of the surface, including phospholipids and...
apolipoproteins C and E, is transferred to HDL. This metabolic cascade leads to the formation of IDL particles, which are either cleared by the liver through LDL B,E receptors or further metabolized to form LDL. The enzyme hepatic lipase, which has both triglyceride lipase and phospholipase activities, is involved in the metabolic process that generates LDL particles from IDL.

1.3. LDLs

LDL is the final product of the VLDL–IDL–LDL cascade. It is the main cholesterol-bearing lipoprotein in plasma. Each LDL particle contains one molecule of apoB100, which plays an important role in LDL metabolism — in particular, the recognition of its dedicated LDL B,E receptor. Clearance of LDL is mediated by the LDL B,E receptor, and 70% of LDL B,E receptors are located on hepatic cells while 30% are found on other cells of the body.

1.4. HDLs

HDL particles are secreted by the hepatocytes as small, lipid-poor lipoproteins that contain mostly apoA-I and receive, via the circulation, phospholipids, apoCs and apoE from chylomicrons and VLDL. Nascent or lipid-poor HDL receives, from peripheral cells, free cholesterol and phospholipids through the ABCA1 (ATP-binding cassette A1) transporter, which allows the transport of free cholesterol and phospholipids from the cell cytoplasm to HDL particles [2]. Within the HDL particles, free cholesterol is esterified by lecithin cholesterol acyltransferase (LCAT), which leads to the formation of HDL3 particles. The fusion of two HDL3 particles, promoted by phospholipid transfer protein P (LTP), leads to the formation of one large HDL2 particle. HDL2 lipoproteins, rich in cholesterol ester, are degraded by hepatic and endothelial lipases, leading to the formation of HDL remnant particles, which are cleared by the liver after recognition by the scavenger receptor class B type 1 (SR-B1) receptor [3].

1.5. Lipid-transfer proteins

Lipoprotein metabolism is largely influenced by lipid-transfer proteins. Of these, cholesteryl ester transfer protein (CETP) and phospholipid transfer protein (PLTP) have important roles to play. CETP facilitates the transfer of triglycerides from triglyceride-rich lipoproteins (mainly VLDL) to HDL and LDL, and the reciprocal transfer of cholesteryl esters from HDL and LDL to VLDL [4]. PLTP facilitates the transfer of phospholipids and α-tocopherol between lipoproteins, and is also involved in the formation of HDL2 lipoproteins from HDL3 particles [5]. Any modification of these CETP and PLTP activities is likely to promote significant qualitative lipoprotein abnormalities.

**Fig. 2.** Main effects of insulin on lipoprotein metabolism. VLDL: very low density lipoprotein; IDL: intermediate density lipoprotein; LDL: low density lipoprotein; HDL: high density lipoprotein; LPL: lipoprotein lipase; HL: hepatic lipase; CETP: cholesteryl ester transfer protein; LCAT: lecithin-cholesterol acyltransferase; B/E rec.: B/E receptor (LDL receptor); LRP: LDL receptor-related protein; FFA: free fatty acids; Chol: cholesterol; TG: triglycerides; PL: phospholipids; Apo: apolipoprotein; CE: cholesterol esters; ABCA1: ATP-binding cassette A1 transporter. 1: insulin inhibits hormone-sensitive lipase; 2: insulin activates lipoprotein lipase (LPL); 3: insulin inhibits hepatic VLDL production; 4: insulin increases LDL B/E receptor expression; 5: insulin activates LCAT; 6: insulin activates hepatic lipase (HL).
2. Insulin and lipoprotein metabolism

Insulin plays a central role in the regulation of lipid metabolism [6]. The main sites of insulin action on lipoprotein metabolism are shown in Fig. 2.

In adipose tissue, insulin inhibits hormone-sensitive lipase. Thus, insulin has an antilipolytic action, promoting storage of triglycerides in the adipocytes while reducing the release of free fatty acids from adipose tissue into the circulation.

Insulin also inhibits VLDL production by the liver. In non-diabetic subjects, it can induce a 67% decrease of VLDL-triglyceride production and a 52% decrease of VLDL-apoB production [7,8]. Insulin reduces VLDL production by diminishing circulating free fatty acids (due to its antilipolytic effects), which are substrates for VLDL, and also by a direct inhibitory effect in hepatocytes [8].

Insulin is a potent activator of lipoprotein lipase (LPL), promoting the catabolism of triglyceride-rich lipoproteins and reducing, as a consequence, plasma triglyceride levels. Insulin not only enhances LPL activity [9], but also has a direct, positive effect on the LPL gene to promote LPL synthesis [10]. Insulin also boosts the clearance of LDL by increasing LDL B,E-receptor expression and activity [11,12].

Insulin also acts on HDL metabolism by activating LCAT and hepatic lipase activities [13].

3. Quantitative lipid abnormalities in type 1 diabetes

3.1. Untreated type 1 diabetes (diabetic ketoacidosis)

In T1D patients with diabetic ketoacidosis, quantitative lipid abnormalities are due to insulin deficiency. Triglyceride-rich lipoproteins (chylomicrons, VLDLs) are increased, leading to hypertriglyceridaemia. This is mainly due to decreased LPL activity [6,14]. Diabetic ketoacidosis is a state of severe insulin deficiency, with reduced LPL activity as a consequence, as insulin usually stimulates its activity. This reduced activity leads to profound decreases in triglyceride-rich lipoprotein catabolism [15]. In such a state of severe insulin deficiency, reduced catabolism of triglyceride-rich lipoproteins is, by far, the main factor leading to hypertriglyceridaemia, which can rapidly be resolved by well-titrated insulin therapy [16].

LDL cholesterol is also decreased during diabetic ketoacidosis [16]. The drop in plasma LDL-cholesterol levels is the direct consequence of the reduced triglyceride-rich lipoprotein catabolism that, in turn, is due to the reduced LPL activity (see above). Furthermore, HDL cholesterol is also significantly decreased [16]. This is a consequence of the hypertriglyceridaemia observed in this condition. Indeed, the elevated levels of plasma triglyceride-rich lipoprotein drives, through CETP, the transfer of triglycerides from triglyceride-rich lipoproteins to HDL, leading to the formation of triglyceride-rich HDL particles. HDL enriched in triglycerides becomes a good substrate for hepatic lipase, leading to an increase in its catabolism and, thus, a decrease in plasma HDL-cholesterol levels. Nevertheless, the resultant low levels of HDL cholesterol can be rapidly resolved by well-titrated insulin therapy [16].

3.2. Treated type 1 diabetes

Patients with treated T1D may have quantitative lipid disorders. In a prospective study involving 895 young T1D patients, 20.1% had plasma triglycerides >1.7 mmol/L, 9.6% had LDL cholesterol >3.4 mmol/L and 25.9% had non-HDL cholesterol levels >3.4 mmol/L [17]. In these patients, HbA1c was independently correlated with LDL-cholesterol, non-HDL-cholesterol and triglyceride levels, indicating that these disorders were mostly observed in patients with poor glycaemic control [17]. In the Diabetes Control and Complications Trial (DCCT), HbA1c correlated positively with total cholesterol, LDL cholesterol and triglycerides at baseline [18]. In addition, in a recent study of 512 young patients with T1D and 188 non-diabetic age-matched controls, patients with suboptimal control (HbA1c ≥ 7.5%) had considerably more quantitative lipid disorders than those with optimal control (HbA1c < 7.5%) [19]. These data suggest that quantitative lipid abnormalities are more frequent when T1D is not well controlled.

3.2.1. Treated type 1 diabetics with poor or suboptimal glycaemic control

In cases of poor or suboptimal control, patients with T1D may present with increased plasma triglyceride levels [14]. Such hypertriglyceridaemia is due to an increased production of VLDL, promoted by elevated circulating free fatty acids secondary to a relative insulin deficiency [20].

T1D patients with poor or suboptimal glycaemic control also have increased LDL-cholesterol levels compared with non-diabetic individuals and T1D patients who have optimal glycaemic control [14,19]. Indeed, in this situation, VLDL production is increased (see above) when catabolism of triglyceride-rich lipoproteins is not sufficiently decreased, which leads to increased LDL production [14].

3.2.2. Treated type 1 diabetics with optimal glycaemic control

The lipid profile in well-controlled type 1 diabetic patients is totally different from that in poorly controlled T1D patients [14,20]. Plasma triglycerides are normal or slightly decreased [14,20]. This slight decrease may be seen with intense insulin therapy because of an increased down-regulation of VLDL production due to augmented plasma insulin levels as a consequence of the subcutaneous route of insulin delivery [21,22]. Also, in patients with well-controlled T1D, peripheral hyperinsulinaemia may be associated with increased LPL activity, which might be an additional factor responsible for the reduction of plasma triglycerides [23].

In such patients, plasma LDL-cholesterol levels are also normal or slightly decreased [24] and, similarly, this slight decrease in plasma LDL cholesterol may be observed with intense insulin therapy as a consequence of decreased VLDL production due to peripheral hyperinsulinaemia (see above).

In addition, plasma HDL-cholesterol levels are normal or slightly increased in well-controlled T1D patients [14]. Some studies have shown an increase in the HDL2 subtraction [25,26] whereas others have found an increase in HDL3 [24]. It has also
been reported that elevation of HDL in T1D patients with good glycaemic control was caused by an increase in HDL particles containing only apoA-I (LpA-I) [26]. This increase in plasma HDL cholesterol could be the consequence of the elevated LPL-to-hepatic lipase ratio observed in patients with well-controlled T1D (increased LPL activity and normal hepatic lipase activity) [26] that, in such patients, is probably due to peripheral hyperinsulinaemia as a consequence of the subcutaneous route of insulin administration [26].

3.2.3. Subcutaneous vs intraperitoneal insulin therapy

Intensive subcutaneous insulin therapy results in normalization of plasma glucose, but at the expense of peripheral hyperinsulinaemia, which is likely to alter lipoprotein metabolism (as described above). Implantable insulin pumps with intraperitoneal insulin administration mimic the physiological route of insulin delivery and are likely to restore the normal portal–peripheral insulin gradient. For this reason, several studies have analyzed the modification of lipoprotein metabolism after replacement of subcutaneous insulin therapy by intraperitoneal insulin therapy. Plasma triglycerides were increased in one study [27], but remained unchanged in three others [28,13,29]. Total cholesterol and apoB were also unchanged [27,28,13,29], while HDL cholesterol was decreased [27] or stayed the same [28,13,30]. The discrepancies across these studies may have been due to confounding factors such as the degree of glycaemic control and peripheral insulin levels during subcutaneous insulin therapy. Further studies are needed to clarify the effect of intraperitoneal insulin administration on lipoprotein metabolism.

3.2.4. Type 1 diabetics with nephropathy

In T1D patients with nephropathy and overt albuminuria, elevated plasma levels of total cholesterol, triglycerides and LDL cholesterol are observed, whereas HDL cholesterol is decreased due to a fall in HDL2 [14,22,31]. In the EURODIAB IDDM Complications Study, macroalbuminuria was associated with a significant increase in plasma triglycerides, cholesterol, LDL cholesterol and LDL-to-HDL ratio in both men and women, and with decreased HDL cholesterol in women [32].

Some quantitative lipid modifications are also seen in T1D patients with microalbuminuria. Such patients, compared with normoalbuminuric patients, have increased plasma apoB [33–35] and LDL-cholesterol levels [33,34], and an increased apoB-to-apoA1 ratio [34,35]. A positive correlation has been found between urinary albumin excretion rate and plasma apoB and apoB-to-apoA1 ratio [34]. In the EURODIAB IDDM Complications Study, microalbuminuria was associated with increased plasma triglycerides [32]. However, the mechanisms responsible for these lipoprotein abnormalities in T1D patients with microalbuminuria are still unclear.

In addition, serum lipids have been shown to be associated with the progression of nephropathy in T1D. In a prospective study involving 152 patients with T1D followed for 8–9 years, LDL cholesterol was an independent risk factor associated with progression of nephropathy [36].

4. Qualitative lipid abnormalities in type 1 diabetes

Several qualitative abnormalities of lipoproteins are observed in patients with T1D, including those with good metabolic control and no significant quantitative lipid changes. These qualitative lipid abnormalities are not totally reversible with optimal glycaemic control and are likely to be atherogenic.

4.1. VLDL abnormalities

The VLDL from patients with T1D is frequently enriched in esterified cholesterol at the expense of triglycerides, leading to an increased VLDL cholesterol-to-triglyceride ratio [37,38]. It has been suggested that this compositional change may be due to increased cholesteryl ester transfer between lipoproteins [38]. It has also been shown that the VLDL cholesterol-to-triglyceride ratio was significantly reduced with intraperitoneal insulin therapy [39]. Furthermore, the free cholesteryl-lecithin ratio within the peripheral layer of VLDL particles is increased [14,38]. Such an increase within the peripheral layer of lipoproteins has been shown to increase the risk for cardiovascular events, possibly by reducing the fluidity and stability of lipoproteins [40]. Moreover, the VLDL from patients with T1D has been shown in vitro to induce abnormal responses in the cellular cholesterol metabolism of human macrophages [41].

4.2. LDL abnormalities

In patients with T1D, LDL is often enriched with triglycerides and an increased number of small, dense LDL particles is observed [42–44]. The presence of small, dense LDL particles is associated with an increased cardiovascular risk [45], and the data indicate that such particles have atherogenic properties. Indeed, small, dense LDL particles have a reduced affinity for the LDL B,E receptor and are preferentially taken up by macrophages through scavenger receptors, leading to the formation of foam cells. In addition, small, dense LDL particles have a greater affinity for intimal proteoglycans than do large LDL particles, which may favour the penetration of LDL particles into the arterial wall [46]. It has even been found that subjects with small, dense LDL particles have an impaired response to the endothelium-dependent vasodilator acetylcholine [47]. Furthermore, small, dense LDL particles show an increased susceptibility to oxidation [48]. However, a reduction in the proportion of small, dense LDL particles has been reported after optimization of glycaemic control in T1D patients [49].

The free cholesteryl-lecithin ratio within the peripheral layer of LDL particles is increased in T1D patients [14,38], and glycation of ApoB occurs within LDL in parallel with plasma hyperglycaemia. ApoB glycation significantly reduces LDL binding to the B,E receptor even when apoB glycation is moderate [50,51]. Also, glycated LDLs are preferentially taken up by macrophages through scavenger receptors, leading to the formation of foam cells in the arterial wall.

Patients with T1D may also show increased oxidation of LDL, which is promoted by glycaemic excursions [52], and oxidative modification of LDL results in rapid uptake by
macrophages, leading to foam-cell formation. In addition, oxidized LDLs promotes monocyte chemotaxis by increasing the synthesis of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), by endothelial cells, and stimulate the formation of cytokines, such as tumour necrosis factor (TNF)-α or interleukin (IL)-1, by macrophages, thereby amplifying the inflammatory atherosclerotic process.

4.3. HDL abnormalities

The HDL from patients with T1D is often enriched with triglycerides [14,38]. This modification has been attributed to an increased cholesteryl ester transfer between lipoproteins [38]. Also, in HDL particles from T1D patients, the sphingomyelin-to-lecithin ratio within the peripheral layer is raised, which can increase HDL rigidity [53]. These alterations are not totally reversible by optimal glycaemic control [54]. The ApoA-I within HDL is glycated in patients with T1D, which can impair the HDL-mediated reverse cholesterol pathway. Indeed, it has been shown that HDL particles containing glycated apoA-I were less effective in promoting cholesterol efflux from cells [55].

In addition to its role in the reverse cholesterol pathway, HDL has antioxidative, anti-inflammatory, antithrombotic and vasorelaxant properties, all of which are potentially anti-atherogenic [56]. However, some of these properties are reduced in patients with T1D. Indeed, a significant reduction in the activity of paraoxonase, an antioxidative enzyme associated with HDL, is observed in such patients [57,58]. As a consequence, the HDL from T1D patients is less efficient at protecting erythrocyte membranes and LDL particles against oxidative damage than the HDL in non-diabetic individuals [57,58]. Using rabbit aorta rings, it has even been shown that the HDL from patients with T1D is no longer able to prevent endothelium-dependent vasoconstriction induced by oxidized LDL, whereas HDL from non-diabetics can do so [59].

4.4. Lipid-transfer proteins

In some studies, an increased cholesteryl ester transfer between lipoproteins [38,60] or CETP activity [61] has been seen in normolipidaemic patients with T1D. In other studies, increased CETP activity has been reported only in T1D patients who smoke or have microalbuminuria [62,63]. This augmented CETP activity might explain the increase in free cholesteryl-to-triglyceride ratio in VLDL and its decrease in HDL. Also, some studies have shown a positive correlation between CETP activity and hyperglycaemia [64,65]. However, the main factor that is most likely to be responsible for the increased CETP activity in T1D is peripheral hyperinsulinaemia secondary to the subcutaneous route of insulin administration. Indeed, peripheral hyperinsulinaemia is responsible for the increased LPL activity seen in patients with T1D [23], and it has been reported that LPL, in the presence of VLDL, enhances CETP activity [66,67]. Moreover, it has been shown that, in patients with T1D, the increase in both LPL and CETP activities is abolished by intraperitoneal insulin administered by implantable insulin pumps, mimicking the physiological portal route, or following pancreatic grafts [60,68].

Increased PLTP activity has also been reported in patients with T1D. In one study, PLTP activity was positively correlated with CETP activity, LDL cholesterol and HDL cholesterol [61]. The reasons and consequences of this increased PLTP activity, however, are yet to be clarified.

5. Conclusion

Quantitative lipid abnormalities are observed in patients with poorly controlled T1D (increased triglycerides and LDL cholesterol), or with micro- or macroalbuminuria (increased triglycerides and LDL cholesterol, decreased HDL cholesterol). In contrast, patients with optimally controlled T1D show normal or slightly decreased triglyceride and LDL-cholesterol levels and, sometimes, increased HDL-cholesterol levels. In addition, qualitative abnormalities of lipoproteins may be observed in patients with T1D despite good glycaemic control. These abnormalities are not fully explained by hyperglycaemia and may be partly due to the peripheral hyperinsulinaemia associated with subcutaneous insulin administration. Nevertheless, the precise consequences of such qualitative lipid changes on the development of cardiovascular disease in T1D patients are, as yet, still unknown.

Conflict of interests

The author has not declared any conflicts of interest.

References


