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Fenofibrate-Induced Hyperhomocysteinaemia

Clinical Implications and Management

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Contents

Abstract

Fenofibrate is among the drugs of choice for treatment of hypertriglyceridaemia and low levels of high-density lipoprotein (HDL)-cholesterol, both recognised as risk factors for cardiovascular disease. Recently, a number of studies have shown an elevation of homocysteine levels with fenofibrate or bezafibrate therapy. Homocysteine is an atherogenic amino acid derived from the methionine cycle. At present, the underlying mechanism for this elevation has not been elucidated. While deterioration of vitamin status does not seem to be involved, impairment of renal function or changes in creatine metabolism are regarded as probable mechanisms. In patients not receiving lipid-lowering drugs, vitamin supplementation with folic acid and vitamin B12 effectively reduces the plasma homocysteine level. Two studies have shown that addition of folic acid or a vitamin combination to fenofibrate prevented most of the homocysteine increase associated with fenofibrate. Although the consequence of increasing homocysteine levels for cardiovascular risk has not been proven at present, it has to be considered that fenofibrate will be given for long-term treatment. Therefore, addition of folic acid and vitamin B12 to fenofibrate can be recommended to prevent the increase of homocysteine associated with fenofibrate, or treatment could be changed to gemfibrozil, which does not increase plasma homocysteine levels.

There has been considerable debate whether elevated triglycerides are an independent risk factor for coronary heart disease or whether this association is mediated by the concurrently observed low levels of high-density lipoprotein (HDL)-cholesterol.[1,2] With respect to cardiovascular risk, hypertriglyceridaemia must be divided into isolated hypertriglyceridaemia and combined hyperlipidaemia. Whereas isolated hypertriglyceridaemia is mostly due to an elevation of chylomicrons, which are most probably not atherogenic, combined hyperlipidaemia is characterised by elevated triglycerides and total cholesterol due to elevation of very low-density lipoprotein (VLDL)-cholesterol, while low-density lipoprotein (LDL)-cholesterol levels are normal or only slightly elevated and HDL-cholesterol levels are low. However, normal LDL-cholesterol in this condition conceals a preponderance of small, dense LDL particles, which are highly atherogenic.[3] Thus, this lipoprotein phenotype has been called the atherogenic lipoprotein phenotype characterised by elevated triglycerides, low HDL-cholesterol and small, dense LDL-cholesterol.[3] It is the result of overproduction of triglyceride-rich lipoproteins and reduced catabolism of LDL-cholesterol and is among the most often observed dyslipidaemias.

Drugs of choice for the treatment of hypertriglyceridaemia are the fibric acid derivatives, with the main substances being fenofibrate, bezafibrate, ciprofibrate and gemfibrozil. They are effective in lowering elevated triglycerides, increasing HDL-cholesterol and lowering LDL-cholesterol.[4,5] Although the hydroxymethyglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are more powerful in reducing LDL-cholesterol, the main strength of the fibrates is the reduction of triglyceride-rich lipoproteins. Fibrates exhibit their lipid-lowering action by activation of the peroxisome proliferation-activated receptors-α (PPAR-α), which form a subfamily of the nuclear receptor gene family. Lowering of triglycerides by 50% and increase of HDL-cholesterol by 10–20% can be achieved by administration of fenofibrate or the other fibrates.[4,5] Worldwide, about 3–4 million patients are being treated with fenofibrate and bezafibrate. Generally, fenofibrate is considered to have a favourable safety profile and is well tolerated.[5,6] According to drug-monitoring programmes and intervention studies,[6-8] serious adverse effects are rare (<0.5%) and include hepatitis with jaundice, cholelithiasis and pancreatitis. Other adverse effects include muscle pain with increase of creatine phosphokinase and abnormal liver function tests.[6] In the drug-monitoring studies, adverse effects were reported in 4–5% of patients receiving micronised fenofibrate.[6,7] In addition, induction of renal failure has been reported after therapy with fibric acid derivatives, especially in recipients of renal transplants[9,10] or after cardiopulmonary bypass surgery.[11]

Recently, it has been reported that fenofibrate and bezafibrate treatment were associated with hyperhomocysteinaemia, which is now recognised as a risk factor for coronary heart disease. This is obviously a newly observed adverse effect of this class of hyperlipidaemic drugs that has not been observed after lipid-lowering therapy with HMG-CoA reductase inhibitors.[12,13] Therefore, this review shows the evidence of hyperhomocysteinaemia as a risk factor for thrombosis and atherosclerosis, analyses the studies on fenofibrate and homocysteine and discusses the underlying causes of fibrate-induced hyperhomocysteinaemia. Finally, studies on the effect of addition of vitamins to fenofibrate are reviewed and their results compared with those of other vitamin studies for homocysteine lowering.

1. Elevation of Total Homocysteine: Implication for Atherosclerotic Risk

Since the discovery of the inborn error of metabolism homocystinuria in 1962, homocysteine has attracted much attention because of its association with thrombosis and cardiovascular disease. The association of homocystinuria with atherosclerotic and thrombotic events was extended to mild hyperhomocysteinaemia, which is now regarded as

an independent risk factor for cardiovascular disease and venous thrombosis.[14] While children with untreated homocystinuria have homocysteine levels of 100 μmol/L or more, the upper limit of the reference range of homocysteine in plasma is as low as 10–15 μmol/L, depending on the population, method of homocysteine determination or risk stratification. Elevations up to 30 μmol/L are called mild hyperhomocysteinaemia, and levels between 30 and 100 μmol/L are classified as moderate hyperhomocysteinaemia. About 10% of the population have mild hyperhomocysteinaemia and fewer than 1% have moderate or severe hyperhomocysteinaemia.[15]

The major causes of mild to moderate hyperhomocysteinaemia are vitamin B12 or folic acid deficiency and impairment of renal function. However, during recent years, a number of drugs have been identified that are associated with or directly cause mild hyperhomocysteinaemia.[16] One of these drug classes is the fibric acid derivatives, represented by fenofibrate, bezafibrate, ciprofibrate and gemfibrozil, with fenofibrate having been studied most intensively with respect to homocysteine metabolism.

The most convincing evidence of whether hyperhomocysteinaemia is a risk factor for cardiovascular disease is derived from epidemiological rather than from mechanistic studies. The biochemical evidence on the atherogenic effects of hyperhomocysteinaemia has been investigated in numerous animal and cell-culture studies. Homocysteine at high concentrations is toxic to endothelial cells, causes platelet aggregation and adhesion, influences clotting factors in a prothrombotic direction and induces proliferation of smooth muscle cells. The mechanisms by which elevated homocysteine levels may be atherogenic have been reviewed in depth by several authors.[17,18] In addition to the manifold effects of hyperhomocysteinaemia shown *in vitro*, acute and chronic hyperhomocysteinaemia has been shown *in vivo* to be associated with endothelial dysfunction, an early event in atherogenesis.[19,20] The endothelial dysfunction induced by acute hyperhomocysteinaemia after methionine loading has been suggested to be the effect of the pronounced elevation of the free homocysteine moiety in plasma.[21] Interestingly, endothelial dysfunction can be attenuated by concurrent application of antioxidative vitamins[22,23] or folic acid.[24,25] The mechanism by which hyperhomocysteinaemia causes endothelial dysfunction is thought to be dependent on the generation of reactive oxygen species through homocysteine and decreased nitric oxide (NO) bioavailability. The concurrent elevation of asymmetrical dimethylarginine (ADMA), a strong inhibitor of the NO synthase,[26] may further contribute to the endothelial dysfunction associated with hyperhomocysteinaemia. However, no mechanism can fully explain the atherogenic effects of elevated homocysteine concentrations.

The association of mild hyperhomocysteinaemia with fatal or nonfatal cardiovascular disease or total mortality was studied in a large number of retrospective studies, which more or less unequivocally identified hyperhomocysteinaemia as a risk factor for cardiovascular disease.[27] Since 1992, a number of prospective studies have been published that investigated the association of homocysteine with either future cardiovascular events or total mortality. Most, but not all of these studies have shown an association of elevated homocysteine concentrations with vascular disease, and the association is even more pronounced with mortality. These studies have been reviewed and subjected to various meta-analyses showing that an increase of homocysteine is associated with increased risk for coronary heart disease, stroke and peripheral arterial and venous occlusive disease.[28,29] Thus, mild to moderate hyperhomocysteinaemia is regarded as a risk factor for occlusive vascular disease by most authors,[14] although the independent association between homocysteine and vascular disease has been questioned by some scientists.[30] Recently, additional studies have been published that investigated the association of hyperhomocysteinaemia with mortality.[31,32] From these studies it appeared that hyperhomocysteinaemia is even more closely related to total or cardiovascular

disease mortality than to cardiovascular disease morbidity. However, the association between hyperhomocysteinaemia and cardiovascular disease has motivated clinical trials investigating the effect of homocysteine lowering on cardiovascular endpoints (including venous thrombosis) involving about 60 000 patients and controls.[28,33-35] These studies will answer whether lowering of homocysteine by vitamin supplementation will also reduce cardiovascular morbidity and mortality. Results of these studies will be published after 2003.

2. Elevation of Total Homocysteine by Fibrates: Review of Published Studies

An increase in total homocysteine in plasma has been reported for different derivatives of fibric acid, namely fenofibrate, ciprofibrate and bezafibrate. Most studies investigated the effect of fenofibrate on the plasma homocysteine level (a total of 173 patients).[36-44] A homocysteine-increasing effect has also been documented for bezafibrate (38 patients in three studies)[39,45,46] and ciprofibrate (26 patients),[46] whereas gemfibrozil had no effect on plasma homocysteine after short-term intervention in 22 patients.[43]

From the published studies, it appeared that the homocysteine-increasing effect of fenofibrate was independent of time, as it was observed after short-term treatment for 6–9 weeks,[37,38,41-44] after intermediate treatment for 10–12 weeks[36,39] and after 6 months.[40] In all studies, the effect was quite comparable and was about a 30–40% increase of the baseline homocysteine level (table I). Some studies also observed an increase in the other sulphur-containing amino acids methionine and cysteine[36,40,41] and the dipeptide cysteinylglycine.[40]

The homocysteine-increasing effect of bezafibrate appears to be smaller: in three studies, homocysteine increases of 17 and 9% and even a decrease were reported.[38,45,46] Ciprofibrate was associated with an increase of homocysteine of 57% in one study.[46] Individual data on the

Table I. Studies investigating the effect of different fibrates on plasma homocysteine level (mean values ± SD)

Reference	Fibrate dose (mg) duration	Population studied	Basal and post-treatment homocysteine (μmol/L)
de Lorgeril et al.[36]	Fenofibrate 200 [12wk]	Hyperlipidaemic men (n = 29)	11.4 ± 3.5 → 16.6 ± 5.2
Landray et al.[37]	Fenofibrate dose according to renal failure [8wk]	Patients with chronic renal failure (n = 8) [GFR 23 ml/min]	15.1 → 21.8[a]
Dierkes et al.[38]	Fenofibrate 200 [6wk]	Hyperlipidaemic men (n = 10) age 39–56y	13.1 → 20.0[a]
	Bezafibrate 400 [6wk]	Hyperlipidaemic men (n = 10) age 39–56y	11.9 → 15.5[a]
Melenovsky[39]	Fenofibrate 200 [10wk]	Hyperlipidaemic men (n = 29)	12.4 + 36.5%
Jonkers et al.[45]	Bezafibrate 400 [6wk]	Hyperlipidaemic men (n = 16)	11.9 ± 2.1 → 14.1 ± 2.9
Giral et al.[40]	Fenofibrate 200 [6mo]	Hyperlipidaemic patients (n = 29)	12.3 ± 3.9 → 16.2 ± 4.6
Bissonnette et al.[41]	Fenofibrate 200 [8wk]	Hyperlipidaemic men (n = 20)	10.3 ± 3.3 → 14.1 ± 3.8
Harats et al.[46]	Ciprofibrate [12wk]	Hyperlipidaemic patients (n = 26)	+ 57%
	Bezafibrate [12wk]	Hyperlipidaemic patients (n = 12)	–16%
Dierkes et al.[42]	Fenofibrate 200 [6wk]	Hyperlipidaemic patients (n = 25)	+ 4.4 ± 5.3 or + 44 ± 47%
	Fenofibrate 200 + vitamins [6wk]	Hyperlipidaemic patients (n = 25)	+ 1.1 ± 2.8 or + 13 ± 25%
Westphal et al.[43]	Gemfibrozil 900 [6wk]	Hyperlipidaemic patients (n = 22)	12.9 (7.1–23.6) →12.4 (6.3–29.5)
	Fenofibrate 200 [6wk]	Hyperlipidaemic patients (n = 22)	10.7 (4.4–24.8) → 14.4 (7.7–23.1)
Stulc et al.[44]	Fenofibrate 200 + folic acid 10 every other day [9wk]	Hyperlipidaemic patients (n = 11)	10.1 ± 2.3 → 12.2 ± 3.1
	Fenofibrate 200 mg/day [9wk]	Hyperlipidaemic patients (n = 11)	12.3 ± 3.2 → 19.1 ± 7.2

a Median.

GFR = glomerular filtration rate; **SD** = standard deviation.

homocysteine increase were provided in three studies.[40,41,44] These studies showed that the homocysteine-increasing effect of fenofibrate occurred over the whole range of baseline homocysteine levels, and that the increase was similar for baseline homocysteine between 4 and 18 μmol/L. The homocysteine-increasing effect was observed in the majority of patients: in one study, an increase was observed in 26 of 29 patients (90%),[40] and other studies reported increases in 100% of patients[41] and in 21 out of 22 patients.[46] In our studies, homocysteine increases after fenofibrate were observed in 9 out of 10 patients[38] and in 23 out of 25 patients.[42] Although analysed in only a few studies, the homocysteine-increasing effect of fenofibrate seems to be independent of baseline vitamin status or methylenetetrahydrofolate reductase (MTHFR) C677T genotype.[41,42]

Thus, the published studies so far show a nearly uniform association of fenofibrate treatment with an increase in plasma homocysteine, although the absolute numbers of patients in whom the effect has been reported are small. The homocysteine-increasing effect of fenofibrate and other fibrates is therefore a newly observed adverse effect. Suspected mechanisms for this effect may be alteration in renal function, creatine metabolism in muscles, vitamin metabolism or PPAR-α activation by fibric acid derivatives.

3. Mechanisms by Which Fenofibrate May Induce Hyperhomocysteinaemia

The major determinants of fasting plasma homocysteine concentration in the average population are the status of folic acid and vitamin B12,[47] renal function,[48,49] the C677T polymorphism in the gene of MTHFR[50] and male sex.[15] The generation of homocysteine is also closely linked to creatine synthesis, thus explaining part of the association with muscle mass and renal function.[51-53] Additionally, various drugs have been identified as influencing the plasma homocysteine level,[16] namely fibric acid derivatives, nicotinic acid, phenytoin, methotrexate and metformin. Mechanisms by which these drugs may influence the homocysteine concentration are their influence on folic acid and vitamin B12 bioavailability and metabolism, deterioration of renal function, or other, as yet unknown interactions on a molecular level.

3.1 Influence on Vitamins

The effect of fenofibrate on the metabolism or plasma level of the vitamins involved in homocysteine metabolism has been addressed by only a few of the studies that investigated the homocysteine-increasing effect of fenofibrate. In our studies,[38,42,43] we found, after short-term treatment with bezafibrate, fenofibrate or gemfibrozil, no effect on plasma levels of folic acid, vitamin B12 or pyridoxal-5-phosphate (the active metabolite of vitamin B6). In another study, vitamin levels (serum folic acid, vitamin B12 and vitamin B6) were also measured and no effect on vitamin level by fenofibrate was observed after 8 weeks of therapy.[41]

Intracellular folic acid concentration, which is thought to be a more reliable marker for long-term folic acid status, was not determined in these studies and has not yet been investigated in any fenofibrate trial. Keeping in mind the short-term nature of most of the trials that investigated homocysteine and fenofibrate, measuring intracellular folic acid concentration would not have shed much light on the association of vitamin status and fenofibrate. Another option to assess changes in vitamin status is the measurement of metabolic markers such as methylmalonic acid for vitamin B12. However, the concentration of this marker is also influenced by renal function[54] and its use for vitamin B12 status measurement may be not appropriate in a situation when a drug may concurrently influence renal function. Another argument against a pronounced effect of fenofibrate on vitamin status is the safe, long-term use of fenofibrate in daily practice. We are not aware of any reports on fenofibrate-induced macrocytic anaemia, the specific sign of folic acid and vitamin B12 deficiency. Thus, at present it can be concluded that fenofibrate has no particular influence on folic

acid, vitamin B12 or vitamin B6 metabolism and that disturbances of these vitamins are most probably not the underlying cause of the homocysteine-increasing effect of fenofibrate.

3.2 Influence on Renal Function/Creatine Metabolism

There is a scientific debate as to whether fenofibrate causes impairment of renal function and whether this may be causative for the increase of homocysteine. Administration of fenofibrate causes a significant, pronounced, but reversible increase in serum creatinine.[10,55] However, in most patients the creatinine levels are within the reference range during fenofibrate therapy and do not attract the particular interest of the physician. Indeed, this adverse effect is not very well known, although some case reports showed that discontinuation of fibrate therapy was necessary because of development of renal failure.[9-11] However, a deterioration of neither glomerular filtration rate nor renal plasma flow due to fenofibrate or bezafibrate therapy was observed in studies using reliable and accurate techniques.[45,56] Thus, a reason for the increase in creatinine other than a decrease of the glomerular filtration rate may be increased creatine turnover in muscles, resulting in increased serum creatinine and increased urinary creatinine.[56] Similar data are also reported on the use of bezafibrate:[45] despite a 20% increase of serum creatinine and a 15% increase of urinary creatinine there was no change of the creatinine clearance in 16 patients. Since urinary creatinine is dependent on muscle mass and turnover, this suggests that fenofibrate or bezafibrate change the creatine/ creatinine metabolism in muscle. On the other hand, the plasma homocysteine level is closely linked to creatine metabolism and muscle mass, as creatine synthesis is dependent on the methyl donor *S*-adenosylmethionine, rendering *S*-adenosylhomocysteine. It was suggested that about 80% of the formed homocysteine during the methionine cycle is due to creatine synthesis.[52] Indeed, dietary administration of the precursor molecule guanidinoacetate to rats resulted in a significant increase in plasma homocysteine, while administration of creatine itself decreased plasma homocysteine in rats[57] or had no effect on plasma homocysteine in humans.[58] Thus, increases in creatine synthesis will stress the methionine cycle and probably also increase the synthesis and the plasma level of homocysteine.

However, two observations are in conflict with the reports on unaltered renal function after fenofibrate.[45,56] First, a 20% increase of cystatin C during fenofibrate therapy was observed in studies[38,42,43] that measured this specific marker of glomerular filtration rate,[48] suggesting impairment of renal function by fenofibrate. A plausible mechanism for the effects of fenofibrate on renal function is down-regulation of the renal cyclooxygenase (COX)-2 enzyme system through activation of PPAR-α, affecting the synthesis of vasodilating prostaglandins.[59] This particularly affects glomerular filtration rate in patients with impaired renal function who are dependent on the vasodilating prostaglandins synthesised by the COX-2 system.[60] Second, in two studies we also measured creatine kinase as a marker of increased creatine metabolism.[42,43] In neither of the studies was a change of creatine kinase observed, which could have been expected if muscle metabolism was affected by fenofibrate.

A present, the effect of fenofibrate on renal function as the underlying cause of hyperhomocysteinaemia remains a subject of debate. Increases of biochemical markers such as serum creatinine, urea and cystatin C suggest an effect of impaired renal function, which was, however, not shown in studies measuring renal blood flow and glomerular filtration rate. More studies are necessary before a final conclusion can be drawn.

However, although the effect of fenofibrate on renal function remains unclear, it can be calculated whether the creatinine increase can fully explain the homocysteine increase. Data from cross-sectional studies show the close relationship between serum creatinine and homocysteine. The theoretical increase of homocysteine associated with a 10–20% increase in serum creatinine can be

calculated by regression analysis and can be compared with the observed increase of homocysteine after fenofibrate. For this purpose, we used data from healthy middle-aged men[15] and from healthy elderly (Dierkes et al., unpublished data). The mean increase of creatinine by fenofibrate in our studies was 12 μmol/L[38,42] and the plasma homocysteine increase was on average 4.4 ± 5.3 μmol/L. Linear regression from the cross-sectional data revealed that a 12 μmol/L higher level of serum creatinine was associated with 1.4 μmol/L higher plasma homocysteine in the healthy elderly men and with 0.7 μmol/L higher homocysteine in the middle-aged men. Similar figures have been reported earlier in healthy men and women.[53] It appears that the fenofibrate-induced homocysteine increase is much higher than the estimated increase of 0.7–1.4 μmol/L. Thus, other mechanisms, which still have to be identified, may additionally play a role in the increase of total homocysteine after fenofibrate therapy.

This finding is in line with the observation that the increase in homocysteine by fenofibrate was not or only weakly associated with the increase in serum creatinine.[37,40] A recalculation of our own data[42] revealed that the correlation between increase of plasma homocysteine and creatinine was weak and nonsignificant (r = 0.28; NS). In other studies, data on a correlation between the increase in plasma homocysteine and creatinine are lacking.

3.3 Other Mechanisms

The option that fenofibrate interacts with methionine/homocysteine metabolism either via increased synthesis or reduced degradation at a molecular level cannot be excluded.

The homocysteine-increasing effect of fibric acid derivatives seems to be independent of the lipid-lowering effect of the fibrates. In a single study, the increase in homocysteine was associated with the increase of HDL-cholesterol.[40] In contrast to fenofibrate and bezafibrate, gemfibrozil has not been observed to have a homocysteine-increasing effect.[42] Gemfibrozil does not activate PPAR-α, suggesting the possibility that activation of PPAR-α may influence homocysteine metabolism.[61] However, currently there are no data on any association between homocysteine metabolism and PPAR-α activation in the scientific literature. One study reported a positive association between homocysteine plasma level and the mRNA expression of PPAR-δ in peripheral mononuclear cells.[62] However, since fibrates do not activate PPAR-δ,[63] this does not seem to be a likely explanation for the homocysteine increase by fibrates.

Interestingly, lipid lowering with niacin also increases the homocysteine concentration.[64-66] The homocysteine-increasing effect of niacin was observed after acute administration of the drug and is believed to be associated with the considerable methyl group demand exhibited by niacin. The methyl groups, however, are derived from *S*-adenosylmethionine, thus rendering *S*-adenosylhomocysteine.[64] In contrast to niacin, fenofibrate is not methylated during its metabolisation, making increased methyl demand an unlikely explanation for the homocysteine increase by fenofibrate.

4. Reversal of Homocysteine Elevation: the Action of Vitamins

To date, numerous studies have investigated the effects of vitamins on the plasma homocysteine level in healthy volunteers, patients with coronary heart disease and patients with varying degrees of renal disease.[67,68] In contrast, only two studies have been published that investigated the effect of vitamins on fenofibrate-induced hyperhomocysteinaemia.[42,44] Both studies showed that the addition of either folic acid or a combination of folic acid, vitamin B12 and vitamin B6 reduced the increase of plasma homocysteine associated with fenofibrate. However, in both studies, a significant increase of plasma homocysteine after fenofibrate plus vitamins was observed, although the increase was significantly lower than the increase with fenofibrate alone. This is in contrast to the decrease of homocysteine that has been observed after vitamin supplementation without fenofibrate

and is demonstrated by comparison of studies with fenofibrate and vitamins with studies that investigated the effect of vitamins on homocysteine without fenofibrate.

With respect to homocysteine lowering by vitamins, two important conditions have to be considered. First, folic acid is responsible for most of the homocysteine lowering that is observed after vitamin supplementation, although there is no clear dose-dependent effect. Second, the reduction of homocysteine is more dependent on the initial homocysteine level than on the dose of folic acid or other vitamins. Therefore, a retrospective comparison of the fenofibrate-vitamin studies with vitamin studies should consider the vitamin combination and dose and the baseline homocysteine concentration.[68]

In our fenofibrate-vitamin study,[42] we used a low-dose vitamin combination consisting of 650μg folic acid, 5mg vitamin B6 and 50μg vitamin B12. Comparable vitamin preparations have been used in hyperhomocysteinaemic men,[69] in normohomocysteinaemic volunteers,[70] in healthy young women,[71] and in two studies with patients with coronary heart disease[72,73] (table II).

In all these studies, a decrease of homocysteine was observed. In one study with coronary artery disease patients,[72] there was a substantial proportion of nonresponders (14%) which could be due to the inclusion of patients with CAD who received drugs that prevented the homocysteine-lowering effect of the vitamin combination.

Stulc et al.[44] investigated the effect of folic acid 10mg every other day together with fenofibrate. This dose is comparable to folic acid 5mg/day given to normohomocysteinaemic volunteers[70] or patients with CAD and normal homocysteine levels.[74] In the vitamin studies without fenofibrate, significant and pronounced decreases of homocysteine were observed which are again in contrast to the increase of plasma homocysteine observed after folic acid and fenofibrate.[44]

Table II. Studies investigating the effect of vitamins in patients treated with fenofibrate and comparison with the effect of vitamin supplementation studies without fenofibrate

Reference	Dose[a] and duration	Basal and post-treatment homocysteine (μmol/L)	Comment
High-dose vitamins			
Stulc et al.[44]	Fenofibrate 200 mg/day + 10mg FA every other day, 9wk	10.1 ± 2.3 → 12.2 ± 3.1	Mean ± SD, hyperlipidaemic men
den Heijer et al.[70]	5mg FA, 56 day (n = 35)	11.8 (7.0–22.1) → 8.7 (5.9–13.8)	Median and range, healthy volunteers
Thambyrajah et al.[74]	5mg FA, 12wk (n = 43)	11.7 (10.6–13.0) → 9.3 (8.5–10.1)	Mean and 95% CI, patients with CAD
Low-dose vitamins			
Dierkes et al.[42]	Fenofibrate 200 mg/day + 0.65mg FA + 0.05mg vitamin B12 + 5mg vitamin B6, 6wk (n = 25)	9.9 (6.7–19.9) → 11.7 (7.0–19.8)	Median and 5th and 95th percentile, hyperlipidaemic men
Schnyder et al.[72]	1mg FA + 0.4mg vitamin B12 + 10mg vitamin B6, 6mo (n = 105)	11.1 ± 4.3 → 7.2 ± 2.4	Mean ± SD, patients with CAD
den Heijer et al.[70]	0.5mg FA, 56 days (n = 36)	12.2 (4.7–22.3) → 10.0 (2.8–13.8)	Median and range, healthy volunteers
Ubbink et al.[69]	0.65mg FA + 0.4mg vitamin B12 + 10mg vitamin B6, 6wk (n = 20)	26.9 → 13.6	Mean, hyperhomocysteinaemic men
Wald et al.[73]	0.2, 0.4, 0.6, 0.8 or 1.0mg FA, 3mo (n = 25 each group)	0.2μg–1.2 μmol/L; 0.4μg–1.3 μmol/L; 0.6μg–1.8 μmol/L; 0.8μg–2.7 μmol/L; 1.0μg–2.5 μmol/L	Median change in each group, median baseline homocysteine was 13.4 μmol/L
Dierkes et al.[71]	0.4mg FA + 2mg vitamin B6, 4wk (n = 36)	7.7 (4.4–13.1) → 6.4 (3.9–10.8)	Geometric mean and range, healthy women

a Vitamin doses are provided as daily dose.

CAD = coronary artery disease; **FA** = folic acid; **SD** = standard deviation.

Hence, it can be concluded that the addition of vitamins to fenofibrate prevents much of the observed increase of homocysteine induced by fenofibrate. However, in contrast to vitamin supplementation studies without fenofibrate, there is no decrease of homocysteine after vitamin treatment. The effect of fenofibrate can obviously mask the effect of the vitamin.

5. Conclusion

A number of studies have shown that lipid-lowering therapy with fenofibrate or bezafibrate is associated with an increase of the plasma concentration of total homocysteine. Fenofibrate exhibits a stronger effect on plasma homocysteine than bezafibrate, and on average, the homocysteine level increases by 30–40%. The increase is obviously not associated with the triglyceride-lowering and HDL cholesterol-increasing effect of fenofibrate, but appears to be related to either changes of renal function or changes in creatine metabolism. However, more studies are needed that investigate the underlying mechanism responsible for the homocysteine increase.

At present, it appears that increasing homocysteine levels are associated with increasing cardiovascular risk, although the association appears to be weaker than for elevated blood cholesterol.[30] However, although the exact meaning of the homocysteine increase remains to be elucidated, this is an unwanted and undesirable effect of fenofibrate and bezafibrate.

Options to manage this problem include switching to other lipid-lowering agents, including HMG-CoA reductase inhibitors or gemfibrozil, or adding vitamins to fenofibrate. HMG-CoA reductase inhibitors have been shown to have no effect on the homocysteine level;[12,13,36] however, these agents lack most of the ability to decrease elevated triglycerides and to increase HDL cholesterol.[5] Therefore, HMG-CoA reductase inhibitors are not an alternative treatment for many patients with hypertriglyceridaemia. However, the homocysteine-increasing effect has not been observed after gemfibrozil,[43] another fibrate that lowers triglycerides effectively. In addition, gemfibrozil has been shown to be effective in lowering cardiovascular morbidity in prospective intervention trials.[75,76] However, there is only one study showing that gemfibrozil has no effect on homocysteine. This finding warrants confirmation in other studies. The other option is the addition of folic acid or a vitamin combination to fenofibrate. Two studies[42,44] have shown that the lipid-lowering effect of fenofibrate is not influenced by the addition of vitamins, and that most of the homocysteine increase can be prevented by concurrent administration of high-dose folic acid or low-dose multivitamins. Addition of vitamins is safe and does not substantially increase the costs of fenofibrate treatment. Since many studies have shown that hyperhomocysteinaemia is a risk factor for cardiovascular disease, one should choose one of the following options: either the choice of gemfibrozil as lipid-lowering drug or the addition of vitamins to fenofibrate as a safe and easy measure to reduce the concurrent homocysteine increase.

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References

1. Jeppesen J, Hein HO, Suadicani P, et al. Triglyceride concentration and ischemic heart disease: an eight-year follow up in the Copenhagen Male Study. Circulation 1998; 97: 1029-36
2. Assmann G, Schulte H, Funke H, et al. The emergence of triglycerides as a significant independent risk factor in coronary artery disease. Eur Heart J 1998; 19 Suppl. M: M8-14
3. Austin MA, King MC, Vranizan KM, et al. Atherogenic lipoprotein phenotype: a proposed genetic marker for coronary heart disease risk. Circulation 1990; 82: 495-506
4. Fruchart JC, Staels B, Duriez P. The role of fibric acids in atherosclerosis. Curr Atheroscler Rep 2001; 3: 83-92
5. Despres JP. Increasing high-density lipoprotein cholesterol: an update on fenofibrate. Am J Cardiol 2001; 88: 30N-6N
6. Kirchgässler KU, Schmitz H, Bach G. Effectiveness and tolerability of 12-week treatment with micronised fenofibrate 200mg in a drug-monitoring programme involving 9884 patients with dyslipidaemia. Clin Drug Invest 1998; 15: 197-204
7. Kornitzer M, Dramaix M, Vandenbroek MD, et al. Efficacy and tolerance of 200mg micronised fenofibrate administered over a 6-month period in hyperlipidaemic patients: an open Belgian multicenter study. Atherosclerosis 1994; 110 Suppl.: S49-54

8. The Diabetes Atherosclerosis Intervention Study Investigators. Effect of fenofibrate on progression of coronary-artery disease in type 2 diabetes: the Diabetes Atherosclerosis Intervention Study, a randomised study. Lancet 2001; 357: 905-10
9. Devuyst O, Goffin E, Pirson Y, et al. Creatinine rise after fibrate therapy in renal graft recipients. Lancet 1993; 341: 840
10. Lipscombe J, Lewis GF, Cattran D, et al. Deterioration in renal function associated with fibrate therapy. Clin Nephrol 2001; 55: 39-44
11. Sharobeem KM, Madden BP, Millner R, et al. Acute renal failure after cardiopulmonary bypass: a possible association with drugs of the fibrate group. J Cardiovasc Pharmacol Ther 2000; 5: 33-9
12. Lüttjohann D, Sigit JI, Locatelli S, et al. High-dose simvastin (80 mg/day) decreases plasma concentrations of total homocyst(e)ine in patients with hypercholesterolemia. Atherosclerosis 2001; 155: 265-6
13. MacMahon M, Kirkpatrick C, Cummings CE, et al. A pilot study with simvastatin and folic acid/vitamin B12 in preparation for the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Nutr Metab Cardiovasc Dis 2000; 10: 195-203
14. Ueland PM, Refsum H, Beresford SA, et al. The controversy over homocysteine and cardiovascular risk. Am J Clin Nutr 2000; 72: 324-32
15. Dierkes J, Jeckel A, Ambrosch A, et al. Factors explaining the difference of total homocysteine between men and women in the European Investigation Into Cancer and Nutrition Potsdam study. Metabolism 2001; 50: 640-5
16. Desouza C, Keebler M, McNamara DB, et al. Drugs affecting homocysteine metabolism: impact on cardiovascular risk. Drugs 2002; 62: 605-16
17. Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998; 338: 1042-50
18. Thambyrajah J, Townend JN. Homocysteine and atherothrombosis: mechanisms for injury. Eur Heart J 2000; 21: 967-74
19. Tawakol A, Omland T, Gerhard M, et al. Hyperhomocyst(e)inemia is associated with impaired endothelium-dependent vasodilation in humans. Circulation 1997; 95: 1119-21
20. Chambers JC, Obeid OA, Kooner JS. Physiological increments in plasma homocysteine induce vascular endothelial dysfunction in normal human subjects. Arterioscler Thromb Vasc Biol 1999; 19: 2922-7
21. Chambers JC, Ueland PM, Obeid OA, et al. Improved vascular endothelial function after oral B vitamins: an effect mediated through reduced concentrations of free plasma homocysteine. Circulation 2000; 102: 2479-83
22. Chambers JC, McGregor A, Jean-Marie J, et al. Demonstration of rapid onset vascular endothelial dysfunction after hyperhomocysteinemia: an effect reversible with vitamin C therapy. Circulation 1999; 99: 1156-60
23. Nappo F, De Rosa N, Marfella R, et al. Impairment of endothelial functions by acute hyperhomocysteinemia and reversal by antioxidant vitamins. JAMA 1999; 281: 2113-8
24. Usui M, Matsuoka H, Miyazaki H, et al. Endothelial dysfunction by acute hyperhomocyst(e)inaemia: restoration by folic acid. Clin Sci (Lond) 1999; 96: 235-9
25. Doshi SN, McDowell IF, Moat SJ, et al. Folic acid improves endothelial function in coronary artery disease via mechanisms largely independent of homocysteine lowering. Circulation 2002; 105: 22-6
26. Böger RH, Lentz SR, Bode-Böger SM, et al. Elevation of asymmetrical dimethylarginine may mediate endothelial dysfunction during experimental hyperhomocyst(e)inaemia in humans. Clin Sci (Lond) 2001; 100: 161-7
27. Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. JAMA 1995 Oct 4; 274 (13): 1049-57
28. Eikelboom JW, Lonn E, Genest Jr J, et al. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. Ann Intern Med 1999; 131: 363-75
29. Refsum H, Ueland PM, Nygard O, et al. Homocysteine and cardiovascular disease. Annu Rev Med 1998; 49: 31-62
30. Brattstrom L, Wilcken DE. Homocysteine and cardiovascular disease: cause or effect? Am J Clin Nutr 2000; 72: 315-23
31. Anderson JL, Muhlestein JB, Horne BD, et al. Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. Circulation 2000; 102: 1227-32
32. Vollset SE, Refsum H, Tverdal A, et al. Plasma total homocysteine and cardiovascular and noncardiovascular mortality: the Hordaland Homocysteine Study. Am J Clin Nutr 2001; 74: 130-6
33. Clarke R. Homocysteine and cardiovascular disease: overview. J Cardiovasc Risk 1998; 5: 213-5
34. Willems HP, den Heijer M, Bos GM. Homocysteine and venous thrombosis: outline of a vitamin intervention trial. Semin Thromb Hemost 2000; 26: 297-304
35. Spence JD, Howard VJ, Chambless LE, et al. Vitamin intervention for stroke prevention (VISP) trial: rationale and design. Neuroepidemiology 2001; 20: 16-25
36. de Lorgeril M, Salen P, Paillard F, et al. Lipid-lowering drugs and homocysteine. Lancet 1999; 353: 209-10
37. Landray MJ, Townend JN, Martin S, et al. Lipid-lowering drugs and homocysteine. Lancet 1999; 353: 1974-5
38. Dierkes J, Westphal S, Luley C. Serum homocysteine increases after therapy with fenofibrate or bezafibrate. Lancet 1999; 354: 219-20
39. Melenovsky V. Fenofibrate, but not atorvastatin treatment increases homocysteine levels in patients with combined hyperlipidemia [abstract]. Eur Heart J 2000; 21: 636
40. Giral P, Bruckert E, Jacob N, et al. Homocysteine and lipid lowering agents: a comparison between atorvastatin and fenofibrate in patients with mixed hyperlipidemia. Atherosclerosis 2001; 154: 421-7
41. Bissonnette R, Treacy E, Rozen R, et al. Fenofibrate raises plasma homocysteine levels in the fasted and fed states. Atherosclerosis 2001; 155: 455-62
42. Dierkes J, Westphal S, Kunstmann S, et al. Vitamin supplementation can markedly reduce the homocysteine elevation induced by fenofibrate. Atherosclerosis 2001; 158: 161-4
43. Westphal S, Dierkes J, Luley C. Effects of fenofibrate and gemfibrozil on plasma homocysteine. Lancet 2001; 358: 39-40
44. Stulc T, Melenovsky V, Grauova B, et al. Folate supplementation prevents plasma homocysteine increase after fenofibrate therapy. Nutrition 2001; 17: 721-3
45. Jonkers IJAM, de Man FHAF, Onkenhout W, et al. Implications of fibrate therapy for homocysteine. Lancet 1999; 354: 1208
46. Harats D, Yodfat O, Doolman R, et al. Homocysteine elevation with fibrates: is it a class effect? Isr Med Assoc J 2001; 3: 243-6
47. Selhub J, Jacques PF, Wilson PW, et al. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. JAMA 1993; 270: 2693-8

48. Norlund L, Grubb A, Fex G, et al. The increase of plasma homocysteine concentrations with age is partly due to the deterioration of renal function as determined by plasma cystatin C. Clin Chem Lab Med 1998; 36: 175-8
49. Wollesen F, Brattstrom L, Refsum H, et al. Plasma total homocysteine and cysteine in relation to glomerular filtration rate in diabetes mellitus. Kidney Int 1999; 55: 1028-35
50. Frosst P, Blom HJ, Milos R, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet 1995; 10: 111-3
51. Fukagawa NK, Martin JM, Wurthmann A, et al. Sex-related differences in methionine metabolism and plasma homocysteine concentrations. Am J Clin Nutr 2000; 72: 22-9
52. Mudd SH, Poole JR. Labile methyl balances for normal humans on various dietary regimens. Metabolism 1975; 24: 721-35
53. Brattstrom L, Lindgren A, Israelsson B, et al. Homocysteine and cysteine: determinants of plasma levels in middle-aged and elderly subjects. J Intern Med 1994; 236: 633-41
54. Lindgren A. Elevated serum methylmalonic acid: how much comes from cobalamin deficiency and how much comes from the kidneys? Scand J Clin Lab Invest 2002; 62: 15-9
55. Broeders N, Knoop C, Antoine M, et al. Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent? Nephrol Dial Transplant 2000; 15: 1993-9
56. Hottelart C, el Esper N, Achard JM, et al. Fenofibrate increases blood creatinine, but does not change the glomerular filtration rate in patients with mild renal insufficiency [in French]. Nephrologie 1999; 20: 41-4
57. Stead LM, Au KP, Jacobs RL, et al. Methylation demand and homocysteine metabolism: effects of dietary provision of creatine and guanidinoacetate. Am J Physiol Endocrinol Metab 2001; 28: E1095-100
58. Steenge GR, Verhoef P, Greenhaff PL. The effect of creatine and resistance training on plasma homocysteine concentration in healthy volunteers. Arch Intern Med 2001; 161: 1455-6
59. Wilson MW, Lay LT, Chow CK, et al. Altered hepatic eicosanoid concentrations in rats treated with the peroxisome proliferators ciprofibrate and perfluorodecanoic acid. Arch Toxicol 1995; 69: 491-7
60. Khan KN, Paulson SK, Verburg KM, et al. Pharmacology of cyclooxygenase-2 inhibition in the kidney. Kidney Int 2002; 61: 1210-9
61. Yoshinari M, Asano T, Kaori S, et al. Effect of gemfibrozil on serum levels of prostacyclin and precursor fatty acids in hyperlipidemic patients with type 2 diabetes. Diabetes Res Clin Pract 1998; 42: 149-54
62. Brude IR, Finstad HS, Seljeflot I, et al. Plasma homocysteine concentration related to diet, endothelial function and mononuclear cell gene expression among male hyperlipidaemic smokers. Eur J Clin Invest 1999; 29: 100-8
63. Guan Y, Breyer MD. Peroxisome proliferator-activated receptors (PPARs): novel therapeutic targets in renal disease. Kidney Int 2001; 60: 14-30
64. Wang W, Basinger A, Neese RA, et al. Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. Am J Physiol Endocrinol Metab 2001; 280: E540-7
65. Basu TK, Makhani N, Sedgwick G. Niacin (nicotinic acid) in non-physiological doses causes hyperhomocysteineaemia in Sprague-Dawley rats. Br J Nutr 2002; 87: 115-9
66. Garg R, Malinow M, Pettinger M, et al. Niacin treatment increases plasma homocyst(e)ine levels. Am Heart J 1999; 138: 1082-7
67. Sunder-Plassmann G, Födinger M. Pathophysiology and clinical importance of hyperhomocysteinemia: clinical intervention studies. Miner Electrolyte Metab 1999; 25: 286-90
68. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomised trials. BMJ 1998; 316: 894-8
69. Ubbink JB, Vermaak WJ, van der Merve A, et al. Vitamin requirements for the treatment of hyperhomocysteinemia in humans. J Nutr 1994; 124: 1927-33
70. den Heijer M, Brouwer IA, Bos GM, et al. Vitamin supplementation reduces blood homocysteine levels: a controlled trial in patients with venous thrombosis and healthy volunteers. Arterioscler Thromb Vasc Biol 1998; 18: 356-61
71. Dierkes J, Kroesen M, Pietrzik K. Folic acid and vitamin B6 supplementation and plasma homocysteine concentrations in healthy young women. Int J Vitam Nutr Res 1998; 68: 98-103
72. Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. N Engl J Med 2001; 345: 1593-600
73. Wald DS, Bishop L, Wald NJ, et al. Randomized trial of folic acid supplementation and serum homocysteine levels. Arch Intern Med 2001; 161: 695-700
74. Thambyrajah J, Landray MJ, Jones HJ, et al. A randomized double-blind placebo-controlled trial of the effect of homocysteine-lowering therapy with folic acid on endothelial function in patients with coronary artery disease. J Am Coll Cardiol 2001; 37: 1858-63
75. Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia: safety of treatment, changes in risk factors, and incidence of coronary heart disease. N Engl J Med 1987; 317: 1237-45
76. Robins SJ, Collins D, Wittes JT, et al. Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial. JAMA 2001; 285: 1585-91

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