Potential contribution of metformin to the management of cardiovascular disease risk in patients with abdominal obesity, the metabolic syndrome and type 2 diabetes

JP Després

SUMMARY
With an evolving landscape of a growing number of obese and/or type 2 diabetic patients in our affluent population, the metabolic syndrome has become a major issue because of its impact on cardiovascular disease risk. In this regard, although it is appropriate to aim at a better glycaemic control in type 2 diabetic patients, hyperglycaemia does not appear to be the main culprit responsible for the markedly increased cardiovascular disease risk in this population. Rather, studies have suggested that a cluster of metabolic abnormalities, which includes an atherogenic dyslipidaemic state, an impaired glucose/insulin homeostasis, and a pro-thrombotic and inflammatory profile, substantially increases the risk of coronary heart disease in type 2 diabetic patients in a manner which is partly independent of glycaemic control. These results imply that in order to reduce the risk of atherosclerotic macrovascular disease in type 2 diabetic patients, physicians need not only to focus on a better glycaemic control but also to improve the features of the metabolic syndrome. As a consequence, in order to evaluate the clinical benefits of pharmacotherapy in type 2 diabetic patients, we need to quantify the impact of any pharmacological intervention beyond glucose control. In this context, metformin has been shown to not only contribute to a better glycaemic control but also to induce some weight loss (especially in the visceral depot) which may contribute to the improvement of the features of the metabolic syndrome. Thus, metformin treatment may represent a relevant element of an integrated lifestyle modification-pharmacotherapy to prevent not only type 2 diabetes but also cardiovascular disease.

Key-words: Type 2 diabetes · Cardiovascular disease · Metformin · Metabolic syndrome · Obesity.

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The epidemic proportions reached worldwide in the prevalence of type 2 diabetes represent a tremendous challenge for the medical community [1, 2]. As a consequence, because of the very high risk of retinopathy, nephropathy and neuropathy associated with hyperglycaemia, type 2 diabetes is a major cause of blindness, renal failure and dialysis, as well as of amputation [3-6]. On that basis, this metabolic disease has to be properly assessed and managed. With the recently published evidence that the risk of coronary heart disease (CHD) in type 2 diabetic patients who are initially asymptomatic for CHD appears to be more or less similar to non-diabetic patients with documented CHD [7], type 2 diabetes is more and more considered as a CHD risk equivalent [8]. In this regard, there is evidence suggesting that the hyperglycaemic state of type 2 diabetic patients only represents the tip of a huge atherothrombotic inflammatory iceberg which is largely responsible for the increased CHD risk [9]. This notion is concordant with data from the UK Prospective Diabetes Study, which showed that a better glycaemic control did not generate substantial clinical benefits in terms of reducing the risk of macrovascular atherosclerotic disease [10]. Therefore, clinicians should also consider targeting the underlying cluster of metabolic abnormalities found in type 2 diabetic patients.

In this context, it should be emphasised that the epidemic of type 2 diabetes results largely from our affluent and sedentary lifestyle where we are exposed to a diet dense in calories (due to a high-sugar and/or fat content). Such an environment favours a positive energy balance, ultimately leading to weight gain. This “toxic environment” is responsible for the increasing prevalence of obesity worldwide [11, 12], a phenomenon that is unlikely to plateau in the near future. Consequently, and as foreseen by Zimmet [2], the prevalence of type 2 diabetes will continue to markedly increase all over the world. Therefore, clinicians who have dealt with the assessment and management of cardiovascular disease risk factors are confronted with an evolving landscape. For instance, smoking, hypercholesterolemia and hypertension were major risk factors in the 50s and 60s [13-15]. However, with a better management of hypertension, with the development of lipid-lowering medications (statins), and with the reduced prevalence of smoking in some countries, the relative contribution of these “classical” risk factors in the population may have decreased. However, such advances are likely to have been offset by the increasing prevalence of obesity and of type 2 diabetes.

The atherothrombotic inflammatory profile of the metabolic syndrome: clinical implications

As mentioned above, hyperglycaemia does not appear to be the major culprit responsible for the increased CHD risk found among type 2 diabetic patients. Rather, studies have indicated that this increased risk may be due to a cluster of metabolic abnormalities including an atherogenic dyslipidaemic state, a pro-thrombotic profile and elevated markers of inflammation [16-19] (Fig 1). This cluster of metabolic abnormalities has been referred to as the insulin resistance syndrome, the plurimetabolic syndrome and more recently National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) guidelines have suggested the use of the term “metabolic syndrome” to describe this condition [8]. In this regard, results from the Québec Cardiovascular Study have provided evidence that some features of the metabolic syndrome including fasting hyperinsulinaemia (as a crude marker of insulin resistance), elevated apolipoprotein (apo) B concentration (as a marker of the concentration of atherogenic lipoproteins) and small LDL particles were predictive of a substantially increased risk of ischaemic heart dis-

![Figure 1](image)

**Figure 1** Cluster of metabolic disturbances resulting from visceral obesity, which contributes not only to the progression of coronary atherosclerosis, but also to the risk of an acute coronary syndrome. Apo: apolipoprotein, PAI-1: plasminogen activator inhibitor-1, CRP: C-reactive protein, IL-6: interleukin-6, TNF-α: tumor necrosis factor-α.
ease (IHD) in a sample of middle-aged men followed for occurrence of a first IHD event over a 5-year follow-up period [20]. We have also shown that, even in the absence of classical risk factors such as hypertension, elevated LDL-cholesterol and smoking, this cluster of metabolic abnormalities was nevertheless predictive of an increased risk of IHD in this sample of initially asymptomatic middle-aged men [20]. Therefore, there is a need to go beyond conventional cardiovascular disease risk factors to properly assess the risk associated with the features of the metabolic syndrome.

In order to achieve this objective, we have suggested that a marker of abdominal obesity, namely the waist circumference, was a relevant anthropometric tool to identify a high-risk obesity phenotype commonly associated with the features of the metabolic syndrome [21, 22]. Indeed, several studies from our laboratory in which we have properly measured body composition and adipose tissue distribution have revealed that the amount of intra-abdominal adipose tissue (commonly referred to as visceral adipose tissue) was the critical correlate of the cluster of abnormalities of the metabolic syndrome in overweight or obese patients [23, 24]. Indeed, equally obese individuals perfectly matched for their excess of total body fat but with either a low or high accumulation of visceral adipose tissue markedly differed in their metabolic risk factor profile, and viscero-albly obese subjects represented the subgroup of individuals characterised by the most substantial alterations in their metabolic risk profile [23, 24]. As waist circumference was found to be a simple but useful correlate of the amount of visceral adipose tissue [25, 26], we were interested in developing an algorithm that would help clinicians to identify individuals with a high likelihood of having the features of the metabolic syndrome. In this regard, we found waist circumference to be a good marker of visceral obesity, of fasting insulin levels as well as of apo B concentration in non-diabetic men [27, 28]. We also found fasting hypertriglyceridaemia to be the best predictor of small LDL particle size [29, 30] which had been reported to be predictive of an increased IHD risk in men of the Québec Cardiovascular Study [31, 32]. Sensitivity and specificity analyses conducted in a sample of middle-aged men revealed that a waist circumference cut-off of 90 cm and a fasting triglyceride concentration of 2.0 mmol/L gave us the best discrimination of carriers vs non-carriers of what we refer to as the atherogenic metabolic triad of hyperinsulinaemia, elevated apo B and small LDL particles [21]. For instance, whereas only 10% of men with a waist circumference < 90 cm and with triglycerides < 2.0 mmol/L had the atherogenic metabolic triad, more than 80% of men with a waist circumference ≥ 90 cm and triglycerides ≥ 2.0 mmol/L were characterised by these features of the metabolic syndrome shown to increase IHD risk. We have validated this screening approach in three independent studies [21, 33, 34], including two angiographic studies [21, 33] and we found that the presence of “hypertriglyceridaemic waist” (waist girth ≥ 90 cm combined with triglycerides ≥ 2.0 mmol/L) was systematically predictive of a very high likelihood (~ 80%) of finding the features of the metabolic syndrome. Unpublished data from our laboratory also indicate that “hypertriglyceridaemic waist” is a better indicator of the presence of the metabolic syndrome than the recently published NCEP-ATPIII criteria.

**Beyond hyperglycaemia: risk of coronary artery disease associated with the metabolic syndrome revealed by “hypertriglyceridaemic waist”**

In order to examine the contribution of the features of the metabolic syndrome on the risk of coronary artery disease (CAD) associated with hyperglycaemia, we have performed a very simple study where we quantified the odds of finding CAD in a sample of men who underwent coronary angiography [33]. As expected from several published studies [35, 36], the presence of impaired fasting glucose was associated with an increased likelihood of finding CAD. However, after further stratifying subjects on the basis of the presence/absence of “hypertriglyceridaemic waist”, we found impaired fasting glucose not to be predictive of an increased likelihood of finding CAD when it was not accompanied by “hypertriglyceridaemic waist”. However, irrespective of the presence/absence of impaired fasting glucose, the “hypertriglyceridaemic waist” phenotype was associated with a substantially increased risk of CAD. Therefore, these results suggest that it is the underlying features of the metabolic syndrome resulting from abdominal obesity, which can be simply appreciated by the simultaneous presence of abdominal obesity and hypertriglyceridaemia that are largely responsible for the increased risk of CAD in patients with elevated fasting glucose concentrations (Fig 2).

These results have the following implications: if hyperglycaemia does not largely mediate the increased risk of CHD in type 2 diabetic patients, even a non-diabetic patient with the metabolic syndrome should also be at increased risk of CHD (Fig 3). Furthermore, although at increased CHD risk, the risk of atherosclerotic macrovascular disease may vary in hyperglycaemic type 2 diabetic patients depending upon the presence/absence of the features of the metabolic syndrome or on the magnitude of the alterations found in these features (Fig 3). From a clinical standpoint, in order to evaluate the clinical benefits of pharmacotherapy in type 2 diabetic patients, we need to quantify the impact of any pharmacological intervention beyond glucose control. In this regard, metformin has been shown not only to contribute to a better glycaemic control but it has also been reported to induce some weight loss and improve some features of the metabolic syndrome. The evidence available regarding the effects of metformin on weight, body fat distribution and features of the metabolic syndrome will be discussed in the next section.
Impact of metformin on lipoprotein-lipid profile and plasma insulin levels

Lipoprotein-lipid profile

Several studies of various sizes have reported the effects of metformin therapy on plasma lipoprotein-lipid levels.

Type 2 diabetic patients

A randomised, double-blind, placebo-controlled crossover study evaluated the effects of 12 weeks of treatment with metformin on plasma lipoprotein-lipid levels in a sample of 27 type 2 diabetic patients who had elevated total cholesterol, LDL-cholesterol and triglycerides at baseline [5.9 mmol/L (228 mg/dL), 3.9 mmol/L (151 mg/dL), and 1.9 mmol/L (168 mg/dL), respectively] [37]. Significant reductions were observed, relative to placebo, in total cholesterol (p = 0.002), LDL-cholesterol (p = 0.002) and triglycerides (p = 0.034) (Fig 4). HDL-cholesterol, which was within the normal range at baseline [1.14 mmol/L (44 mg/dL)], was not significantly affected by metformin treatment. Similarly, a 3-month, randomised study in 35 hyperlipidaemic type 2 diabetic patients showed that metformin treatment significantly reduced total cholesterol [from 6.13 mmol/L (237 mg/dL) to 5.74 mmol/L (222 mg/dL), p < 0.01] and LDL-cholesterol [from 4.21 mmol/L (163 mg/dL) to 3.85 mmol/L (149 mg/dL), p < 0.01] [38]. Both triglycerides and HDL-cholesterol were normal at baseline, and were not significantly affected by metformin.

A rather large double-blind study randomised a total of 921 dyslipidaemic type 2 diabetic patients, in comparison with placebo in one evaluation, and in a second three-arm study
Metformin and cardiovascular disease risk profile

Comparing metformin with glyburide (known as glibenclamide in Europe), and with metformin and glyburide co-administered [39]. Total cholesterol, LDL-cholesterol and triglycerides were reduced in one or both of the evaluations (Fig 5). Trends for an increase in HDL-cholesterol were observed but failed to achieve statistical significance.

Metformin is also frequently administered in combination with insulin, as it improves glycaemic control and reduces insulin requirements [40]. A double-blind, randomised study in 50 insulin-treated obese type 2 diabetic patients [41] showed that 6 months of additional placebo treatment left lipid parameters essentially unchanged, whereas additional metformin treatment significantly reduced total cholesterol from 5.9 mmol/L (228 mg/dL) to 5.7 mmol/L (220 mg/dL), and triglycerides from 2.9 mmol/L (257 mg/dL) to 2.6 mmol/L (230 mg/dL), these changes being significant (p < 0.05) compared with baseline and with placebo.

A number of studies without randomisation or blinding in their designs have also demonstrated significant improvements in lipid profiles following the administration of metformin in diabetic or largely diabetic patients, in populations of type 2 diabetic patients without defined lipid abnormalities at baseline [42-45]. Several other studies have also been conducted in patients with defined dyslipidaemic states. Two rather small studies have been carried out in hypertriglyceridaemic subjects: one in 9 patients with an average plasma triglyceride concentration level of 2.54 mmol/L (225 mg/dL) at baseline [46], and the other in 19 patients with a plasma triglyceride level of 4.9 mmol/L (431 mg/dL) at baseline, of whom 11 had type 2 diabetes [47]. Significant improvements in triglycerides (p < 0.001), and in total cholesterol (p < 0.01) were observed following a 3-month metformin treatment. The first study also demonstrated a significant reduction in VLDL-cholesterol (p < 0.01) and an increase in HDL-cholesterol (p < 0.02). Finally, a study in 16 patients showed that treatment with metformin for 11 weeks not only improved fasting triglycerides (p = 0.02), total cholesterol (p = 0.002), VLDL-cholesterol (p = 0.005) and the total cholesterol/HDL-cholesterol ratio (p = 0.01), but also significantly reduced postprandial lipaemia [48].

Non-diabetic populations

As discussed above, insulin resistance usually clusters with other features of the metabolic syndrome including an atherogenic dyslipidaemic state and this profile is most often accompanied by abdominal obesity. Thus, the presence of the metabolic syndrome is strongly associated with the development of type 2 diabetes and with CHD [49-51]. The two BIGuanides and Prevention of Risks in Obesity (BIGPRO 1

Metformin and lipid profiles in type 2 diabetic patients [39]. Protocol 1 compared metformin with placebo. Data shown from protocol 2 are from part of a study comparing metformin with glyburide (glibenclamide) and metformin and glyburide co-administered (not shown). *Significantly different from placebo (protocol 1) or glyburide alone (protocol 2). TC: total cholesterol; TG: triglycerides.
and 2) trials recruited subjects with abdominal obesity as a strategy to recruit an insulin-resistant population with the features of the metabolic syndrome [52, 53]. The two studies together randomised a total of 625 dyslipidaemic subjects to treatment with metformin 850 mg b.i.d. for 1 year, and for 3 months, respectively. BIGPRO 1 reported trends for improvements in total cholesterol (p < 0.09) and LDL-cholesterol (p < 0.07), compared with placebo, while BIGPRO 2 reported a significant reduction in total cholesterol (p = 0.05). Triglycerides were not reduced significantly in either study, despite being markedly elevated at baseline in BIGPRO 2 [2.8 mmol/L (248 mg/dL)].

As the features of the metabolic syndrome are highly prevalent in CHD patients [54], it is also relevant to examine the effects of metformin in this population. Carlsen et al. [55] randomised 60 patients with CHD (history of coronary artery bypass surgery or angioplasty) to receive metformin or no treatment for 12 weeks. Significant reductions in total cholesterol were observed in lean patients (body mass index < 27 kg/m²) after 4 and 12 weeks of treatment (p < 0.05). In addition, significant reductions in LDL-cholesterol (p < 0.05 at either time point), and the LDL-cholesterol/HDL-cholesterol ratio (p < 0.05 at 4 weeks and p < 0.001 at 12 weeks) were observed in the metformin group, relative to control. Finally, in patients selected for their dyslipidaemic states, metformin therapy was found to induce significant reductions in total cholesterol and triglycerides in all three studies (p < 0.05-0.0001) [56-58].

Plasma insulin

Because of its effect on insulin sensitivity, metformin tends to reduce plasma insulin levels (Table I). Statistically significant reductions in fasting plasma insulin compared to baseline levels have been observed following administration of metformin for 4 months to obese type 2 diabetic patients [59, 60]. In another study, 20 weeks of metformin therapy significantly reduced the magnitude of postprandial insulin excursions, compared to baseline, in type 2 diabetic patients who had failed to respond to dietary management and who were thus involved in a double-blind, randomised study [61]. A similar effect on postprandial insulin was observed in other studies conducted in type 2 diabetic patients [43, 46]. In non-diabetic patients with abdominal obesity, the BIGPRO 2 study reported a significant reduction (p = 0.04) in fasting plasma insulin compared with placebo [53], whereas a trend towards a reduction was observed in the BIGPRO 1 study (p < 0.06 vs placebo) [52]. Significant reductions in fasting plasma insulin have also been observed in patients with dyslipidaemia [47] and hypertension [62].

### Metformin and the metabolic syndrome: contribution of visceral adipose tissue

Unlike sulphonylureas or glitazones, which tend to increase body weight over time [63], metformin is not associated with an increase in body weight. For instance, it is common in studies in type 2 diabetic patients and in abdominally obese subjects to observe either a modest decrease in body weight, or no change at all in response to metformin therapy (Table II). As weight loss in abdominally obese patients is generally associated with a preferential loss of abdominal visceral fat [64, 65], metformin may reduce the proportion of visceral fat [66]. Treatment of 7 obese (BMI 29 kg/m²) type 2 diabetic subjects with their maximally tolerated dose of metformin for 6 months induced a mean decrease in weight of 3.3 kg (p < 0.008) [66]. Visceral and subcutaneous adipose tissue depositions were measured using a combination of computed tomography scanning and dual-energy X-ray absorptiometry scanning. Visceral fat decreased by an average of 15.7% (p < 0.03), while total subcutaneous fat was not significantly reduced. On the basis of the well-documented impact of visceral adipose tissue as a critical correlate of the cluster

<table>
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<th>Study</th>
<th>Patients (N)</th>
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<th>Duration</th>
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<th>Baseline</th>
<th>Change</th>
<th>p</th>
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<td>- 2</td>
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<td>R, DB</td>
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<td>- 4.2</td>
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<td>R, DB</td>
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<td>14.7</td>
<td>- 4.4</td>
<td>&lt;0.01</td>
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R: randomised; DB: double-blind; X: crossover; NA: not available from source, NS: not significant.
Metformin and cardiovascular disease risk profile

Metformin and body weight.

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<td>80</td>
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R: randomised; DB: double-blind; X: crossover; NA: not available from source. Significance values vs baseline except where indicated; NS: not significant, *Compared with increase of 1.6 kg in patients receiving glipizide; ‘body mass index shown (kg/m²), p value is vs placebo (mean change 0 kg/m²); ‘similar decrease (– 5.5 kg, p < 0.05) observed in the placebo group; ‘described as “significant” in source paper but no p value given.

Figure 6
Model showing the potential contribution of the related loss of visceral adipose tissue to the beneficial effects of metformin on the features of the metabolic syndrome. FFA: free fatty acids.

of abnormalities of the metabolic syndrome, such selective loss of visceral adipose tissue, even in the presence of a rather apparently trivial weight loss could largely explain the beneficial effects of metformin therapy on the lipoprotein-lipid profile of abdominally obese patients with the features of the metabolic syndrome (Fig 6). Further work to explore the therapeutic potential of metformin on visceral adipose tissue and related features of the metabolic syndrome is clearly warranted.

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