

# Cardiac considerations in the treatment of the metabolic syndrome

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## Abstract

To treat insulin resistance and avoid type 2 diabetes the condition must first be diagnosed. When diagnosed it can be assumed that with or without type 2 diabetes the insulin resistant subject has significant cardiovascular disease. Once diagnosed, aggressive therapy of insulin resistance and its associated risk factors has the potential to avoid cardiac events in both the diabetic and non-diabetic insulin resistant subjects. Treating insulin resistance can also avoid the development of diabetes and improve glycemic control and long-term complications in the established type 2 diabetic patient.

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## Diagnosing the insulin resistance (metabolic) syndrome

To treat a patient with the insulin resistance syndrome or metabolic syndrome, the syndrome must first be identified. The gold standard for diagnosing insulin resistance in the USA is represented by the criteria of the National Cholesterol Educator Program, and three of these criteria need to be present to make the diagnosis of insulin resistance [1] (*Table 1*). Under most circumstances, patients never have their waist circumference measured or, if measured, it is often measured inaccurately. In addition, a normal waist circumference is dependent upon the patient's height and a more predictive value is a waist to height ratio greater than 0.6 (ideally the waist circumference should be half of the patient's height) [2]. As the waist circumference is the only clinical criterion that is diagnostic of excess peritoneal fat (the key factor in

the insulin resistance syndrome), omission of this measurement results in the insulin resistance syndrome being greatly underdiagnosed.

The fallacy that insulin resistance is simply a manifestation of obesity is not true, because approximately 40% of those with a body mass index (BMI) greater than 35 kg/m<sup>2</sup> are not insulin resistant, and 6% of those with a BMI less than 25 kg/m<sup>2</sup> are insulin resistant [3]. This is because many overweight individuals have mainly increased subcutaneous fat, and some thin persons have excessive peritoneal fat.

In the absence of a waist circumference measurement, a more convenient and remarkably accurate test for the diagnosis of metabolic syndrome is the fasting triglyceride to high-density lipoprotein (HDL) ratio [4]. If this ratio exceeds 3.8, the presence of insulin resistance is very likely. The accuracy of the triglyceride to HDL ratio has been validated by

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Table 1. Criteria for diagnosing the metabolic (insulin resistance) syndrome [1].

1.	Fasting glucose concentration of at least 100 mg/dL
2.	Fasting triglyceride concentrations of at least 150 mg/dL
3.	High-density lipoprotein cholesterol concentration less than 50 mg/dL in women; less than 40 mg/dL in men
4.	Blood pressure of at least 130/85 mm Hg
5.	Central obesity: abdominal waist circumference greater than 77 cm (35 inches) in women; greater than 88 cm (40 inches) in men

euglycemic insulin clamp studies, which are the “gold standard” for measuring insulin resistance [5].

### Why is insulin resistance associated with more cardiac events?

Approximately 50% of hypertensive individuals are insulin resistant and have the metabolic syndrome, and 75% of patients with type 2 diabetes are hypertensive [6]. This is mainly because high concentrations of insulin stimulate both the sympathetic nervous system and the angiotensin II type 1 receptor. Furthermore, through its action on the distal tubule of the kidney, insulin is a salt- and water-retaining hormone. In addition, insulin is an anabolic growth-promoting hormone that causes proliferation of vascular smooth muscle cells and remodeling of the arterial wall. The progression of insulin resistance to the development of hyperglycemia causes an additional increase in sodium retention because, for every molecule of glucose filtered and reabsorbed in the proximal tubule of the kidney, one molecule of sodium is also absorbed [6]. An additional factor in the increased prevalence of hypertension in metabolic syndrome is the increased concentration of free fatty acid (FFA) that is associated with resistance to the action of insulin on peritoneal adipocytes. Increased FFA concentrations, experimentally induced by heparin and Intralipid infusion, worsen inflammation, oxidative stress, and endothelial function, and increase both systolic and diastolic blood pressures [7].

Hyperinsulinemia therefore results, not only in hypertension, but, as a result of a combination of hypertension with the growth-inducing anabolic effects of insulin, also in left ventricular hypertrophy (LVH) [8]. LVH is present in 71% of individuals with established type 2 diabetes and in 30% of non hypertensive patients with new-onset diabetes [9,10]. The combination of ventricular hypertrophy and diastolic dysfunction, which occurs in 50–60% of patients with type 2 diabetes, in association with coronary artery disease leads to a greater prevalence and an earlier onset of heart failure in the diabetic patient [11].

Currently, 43% of patients admitted to hospital with heart failure in the USA have diabetes.

Patients with metabolic syndrome have the characteristic dyslipidemic pattern of increased triglyceride and decreased HDL concentrations. The syndrome results, not only in an increased release of FFAs from the adipocyte, but also in decreased FFA utilization and increased serum FFA concentrations. Resistance to the hepatic action of insulin results in decreased suppression of triglyceride production and increased triglyceride concentrations [12]. When acted upon by hepatic lipase, triglyceride-laden low-density lipoprotein (LDL) and HDL particles form small dense particles [13]. The small dense HDL particle is less cardioprotective than the larger HDL particles, with decreased effects on inflammation, oxidative stress, endothelial dysfunction, oxidation of LDL, and reverse cholesterol transportation. In addition, the smaller HDL particle has a shorter half-life as a result of an increased rate of hepatic breakdown, which accounts for the decrease in total HDL concentration that is typical of the metabolic syndrome [14]. The smaller LDL particle is more easily taken up by the scavenger receptor on the macrophage, which leads to increased formation of atheromatous plaque [15]. Therefore, the calculated LDL cholesterol concentration can be very misleading in patients with the metabolic syndrome because, in the presence of an increased number of very small highly atherogenic LDL particles, the total calculated LDL may be normal [16]. Because of this, measurement of apolipoprotein B (one molecule per LDL particle) or the easily calculated non HDL cholesterol (total cholesterol minus HDL cholesterol) that reflects the total number of atherogenic particles (LDL, remnant intermediate-density, and small VLDL particles) are more predictive measurements of cardiac risk in patients with metabolic syndrome. Indeed, in the diabetic patient, especially in the presence of increased triglycerides, the non HDL cholesterol has been shown to be more predictive of a cardiac event than the calculated LDL concentration [17].

Although the fasting triglyceride concentration has been shown to be only weakly predictive for a cardiovascular event, the postprandial triglyceride concentration, which is increased in the metabolic syndrome, has been shown to be highly predictive. This is because postprandial hyperlipidemia (triglycerides and FFAs) is an inflammatory state associated with oxidative stress and endothelial dysfunction, as well as the formation of atheromatous plaque. In addition, postprandial dyslipidemia is associated with increased inflammation within the atheromatous plaque, leading to an increased risk of plaque rupture and an acute cardiac event [18]. Postprandial dyslipidemia occurs in the metabolic syndrome as a result of increased intestinal absorption of triglycerides.

Interestingly, this increased intestinal absorption is reversed with the thiazolidinediones [19].

Even in the absence of diabetes, hyperglycemia – especially postprandial hyperglycemia – is present in the insulin resistance syndrome. In the Norfolk-EPIC study, the greater the glycated hemoglobin (HbA<sub>1c</sub>) value above 5.0%, the greater was the frequency of cardiac events. In fact for every 1% by which the HbA<sub>1c</sub> value was above 5%, the rate of cardiac events increased by 26% in men and by 28% in women [20]. At lower HbA<sub>1c</sub> values, the postprandial, rather than fasting or preprandial, glucose is responsible for the HbA<sub>1c</sub>, and therefore the most logical reason for the increase in cardiac events with increasing HbA<sub>1c</sub> is postprandial hyperglycemia [21].

Especially when accompanied by postprandial dyslipidemia (postprandial dysmetabolism), postprandial hyperglycemia is an inflammatory state associated with oxidative stress, endothelial dysfunction, a hypercoagulable state, increased formation of atheroma, and an increased risk of rupture of the atheromatous plaques [18]. Indeed, even within the normal range of postprandial glucose concentrations, the lower the postprandial glucose concentration, the lower the rate of progression of coronary artery disease over a 3 year period. Furthermore, a 2 h glucose concentration less than 90 mg/dL has been found to be associated with regression of atheromatous plaque [22].

The metabolic syndrome in itself is an inflammatory state caused by an excessive production of cytokines, such as tumor necrosis factor  $\alpha$  and interleukin-6, by the macrophages that infiltrate peritoneal fat [23]. The increased inflammation leads to oxidative stress, endothelial dysfunction, increased atherogenesis and thrombosis, and an increased frequency of plaque rupture and cardiac events [24]. Increased urine albumin is a marker for endothelial dysfunction, and albuminuria is recognized as being a feature of the metabolic syndrome [25].

## Treating the risk factors of the metabolic syndrome

Obviously, weight loss and exercise are the cornerstones of treatment of the metabolic syndrome. Although weight loss is difficult to achieve, many patients are willing to embark on a long-term program of aerobic exercise. Fortunately, exercise is a more powerful tool in decreasing insulin resistance than is weight loss. Decreasing the fat and carbohydrate content of the diet is helpful, not only to achieve weight loss, but also to decrease further the insulin resistance and postprandial dysmetabolism [26].

Decreasing blood pressure to 130/80 mm Hg or less is a goal of therapy. However, in the patient with

metabolic syndrome, blockade at the various points of the renin–angiotensin system (RAS) will also decrease insulin resistance. Therefore a RAS blocker (angiotensin-converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB]) should be the first antihypertensive agent utilized in patient with metabolic syndrome, type 2 diabetes, or both [27]. Following the use of a RAS blocker, most practitioners would recommend the addition of a thiazide diuretic [28]. Furthermore, the ACCOMPLISH trial [29] showed that the combination of the ACE inhibitor, benazepril, and the dihydropyridine calcium-channel blocker, amlodipine, resulted in 19.6% fewer cardiac events than occurred with the combination of benazepril and hydrochlorothiazide. Unlike thiazide diuretics that increase insulin resistance, amlodipine has been shown not only to improve insulin resistance, but also to decrease inflammation and oxidative stress [30]. In addition, calcium-channel blockers, through increasing the expression of ATP-binding transporter A<sub>1</sub>, mediate both cellular lipid release and the production of HDL, in addition to improving inflammation and endothelial function [31]. Therefore, in the hypertensive patient with insulin resistance, after a RAS inhibitor has been given, a calcium-channel blocker, preferably amlodipine, rather than a thiazide diuretic, should be the next addition.

Recently,  $\beta$ -blockers have fallen into disrepute for the treatment of hypertension, because of a small increase in the incidence of stroke [32]. However, because of the high prevalence of coronary artery disease in patients with type 2 diabetes and those with metabolic syndrome, these patients should benefit from the utilization of a  $\beta$ -blocker [33]. Unfortunately, vasoconstricting  $\beta$ -blockers increase insulin resistance, which results in the incidence of new-onset type 2 diabetes being increased by 25–30% when a vasoconstricting  $\beta$ -blocker is used to treat hypertension [34]. Furthermore, through increased insulin resistance, glycemic control worsens in the patient with type 2 diabetes. Fortunately, vasodilating  $\beta$ -blockers, such as carvedilol, which has  $\alpha_1$ - in addition to  $\beta_1$ - and  $\beta_2$ -blocking properties, decrease insulin resistance and improve glycemic control. In addition, carvedilol has powerful anti-inflammatory properties, which may lead to carvedilol being more cardioprotective than other  $\beta$ -blockers. Therefore, third-line treatment for the insulin-resistant, hypertensive patient should be a  $\beta$ -blocker, and  $\beta$ -blocker therapy must be utilized in every patient with metabolic syndrome who has coronary artery disease, heart failure, or both [35]. In all these situations, a vasodilating  $\beta$ -blocker should be utilized.

Treatment of hyperlipidemia in the patient with metabolic syndrome should be very aggressive,

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because studies of the combined thickness of the intima and media of the carotid artery – a surrogate marker for atherosclerosis – have clearly shown that atherosclerosis is more prevalent and severe in the patient with metabolic syndrome [36]. Therefore, the patient with the syndrome should be treated with the same intensity as the patient who has already been diagnosed as having coronary artery disease. Because of this, the target total LDL concentration in the patient with metabolic syndrome, type 2 diabetes, or both, should be 70 mg/dL or less. To achieve this, a powerful statin, such as rosuvastatin, which does not decrease HDL at high doses in the way that atorvastatin does, should be utilized.

Statins will increase HDL concentrations by as much as 10–15%, but achieving HDL goals in the insulin-resistant patient usually requires the addition of other lipid-decreasing therapies [37]. The use of nicotinic acid is ideal, as it increases HDL and decreases triglyceride concentrations. However, compliance is a major problem because of flushing, and nicotinic acid also increases insulin resistance and may therefore both increase the risk of new-onset diabetes and worsen glycemic control in the patient with established diabetes [38]. An alternative treatment is to add a fibrate to existing statin medication. The only fibrate that has been shown to decrease cardiac events is gemfibrozil but, unfortunately, gemfibrozil is associated with several drug–drug interactions. Particularly problematical is that the combination of gemfibrozil and a statin decelerates the hepatic breakdown of the statin, leading to toxic concentrations of statins, which causes varying degrees of myositis and the more severe myopathies [39]. An alternate fibrate is fenofibrate, which does not have adverse myopathic effects when it is combined with a statin, although its efficacy in decreasing cardiac events has never been proven [40,41]. Weight loss, a low carbohydrate diet, daily small amounts of alcohol, and thiazolidinediones can also increase HDL concentrations.

Decreasing triglyceride concentrations and insulin resistance will result in an increase in the size of both the HDL and LDL particle, which makes the LDL particle less atherogenic and the HDL particle more cardioprotective [15]. Again, the insulin-sensitizing thiazolidinediones, particularly pioglitazone, are efficacious in increasing both the LDL and the HDL particle sizes. Unfortunately, the thiazolidinedione, rosiglitazone, has been shown to increase the number of LDL particles, whereas the other available thiazolidinedione, pioglitazone, decreases the number of LDL particles [42]. This difference is a possible explanation for the better cardioprotective effect that has been shown to be achieved with pioglitazone in type 2 diabetes [43,44].

Statins, while the cornerstone of preventative therapy in the insulin-resistant patient, may increase the risk of development of diabetes, as was shown with rosuvastatin in the JUPITER study [45]. This is unlikely to be as a result of increased insulin resistance, because simvastatin has been shown neither to increase nor to decrease insulin resistance. However, a meta-analysis of statin studies has shown a trend for statins, with the exception of pravastatin, to increase the risk of developing diabetes [46]. The protective effect of pravastatin was largely attributable to pravastatin decreasing the development of diabetes by 30% in the West of Scotland Study, although it did not do so in other studies [47]. The likely increase in diabetes with statins appears to be the result of increased hepatic production of glucose, which is increased more with lipophilic than with hydrophilic statins.

Antiplatelet therapy with low-dose aspirin is advisable in patients with metabolic syndrome; however, justification for its use is lacking, as there is no evidence that aspirin is effective in decreasing cardiac events in these patients. Indeed, resistance to the antiplatelet effect of aspirin is more common in patients with type 2 diabetes, and it is probable that this is also true in those with the metabolic syndrome [48,49].

Many physicians believe that early treatment of the metabolic syndrome is indicated in the non diabetic patient with the syndrome, to avoid the development of diabetes and cardiac events. Certainly, weight loss, including that achieved with bariatric surgery (gastric banding and gastric bypass), and an aerobic exercise program are recommended and acceptable therapies for this group [50]. However, the use of drugs such as metformin or thiazolidinediones in this situation is questionable, largely because of the side effects of both these drugs, making them unsuitable as preventive therapies. In the Diabetes Prevention Program, both troglitazone and metformin (especially in younger persons) decreased the incidence of new-onset diabetes [51]. Rosiglitazone in the DREAM trial, and pioglitazone in the ACT NOW trial, both decreased the progression of impaired glucose tolerance to diabetes, perhaps by decreasing insulin resistance [52]. The addition of pioglitazone to existing diabetes therapy in the PROACTIVE study significantly decreased the incidence of the combination of death, myocardial infarction, acute coronary artery syndrome, and stroke [43,53,54]. However, the potential for side effects – particularly fluid retention and weight gain – with thiazolidinediones, and especially the potential increase in cardiac events with rosiglitazone, preclude the utilization of these drugs in a non diabetic patient [44]. However, when being appropriately utilized for approved indications, drugs such as RAS inhibitors, vasodilating  $\beta$ -blockers,

and perhaps even dihydropyridine calcium-channel blockers, will decrease insulin resistance and help avoid diabetes and cardiac events in non diabetic patients with metabolic syndrome [55]. In addition, avoiding, where possible, drugs such as thiazide diuretics, vasoconstricting  $\beta$ -blockers, and nicotinic acid derivatives will avoid an increase in insulin resistance and may decrease the risk of a cardiac event and delay, or even avoid, the development of type 2 diabetes in patients with the metabolic syndrome [55].

## Conclusion

To treat insulin resistance, the condition must first be diagnosed and, when diagnosed, treated aggressively, assuming that, like the individual with type 2 diabetes, the insulin-resistant patient has significant cardiovascular disease. Aggressive treatment, which should include choosing medication that will decrease rather than increase insulin resistance, has the potential to avoid cardiac events in both the diabetic and non diabetic insulin-resistant patient, improve glycemic control in the patient with established type 2 diabetes, and delay or avoid the onset of diabetes in the non diabetic insulin-resistant patient. ■

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