



# Mechanisms Linking the Metabolic Syndrome and Cardiovascular Disease: Role of Hepatic Insulin Resistance

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## Abstract

The worldwide prevalence of insulin resistant states such as the metabolic syndrome has grown rapidly over the past few decades. The metabolic syndrome is a constellation of common metabolic disorders that promote the development of atherosclerosis and cardiovascular disease. Studies in both human and animal models suggest that hepatic inflammation and insulin resistance are key initiating factors in the development of the metabolic syndrome. Chronic inflammation is known to be associated with visceral obesity and is characterized by production of abnormal adipokines and cytokines such as tumor necrosis factor  $\alpha$ , interleukin-1 (IL-1), IL-6, leptin, and resistin. These factors inhibit insulin signaling in the liver (hepatocytes) by activating suppressors of cytokine signalling proteins; several kinases such as c-Jun N-terminal kinases, IKK- $\beta$ , and Protein kinase C; and protein tyrosine phosphatase 1B, that in turn impair insulin signaling at insulin receptor and insulin receptor substrate level. Hepatic insulin resistance in turn causes impaired suppression of glucose production by insulin in hepatocytes leading to hyperglycemia, induction of very low density lipoprotein production, and de novo lipogenesis. Increased production of C-reactive protein (CRP) and plasminogen activator inhibitor-1, both markers of an inflammatory state, is also observed in insulin resistance. All of the above metabolic abnormalities can directly or indirectly promote atherosclerosis. In particular, hyperglycemia induces endothelial dysfunction, cellular proliferation, changes in extracellular matrix conformation, and impairment of low density lipoproteins (LDL)-receptor-mediated lipoprotein uptake. Small dense LDLs have higher affinity to the intimal proteoglycans, leading to the penetration of more LDL particles into the arterial wall. CRP can also accelerate atherosclerosis by increasing the expression of PAI-1 and adhesion molecules in endothelial cells, inhibition of nitric oxide formation, and increasing LDL uptake into macrophages. In summary, hepatic insulin resistance is a critical early event that underlies the development of the metabolic syndrome and progression to atherosclerosis and cardiovascular disease.

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## Introduction

The liver plays a central role in coordinating the whole body metabolism; including carbohydrate, lipid and protein metabolism, xenobiotic metabolism, and detoxification.<sup>1</sup> Many of these hepatic functions are under tight metabolic control by circulating hormones such as insulin. Insulin promotes glucose disposal in the adipose tissue and muscle and prevents glucose production in the liver. Insulin also

plays a key role in the other important processes such as synthesis and storage of fat, protein synthesis, and cell growth, proliferation, and differentiation.<sup>2</sup> The presence of insulin resistance in insulin sensitive target tissues (muscle, fat, and liver) results in major abnormalities such as hyperglycemia, hyperinsulinemia, and hypertriglyceridemia, which are the common features of type 2 diabetes (T2D) and metabolic syndrome (MtS).<sup>3</sup> Given the important role of the liver in insulin resistance and MtS, the present review is focused on

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the molecular mechanisms involved in the development of hepatic insulin resistance as a major initiating factor in MtS driving cardiovascular disease (CVD).

### ***Metabolic syndrome and cardiovascular disease***

The term MtS refers to a cluster of correlated disorders that include glucose intolerance, insulin resistance, obesity, dyslipidemia, and hypertension.<sup>4</sup> Several definitions of MtS have been introduced by the WHO, the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP) and the International Diabetes Federation (IDF). While the WHO definition emphasizes on insulin resistance and glucose intolerance, the IDF definition is based on central obesity and all the factors considered equally in NCEP definition.<sup>4</sup>

Regardless of which definition is used, there is now convincing evidence that MtS associates with CVD. Numerous data from population-based studies using the NCEP definition show a 2 fold increase of CVD risk in subjects with MtS compared to those who do not have the syndrome.<sup>5</sup> In the Framingham Heart Study, MtS alone predicted 25% of all new-onset CVD.<sup>6</sup> Other MtS components including hypertension, hypertriglyceridemia, and low HDL have been shown previously to be independent risk factors for CVD.<sup>7</sup>

### ***Pathophysiology of metabolic syndrome***

Various mechanisms have been proposed for the etiology of the metabolic syndrome. While some believe that insulin resistance is the fundamental disorder in the metabolic syndrome, others place a greater importance on obesity in its pathogenesis.<sup>7</sup>

Insulin resistance in liver and adipose tissue leads to most of the abnormalities observed in the metabolic syndrome. While muscle insulin resistance causes reduced glucose uptake, it leads to enhance lipolysis in adipose and increased glucose output and increased very low density lipoprotein (VLDL) production in the liver.<sup>7</sup> Obesity is also implicated as an important underlying cause of MtS. Excessive release of free fatty acids (FFAs), cytokines, and other pro-inflammatory products from the adipose tissue induces insulin resistance in the muscle and liver. Decreased insulin clearance (hyperinsulinemia), increased hepatic glucose production, increased VLDL secretion, increased production of pro-inflammatory factors such as C-reactive protein (CRP), and increased production of thrombotic factors such as fibrinogen are important consequences of obesity and hepatic insulin resistance. However, considering the close relation between insulin resistance and visceral obesity, dissociation of these two major underlying factors

in the pathogenesis of MtS has been difficult. Nevertheless, regardless of whether insulin resistance is the primary causative role in MtS or the consequence of obesity, it is widely considered a major factor in the pathogenesis of MtS.<sup>7</sup>

### ***Insulin signaling in insulin sensitive tissues***

The effects of insulin on cell metabolism are mediated by a heterotetramer receptor expressed on most cells especially on the liver, adipose, and skeletal muscle cells. Binding of insulin to its receptor initiates a cascade of events that subsequently activate the downstream signaling molecules.<sup>8</sup> Three major pathways are activated by insulin. The phosphatidylinositol-3-kinase (PI3-K) pathway mediates the metabolic effects of insulin (glucose, lipid, and protein metabolism). The mitogen-activated protein kinase (MAPK) pathway controls the mitogenic, growth, and cell differentiation effects; and the CAP/Cbl/Tc10 pathway mediates the membrane translocation of glucose transporter 4, in the muscle and adipose tissues.<sup>8</sup>

### ***Molecular mechanisms of insulin resistance***

Insulin resistance is defined as a pathophysiological condition in which normal insulin concentration does not adequately produce a normal insulin response in target tissues such as adipose, muscle, and liver. Under this condition, pancreatic beta cell secretes more insulin (i.e. hyperinsulinemia) to overcome the hyperglycemia in these individuals. Over time, the inability of the pancreatic beta cells to produce sufficient insulin to correct worsening tissue insulin resistance leads to hyperglycemia and overt T2D.<sup>3</sup>

Several mechanisms, including abnormal insulin production, mutations in insulin receptor and its substrates, and insulin antagonists, have been proposed, but it appears that defects in post-receptor signaling are the major cause of insulin resistance in target tissues.<sup>9</sup> A decreased autoactivation of the insulin receptor has been reported in the muscle and adipose tissues of T2D patients.<sup>10</sup> Furthermore, reduced expression of PI3-K has been described in the skeletal muscle of lean and obese patients.<sup>10</sup> Therefore, reduced expression and/or diminished phosphorylation of early insulin signaling molecules have been observed in the insulin target tissues of obese and T2D patients.

Several mechanisms have been suggested to be involved in defective insulin signaling pathways. Decreased expression or increased degradation of key components of insulin signaling can induce insulin resistance.<sup>1</sup> While insulin receptor substrate (IRS-1) knockout mice were found to be



insulin resistant but not hyperglycemic,<sup>11</sup> IRS-2-deficient mice were shown to be severely hyperglycemic due to insulin resistance in the liver and failure of  $\beta$ -cell secretion.<sup>12</sup>

Post-transcriptional modifications altering the activity of insulin signaling molecules are the second proposed mechanism for the inhibition of the insulin pathway. Various kinases, including stress activated protein kinase, c-Jun N-terminal kinases (JNK), and protein kinase C (PKC), can phosphorylate IRS-1,2 at specific serine and threonine residues, leading to the inhibition of insulin signaling.<sup>12</sup> Another underlying mechanism is related to the induction of inhibitory factors such as suppressors of cytokine signaling (SOCS-1,3). SOCS proteins block insulin signaling via competition with IRS-1 for the association with the insulin receptor and by the augmentation of the proteosomal degradation of IRS-1.<sup>13</sup> Finally, increased activity of phosphatases which dephosphorylate intermediate signaling molecules can inhibit the insulin pathway.<sup>14</sup> While several different phosphatases have been implicated as inhibitors of insulin action, in-vivo analysis in mice strongly supports protein tyrosine phosphatase 1B (PTP1B) as the major regulator of insulin signaling.<sup>14</sup> Obese, insulin resistance, and T2D patients show high expression of PTP1B in their muscle and liver tissues.<sup>15</sup> In addition, genetic variations within promoter and un-translated regions of the PTP1B gene have been reported to associate with insulin resistance and type 2 diabetes in an Iranian population.<sup>16,17</sup>

### ***Hepatic Insulin resistance and related metabolic disorders***

The liver is an insulin sensitive organ that plays a key role in the regulation of whole body energy homeostasis. Defective insulin signaling and development of insulin resistance in the liver can have major consequences on energy balance and metabolism. Hepatic insulin resistance has thus been suggested as an underlying cause of MtS and its related abnormalities, including hyperglycemia, dyslipidemia, and increased inflammatory factors. The role of hepatic insulin resistance in the pathogenesis of MtS and its proposed molecular mechanisms will be discussed in the following sections of this review.

### ***Hepatic insulin resistance and increased glucose production***

The fasting hyperglycaemia results from reduced glucose uptake by peripheral tissues and increased production of glucose by hepatocytes resistant to insulin action. Hepatic insulin resistance refers to the impaired suppression of glucose production by insulin in hepatocytes. Insulin mediates its

inhibitory effects on glucose production by inhibiting two key gluconeogenic enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and the glucose-6 phosphatase (G6Pase).<sup>18</sup>

In insulin resistant states as observed in T2D patients, defects in insulin signaling molecules is a common finding that correlates with hyperglycemia. Animals with liver specific deletion of the insulin receptor show severe glucose intolerance,<sup>18</sup> whereas normal glucose and insulin levels were found in mice with a deletion of the insulin receptor in skeletal muscle and adipose,<sup>19</sup> suggesting that hepatic insulin resistance is necessary to develop hyperglycemia and glucose intolerance. Taken together, data from animal and human studies demonstrate that resistance to insulin action in the liver tissue leads to hyperglycemia and progression to MtS and T2D.

### ***Hepatic insulin resistance and dyslipidemia***

As discussed earlier, insulin resistance is the underlying cause of T2D and MtS, which are commonly accompanied by metabolic or diabetic dyslipidemia. Several lines of evidence suggest that insulin resistance plays a central role in the development of dyslipidemia, even in non-diabetic insulin resistant subjects.<sup>20</sup> This dyslipidemia is characterized by increased levels of plasma triglyceride and small dense low density lipoproteins (sdLDL) and decreased levels of high density lipoprotein (HDL) cholesterol.<sup>20</sup>

It is now clear that the various components of metabolic dyslipidemia are metabolically linked abnormalities that are the result of hepatic overproduction of large triglyceride rich VLDL1.<sup>20</sup> Evidence from both animal and human studies suggests that insulin resistance (in adipose and liver tissues) is an important underlying cause of hypertriglyceridemia in subjects with MtS and T2D. Insulin resistance controls hepatic VLDL production, especially VLDL1, by affecting the rate of apoB synthesis and degradation and hepatic de novo lipogenesis (DNL), as well as indirectly by modulating FFA flux from the adipose tissue into the liver.<sup>21</sup>

### ***Increased FFA flux induces hepatic VLDL overproduction***

Hepatic lipid content is increased in insulin resistance partly due to the increased flux of FFA from the adipose tissue to the liver and increased uptake of chylomicron remnants by the liver and dietary FFAs that are transported via chylomicrons.<sup>20</sup> In insulin resistant states, failure of insulin to suppress hormone sensitive lipase leads to enhanced lipolysis and enhanced flux of FFA to other tissues, including the liver.<sup>20</sup> Data from T2D patients, animal models, and hepatocytes have shown that increased FFA flux to the liver leads to enhanced assembly and secretion of VLDL.<sup>22</sup> Furthermore, an increase in FFAs levels can attenuate insulin

signaling and exacerbate insulin resistance. It has also been shown that several intracellular metabolites of FFAs such as ceramides and diacylglycerol can attenuate the insulin signaling pathway.<sup>23</sup> Moreover, increased FFA pool in the hepatocytes can activate DNL by activating sterol response element-binding protein (SREBP1-c). It appears that some cellular pathways, including DNL, remain sensitive to insulin action in the liver.<sup>24</sup> Results obtained from in vivo studies reveal that the main factor responsible for the activation of SREBP1-c is hyperinsulinemia per se rather than insulin resistance.<sup>24</sup> Elevated circulating FFA levels cause a decline in hepatic insulin extraction which results in a hyperinsulinemic condition that ultimately enhances DNL resulting in VLDL overproduction.<sup>24</sup>

#### ***Link between Hepatic insulin resistance and VLDL overproduction***

The increase in VLDL production in insulin resistance mostly appears to result directly from decreased sensitivity of the liver to the inhibitory effects of insulin on VLDL secretion. Among obese and T2D subjects, there is ample evidence for defects in insulin signal transduction in target tissues.<sup>10</sup> Insulin resistant and T2D subjects show a decreased activity of PI3-K pathway, resulting in impaired insulin signaling and overproduction of VLDL.<sup>10</sup> In addition, insulin down regulates microsomal triglyceride transfer protein (MTP) expression via the activation of MAPK pathway.<sup>25</sup>

Our laboratory has developed and characterized a diet-induced animal model of insulin resistance, the fructose-fed Syrian golden hamster whose lipoprotein physiology has a number of similarities to that of humans and in vitro in cultured hamster hepatocytes. Hepatic VLDL-apoB overproduction was found to be associated with whole-body insulin resistance and attenuated hepatic insulin signaling.<sup>26</sup> We have also shown impairments in hepatic insulin signaling, including reduced tyrosine phosphorylation of the insulin receptor, IRS-1 and IRS-2, and suppressed activity of PI3-K associated with IRS proteins in this animal model.<sup>26</sup> In addition, we observed an increased activity and mass of protein PTP1B in the liver, contributing to the impairment in insulin signaling. Moreover, we were able to demonstrate the suppression of ER-60, a cysteine protease which induces apoB degradation in the ER (endoplasmic reticulum) lumen.<sup>27</sup>

Overall, the results from our laboratory and others suggest that attenuated insulin signal transduction, most probably by PTP1B overexpression, leads to the suppression of ER-60 and overexpression of MTP giving rise to increased apoB stability and facilitating VLDL assembly and secretion, respectively. Under these conditions, increased FFA flux to the liver along with up-regulation of SREBP-1c inducing

DNL and reduced hepatic lipoprotein remnant uptake further drives the VLDL assembly and secretion process.

#### ***Role of insulin resistance in the generation of small dense LDL and low levels of HDL***

The formation of sdLDL and low levels of HDL are two major components of metabolic dyslipidemia that are observed in MtS and T2D patients. The basis for the formation of sdLDL in insulin resistant states relates to the action of two proteins: cholesteryl ester transfer protein (CETP) and hepatic lipase. Increased CETP and hepatic lipase activity, observed in insulin resistant and T2D subjects, favor the formation of sdLDL.<sup>28</sup> Reduced HDL levels have also been commonly observed in MtS and T2D subjects. Similar to sdLDL, low HDL is associated with high hepatic VLDL secretion. Increased activity of CETP and hepatic lipase lead to the formation of small triglyceride-rich HDL particles, resulting in their increased catabolism by the kidney.<sup>29</sup>

#### ***Insulin resistance and a pro-Inflammatory state***

Insulin resistance, obesity, and T2D are all closely associated with a chronic inflammatory state resulted from abnormal cytokine production, increased acute phase proteins and other mediators, and activation of a network of inflammatory signaling pathways. CRP is a major human acute phase protein largely synthesized in hepatocytes following inflammatory stimuli. Evidence from prospective studies has shown a correlation between serum CRP concentration and MtS components. CRP has also been shown to be an independent predictor of both diabetes and CVD.<sup>30</sup>

The liver is the target of systemic inflammation. Long-term exposure of the liver to inflammatory mediators mostly from the adipose tissue increases the production of a number of acute phase proteins such as CRP. Low grade inflammation observed in obesity leads to a chronic elevation of pro-inflammatory factors such as tumor necrosis factor (TNF- $\alpha$ ), interleukin-6 (IL-6), and interleukin-8 (IL-8), which have been shown to induce insulin resistance in insulin target tissues, especially the liver.<sup>31</sup> These factors inhibit insulin signaling in the liver, which in turn might interfere with the anti inflammatory effect of insulin leading to prolonged acute-phase reaction. Of interest, cytokines particularly IL-6, has been found to induce CRP production in primary human hepatocytes and hepatoma cells at the transcriptional level, an effect which can be enhanced by interleukin-1 $\beta$  (IL-1 $\beta$ ).<sup>32</sup> Collectively, there is much evidence from human, animal, and in vitro studies supporting the hypothesis that CRP may be a key component of the





syndrome that increase the risk of CVD in subjects with MtS.

### ***Insulin resistance and a pro-thrombotic state***

Prothrombotic state is now considered a component of MtS. Various factors have been proposed to be involved in hemostasis dysregulation in MtS, including hypercoagulability and hypofibrinolysis. The main haemostasis disorder related to MtS is the increase in PAI-1, which is a major inhibitor of fibrinolysis.<sup>33</sup>

PAI-1, a serine protease inhibitor, is a marker of impaired fibrinolysis and atherothrombosis. It exerts its effects by inhibiting tissue plasminogen activator (tPA).<sup>33</sup> Epidemiological studies have shown that elevated plasma PAI-1 is a predictor of myocardial infarction.<sup>34</sup> Plasma PAI-1 levels are elevated in insulin resistant subjects, including obese individuals with or without diabetes. Although PAI-1 is expressed in several tissues, including platelets, adipocytes, hepatocytes, monocytes, and smooth muscle cells, endothelial/hepatic tissues appear to be the main source of PAI-1 in plasma.<sup>35</sup> Several groups have reported that liver steatosis is a major contributor to elevated plasma PAI-1 concentration in individuals with MtS.<sup>36,37</sup> Overall, the results obtained from human, animal, and in vitro studies clearly implicate PAI-1 as a true component of MtS that can be induced by hepatic insulin resistance (although PAI-1 induction by other sources should also be considered).

MtS is also associated with increased plasma levels of fibrinogen, factor VII, and factor VIII, leading to a hypercoagulable state.<sup>38</sup> Fibrinogen, an acute-phase protein, is synthesized in the liver and increases the risk of CVD.<sup>38</sup> Increased levels of fibrinogen are associated with both chronic inflammation and insulin resistance in MtS.<sup>39</sup> However, the precise mechanism underlying the increased fibrinogen levels from the liver is not yet clear. It has been suggested that FFAs and cytokines associated with insulin resistance induce the hepatic synthesis of fibrinogen.<sup>38</sup>

### ***Visceral obesity and hepatic insulin resistance***

Visceral obesity is regarded as the major cause of insulin resistance. Visceral obesity has also been defined as an important component of the MtS, and increased visceral fat mass contributes to the development of obesity related disorders such as insulin resistance, non-alcoholic fatty liver disease, hypertension, diabetes and CVD.<sup>40</sup> Chronic systemic inflammation has been proposed to have an important role in the pathogenesis of obesity-related insulin resistance.<sup>40</sup> There is strong evidence that adipose tissue not only releases FFA that contributes to insulin resistance in liver and muscle,

but also produces a wide range of inflammatory molecules including TNF- $\alpha$  and IL-6 which may have local effects on adipose physiology and also systemic effects on other tissues.

TNF- $\alpha$  is a cytokine that inhibits insulin signaling in the liver by mechanisms including the activation of serine kinases such as JNK-1 and induction of SOCS proteins.<sup>41</sup> IL-6 induces hepatic CRP synthesis, and this may promote the onset of cardiovascular complications. Like TNF- $\alpha$ , IL-6 alters insulin sensitivity in hepatocytes by impairing insulin signaling through serine phosphorylation of IRS-1 and activating SOCS proteins.<sup>42</sup> Resistin, an adipocyte-specific secreted protein, has also been implicated in the pathogenesis of obesity-associated insulin resistance and T2D in mouse models, whereas such an effect is still a matter of debate in humans.<sup>43</sup> Resistin has been shown to induce the expression of SOCS-3, a negative regulator of insulin signaling.<sup>43</sup> Adiponectin, another adipokines, plays a key role in the maintenance of insulin sensitivity. Serum levels of adiponectin are reduced in individuals with increased visceral obesity.<sup>44</sup> Hypoadiponectinemia is associated with high body mass index, insulin resistance, dyslipidemia, endothelial dysfunction, and increased risk of CVD.<sup>44</sup> An important consequence of insulin resistance in the adipose tissue is increased FFA flux, leading to the induction of gluconeogenesis and VLDL overproduction in the liver.<sup>45</sup> Increased FFA, especially its metabolites such as acyl-CoAs, ceramides, and diacylglycerol, has been shown to inhibit insulin signaling by activating protein kinases such as PKC, JNK, and the inhibitor of nuclear factor- $\kappa$ B (IKK- $\beta$ ).<sup>3</sup>

### ***Mechanistic links between hepatic insulin resistance and CVD***

CVD is the leading cause of death in many parts of the world. Atherosclerosis is the main cause of CVD. MtS has been shown to associate with almost a 2 fold increase in CVD risk.<sup>5</sup> MtS is composed of several factors contributing to CVD, namely hypertension, hyperlipidemia, obesity, procoagulability, and hyperglycemia. Among these factors, hyperlipidemia, procoagulability, and hyperglycemia are directly the result of hepatic insulin resistance and their relationship with atherosclerosis is discussed below.

It has been well known for a long time that prolonged exposure to hyperglycemia has a major effect on the pathogenesis of atherosclerosis.<sup>46</sup> Hyperglycemia induces a series of alterations at the molecular and cellular levels that potentially accelerate the atherosclerotic process. Non-enzymatic glycosylation of proteins and lipoproteins in the arterial wall is one of the mechanisms that change the normal function of proteins, leading to interference with receptor recognition, changing enzymatic activity, and disruption of molecular conformation. A second proposed

mechanism is PKC activation following exposure to high glucose. Following PKC activation, transforming growth factor- $\beta$  (TGF- $\beta$ ) expression increases.<sup>47</sup> This factor plays an important role in regulating extracellular matrix production by activating gene expression of proteoglycans and collagen. Finally, an increase in oxidative stress by hyperglycemia can promote atherosclerosis by activating PKC.<sup>46</sup>

VLDL overproduction resulting from hepatic insulin resistance can lead to the formation of sLDL. It has been found that the intimal proteoglycans have higher affinity for sLDL than large LDL.<sup>47</sup> Furthermore, sLDL has reduced affinity for LDL apoB/E receptor that in turn leads to the uptake of these particles by macrophages leading to the formation of foam cells.<sup>48</sup> CRP is another factor in hepatic insulin resistance that plays a role in the pathogenesis of atherosclerosis. There is now clear evidence that CRP can directly promote atherosclerosis by binding to the oxidized LDL, increasing the expression of PAI-1 and adhesion molecules in endothelial cells, inhibition of nitric oxide formation, and increasing LDL uptake into macrophages.<sup>49</sup> Collectively, the evidence indicates that hepatic insulin resistance has an important role in providing the key elements which directly or indirectly accelerate atherosclerosis.

## Conclusion

A growing body of evidence suggests that insulin resistance is a fundamental initiating event in the development of MtS. Hepatic insulin resistance has a major role in eliciting the key components of MtS such as dyslipidemia, hyperglycemia, and development of pro-inflammatory and pro-thrombotic states, all of which have been shown to directly promote atherosclerosis. Further studies are currently underway to investigate the molecular and cellular mechanisms that underlie hepatic insulin resistance and MtS and to elucidate the causative factors in the development of this growing worldwide epidemic.

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