1. Introduction

Normal insulin sensitivity is essential for the maintenance of normal circulating carbohydrate and lipid levels and their metabolism. In healthy individuals, elevated blood glucose levels stimulate the pancreas to release insulin, which lowers blood glucose levels by stimulating glucose uptake and metabolism in muscle, adipose tissue, and several other insulin-sensitive organs. Blood glucose increases are not only countered by increased tissue glucose uptake but also by insulin-induced suppression of hepatic glycogenolysis and gluconeogenesis. Besides its effects on blood glucose, insulin also affects circulating lipid levels by reducing hepatic very low density lipoprotein cholesterol (VLDL-cholesterol) formation from free fatty acids (FFAs). This is primarily due to the reduced free fatty acid supply to the liver caused by insulin-induced suppression of lipogenesis in adipose tissue [1]. In addition to its effects on lipogenesis, insulin also reduces lipolysis in adipose tissue by inhibiting hormone-sensitive lipase. The latter hydrolyses adipocyte triglycerides to release free fatty acids and glycerol into the circulation. When delivered acutely, insulin inhibits fatty acid synthase while chronic hyperinsulinaemia (as occurs in insulin resistance) may induce fatty acid synthase activity and increase fatty acid synthesis [2]. The net effect of elevated insulin in normal healthy individuals is to reduce circulating glucose and free fatty acid levels.

When an individual becomes insulin resistant, control of circulating lipid and blood glucose levels is compromised. Insulin resistance ensues when normal physiological concentrations of insulin are unable to induce effective uptake of glucose by insulin-sensitive tissue. As a compensatory mechanism aimed at maintaining euglycaemia, pancreatic insulin secretion increases leading to a state of hyperinsulinaemia. If the elevated insulin levels are inadequate to fully compensate for the insulin insensitivity, glucose intolerance ensues. The degree of glucose intolerance in insulin-resistant individuals is thus dependent on the extent...
of the loss of the *in vivo* function of insulin, and the ability of the pancreas to adjust for this by secreting more insulin [3, 4]. Once elevated circulating levels of insulin are no longer able to maintain euglycaemia, and glucose levels deviate beyond normal physiological ranges an individual is considered to be frankly diabetic.

Myocardial insulin resistance translates to compromised intracellular insulin signalling and reduced glucose oxidation rates in animal models of obesity [5] and adversely affects myocardial mechanical function and tolerance to ischaemia and reperfusion. In this chapter we will review the mechanisms implicated in the aetiology of insulin resistance (skeletal and heart muscle) and discuss the effects of insulin resistance on cardiac metabolism, mechanical function and tolerance to ischaemia and reperfusion. We will also briefly review therapies used to prevent or counter insulin resistance and its associated adverse effects on the cardiovascular system.

2. Myocardial insulin signalling

Insulin induced activation of the insulin receptor (IR) invokes a cascade of events which ultimately enhances myocardial glucose uptake and metabolism. Insulin binding to its receptor results in autophosphorylation and activation of the insulin receptors (IRs) intrinsic tyrosine kinases. Following phosphorylation the insulin receptor phosphorylates insulin receptor substrate (IRS) [6] which subsequently associates with phosphoinositide 3-kinase (PI3K) via its p85 subunit [7, 8]. These events are vital for initiating insulin’s effects on glucose metabolism [6, 9, 10]. Activated PI3K will induce (via various signalling mechanisms) protein kinase B (PKB/Akt)[11] which plays a pivotal role in glucose metabolism by regulating the translocation of the cytosolic glucose transporter type 4 (GLUT4), to the sarcolemma [12, 13]. Inhibition of PI3K and/or PKB/Akt attenuates sarcolemmal GLUT4 translocation, effectively reducing insulin stimulated signalling and glucose uptake [14, 15]. Besides facilitating glucose uptake via GLUT4, insulin stimulation also increases glycolytic flux rates through activation of phosphofructokinase 2 (PFK-2) which promotes the production of fructose-2,6-bisphosphate from fructose-6-phosphate [16-18]. Fructose-2,6-bisphosphate stimulates PFK-1 activity, which will also enhance glycolysis (see review by Hue *et al.* [18]).

Although insulin increases long chain fatty acid (LCFA) uptake into the cardiomyocyte by increasing sarcolemmal fatty acid translocase/cluster of differentiation 36 (FAT/CD36) [19], elevated insulin levels also suppress tissue fatty acid β-oxidation rates. This suppression is most likely due to the effects of by-products of elevated glucose oxidation on malonyl-CoA levels [20]. As acetyl-CoA levels increase, acetyl-CoA carboxylase (ACC) is activated which increases malonyl-CoA induced inhibition of fatty acid oxidation.

3. The role of obesity or a high fructose diet in the aetiology of insulin resistance

Insulin resistance is strongly associated with both obesity and the consumption of high fructose containing diets [21-25]. Although not all obese individual are insulin resistant,
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there is a strong association between obesity and insulin resistance [21, 25]. Adipose tissue is not only a storage organ but also a metabolically active organ synthesising and secreting a large range of substances that include fatty acids, pro-inflammatory cytokines, angiotensin II, leptin, resistin, visfatin and other adipocytokines [26] that can all influence tissue metabolism. Obesity and high fructose diets both induce increases in: 1) circulating FFAs [27, 28], 2) renin-angiotensin system (RAS) activity [29, 30], and 3) inflammation (caused by tissue and macrophage derived pro-inflammatory cytokines) [31] that are all associated with, and implicated in insulin resistance.

Besides the negative impact of obesity on circulating lipids, recent studies provide convincing evidence for a role for high fructose diets in dyslipidaemia and insulin resistance [24, 27, 32]. These lipid profile altering effects of high fructose diets are primarily caused by fructose induced alterations in hepatic lipid metabolism [22-24]. Hepatic fructose metabolism differs significantly from glucose metabolism with fructose being a lipogenic sugar that promotes the deposition of triglycerides in adipose tissue and ectopic organs such as the liver and muscle. This tissue triglyceride accumulation eventually contributes to dyslipidaemia and insulin resistance [22, 27, 33].

Increasing dietary fructose consumption increases plasma triglyceride levels through stimulation of hepatic lipogenesis [34] and decreased VLDL-triglyceride removal from the plasma by adipose tissue [35]. Fructose evidently also activates genes involved in hepatic de novo lipogenesis [36, 37] which causes increased hepatic fatty acid generation. These fatty acids are incorporated into hepatic triglycerides which promotes VLDL-triglyceride synthesis and release from the liver (Figure 1)[38].

A recent review highlights the possible effects of high fructose diets on hepatic insulin resistance [22]. These authors propose that high fructose diets promote hepatic inflammation by increasing fatty acid β-oxidation (secondary to hepatic lipid accumulation) which generates peroxidation products that stimulate inhibitor of nuclear factor kappa-B kinase subunit beta (IKKβ) and activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB). The NFκB then enters the nucleus and induces the transcription of genes that encode for pro-inflammatory cytokines that include tumour necrosis factor alpha (TNFα) and interleukin-6 (IL-6). These cytokines potentially activate c-Jun N-terminal kinase-1 (JNK-1) which will increase inhibitory serine307 phosphorylation of IRS-1 and contribute to hepatic insulin resistance [22] (Figure 2).

Because of its lipogenic effects, fructose causes more marked changes in 24 hour lipid profiles than does the consumption of glucose while also favouring visceral rather than subcutaneous fat deposition [33]. This fat deposition pattern differs from that of glucose which promotes subcutaneous adipose tissue deposition rather than visceral fat deposition in men [39]. In rodents, a high fructose diet increases intrahepatic fat content and serum VLDL-triglyceride concentrations within 6 weeks of feeding. In the same study intramuscular fat content was increased within 3 months of initiating the high fructose feeding with these changes being closely followed by hepatic and muscle insulin resistance [32]. Another animal based study supports a role for high fructose diets in increased hepatic VLDL-triglyceride
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secretion [40]. In humans increasing fructose content in the diet increases plasma triglycerides [34, 41], decreases VLDL-triglyceride clearance [35] and increases triglyceride deposition in hepatocytes and skeletal muscle within a week of increasing dietary fructose content [41].

Figure 1. Mechanism for high fructose diet induced dyslipidaemia and ectopic lipid accumulation. High fructose diets promote hepatic de novo lipogenesis and lipid accumulation and reduce extrahepatic VLDL-triglyceride clearance. The associated hypertriglyceridaemia promotes adipose tissue expansion (obesity) and muscle lipid accumulation which induces insulin resistance.

Since high fructose diets are often also associated with obesity, it is difficult to differentiate between the effects of the changes in dietary fructose content and the effects of obesity on tissue insulin sensitivity. Data from studies demonstrating that some individuals are obese but metabolically healthy [42] and metabolic syndrome appears to be more closely linked to intrahepatic fat content than obesity per se [1, 41, 43], suggests that hepatic lipid metabolism and circulating lipid levels play a critical role in the induction of insulin resistance in response to obesity and high fructose diets. Tappy and co-workers [23, 24] recently proposed that fructose increases hepatic de novo lipogenesis which leads to intrahepatic lipid deposition, hepatic insulin resistance and increased VLDL-triglyceride secretion. This
potentially leads to increased visceral fat deposition while the elevated VLDL-triglyceride and inhibition of lipid oxidation (induced by fructose) may promote ectopic fat deposition in muscle with lipotoxicity leading to systemic insulin resistance (Figure 1) [22-24].

**Figure 2.** The proposed mechanism for intrahepatic lipid accumulation induced stimulation of \( \beta \)-oxidation and ROS generation. ROS induced increases in cytokine (TNF\( \alpha \) and possibly other cytokines) expression and synthesis activates JNK which phosphorylates IRS-1 (insulin receptor substrate) at the serine\(^{307} \) residue. This inhibitory phosphorylation of IRS-1 prevents its tyrosine phosphorylation by the insulin receptor and interferes with the normal insulin signalling cascade (Illustration modified from review by Rutledge and Adeli [22]).
The experimental evidence implicating inflammation/pro-inflammatory cytokines and overactive renin-angiotensin systems (organ and systemic) in the aetiology of insulin resistance will be discussed later. We will first review the evidence for a role for elevated circulating free fatty acids, and tissue triglycerides and lipid intermediates accumulation in the aetiology of insulin resistance in skeletal and heart muscle.

4. The role of free fatty acids and intracellular lipid accumulation in insulin resistance

A prevalent metabolic change associated with obesity [44-49] and high fructose feeding [22-24] is the increase in the circulating free fatty acids and triglycerides. Under conditions of over-nutrition and dyslipidaemia, not all fatty acids entering the cell are utilized for oxidative purposes. Long chain fatty acyl-CoA accumulation provides substrates for non-oxidative processes such as triglyceride, diacylglycerol (DAG) and ceramide synthesis [50, 51]. In the myocardium lipid accumulation is a direct result of a mismatch between fatty acid uptake and oxidation by the cell [47, 52]. What is not clear is whether this accumulation is due to: 1) increased FFA uptake by the heart 2) compromised FFA oxidation, or, 3) a combination of the two.

There is a strong link between increased circulating free fatty acids, myocardial triglyceride accumulation and insulin resistance. Increased circulating free fatty acids increase the expression of sarcolemmal fatty acid transporters and increases fatty acid uptake into the myocyte. Obese Zucker rats [46, 48] and db/db mice [53] with insulin resistance have increased FAT/CD36 localised to the sarcolemma. The exact mechanism for the increased localisation of FAT/CD36 in the sarcolemma is not clear but may relate to the chronic hyperinsulinaemia associated with insulin resistance. It is well established that insulin stimulates FAT/CD36 translocation to the sarcolemma [54, 55]. Besides its adverse effects on insulin signalling and glucose metabolism, excessive intramyocellular lipid accumulation may also have direct lipotoxic effects [50, 57]. Both altered substrate utilization and excess intramyocardial lipid accumulation which is characteristic of obesity, dyslipidaemia and insulin resistance may have serious cardiac consequences that ultimately lead to compromised cardiac metabolism, morphology and mechanical function.

Lipid intermediates may adversely influence insulin signalling and contribute to insulin resistance [5, 58, 59]. The accumulation of triglycerides, diacylglycerol (DAG) and ceramide is known to activate kinases that down-regulate insulin signalling [60-62]. These kinases include JNK, IKK and protein kinase C (PKC) that is known to inhibit insulin signalling via serine phosphorylation of IRS-1 [5, 63].

Ceramide accumulation occurs through de novo synthesis from saturated fatty acids [64] or hydrolysis of sphingomyelin [65]. It has been shown to cause insulin resistance by inhibiting Akt phosphorylation in skeletal muscle [66-68] and adipocytes [69] with the
pharmacological inhibition of ceramide synthesis being effective in preventing lipid induced insulin resistance in rats [67, 70].

Models of lipotoxicity have also demonstrated that elevated myocardial ceramide levels are associated with increases in indices of apoptosis [52, 71]. Rat neonatal cardiomyocytes incubated with physiological concentrations of palmitate have increased intracellular triglycerides, increased ceramide levels and increased indices of apoptosis [72]. The mechanism implicated in ceramide induced apoptosis may involve activation of NFκB which in turn up regulates inducible nitric oxide synthase (iNOS) expression [73]. The resulting increase in nitric oxide production [74] may cause a subsequent rise in the formation of peroxynitrite, which induces mitochondrial cytochrome C release [75] and subsequent apoptosis. In addition, ceramide has been shown to directly induce the generation of damaging reactive oxygen species in the mitochondria [76]. Obese insulin resistant (prediabetic) Zucker rats also have elevated intramyocardial triglycerides which are accompanied by increased myocardial ceramide levels and cardiomyocyte apoptosis. These cellular alterations are present before the onset of diabetes and cardiac dysfunction [71]. Reducing myocardial lipid levels by treating the rats with peroxisome proliferator-activated receptor gamma (PPARγ) agonists lead to reduced cardiac ceramide levels and apoptosis and prevented cardiac dysfunction [71]. In a similar study, mice over-expressing cardiac specific long chain acyl-CoA synthase display high intramyocardial triglycerides and ceramide levels. These changes were accompanied by increased DNA fragmentation and cytochrome C release with the mice developing cardiac hypertrophy and left-ventricular dysfunction [52].

Lipid infusion increases intracellular DAG and causes skeletal muscle insulin resistance in rodents [60]. This association between intracellular DAG levels and skeletal muscle insulin resistance has been confirmed in several rodent and human studies [77-79]. Increased muscle DAG is associated with increased activation of protein kinase C theta (PKC-θ) in obese and diabetic patients [80, 81]. Increased PKC-θ activation interferes with insulin signalling by increasing IRS-1 serine307 phosphorylation (Figure 3) [60, 81]. Accelerating fatty acid oxidation rates potentially prevents fatty acid, acetyl-CoA and subsequent DAG accumulation and may improve insulin sensitivity. This proposal was recently supported by a study showing that carnitine palmitoyltransferase I (CPT-1) over-expression in L6E9 myotubes increases mitochondrial fatty acid uptake, decreased intracellular DAG concentrations and protects against elevated fatty acid induced insulin resistance [82].

4.1. Evidence for lipid accumulation in skeletal muscle insulin resistance

An inverse correlation exists between intramuscular lipid content and insulin sensitivity. Measurements of insulin sensitivity (120 min euglycaemic hyperinsulinaemic clamp) in skeletal muscle from healthy subjects demonstrated that high intramuscular lipid content was associated with lower whole body insulin stimulated glucose uptake. These subjects also exhibited elevated circulating free fatty acids, reduced tyrosine phosphorylation of the insulin receptor (IR) and lower (insulin receptor substrate) IRS-1 mediated PI3K activation during hyperinsulinaemia than subjects with low intramuscular lipids [83]. Studies
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comparing lean and obese individuals have made similar observations linking intracellular lipid accumulation to skeletal muscle insulin resistance [84, 85]. Boden and colleagues [86] reported a strong association between serum free fatty acid levels, intramuscular lipid content and insulin resistance after lipid injection in healthy subjects. Elevated circulating free fatty acid levels, induced by lipid injection, was associated with a gradual increase in intramuscular lipid content and a 40% increase in insulin resistance. These observations also corroborated earlier studies demonstrating that elevated fatty acids reduced skeletal muscle glucose uptake in humans [87].

![Figure 3. The proposed mechanism for dyslipidaemia induced insulin resistance. Increased circulating free fatty acids as occurs during overfeeding/obesity and/or high fructose diet feeding will increase fatty acid uptake. Long chain acetyl CoA not oxidised can be used in non-oxidative pathways with the generation of triglycerides, diacylglycerol (DAG) and ceramide. Both the latter lipid metabolites have been implicated in aetiology of insulin resistance through the activation of PKC, IKK and JNK.](image)

In rodent skeletal muscle, experimentally elevated circulating free fatty acids increased intracellular acetyl-CoA and DAG levels which was coupled to increased active protein kinase C (PKC) theta. These changes were accompanied by increased IRS-1 serine phosphorylation, reduced IRS-1 tyrosine phosphorylation and reduced IRS-1 associated PI3K activity [60, 88]. Phosphorylation of IRS-1 at serine307 evidently hinders IRS-1’s interaction with PI3K and therefore interferes with normal insulin signalling.
4.2. Evidence for lipid accumulation in cardiac muscle insulin resistance

Similar associations between increased intracellular lipid accumulation and reduced insulin sensitivity have been observed in cardiac muscle from obese insulin resistant animals [47, 71, 89, 90]. In obese insulin resistant JCR:LA-cp rats, the increased supply of circulating free fatty acids was associated with a 50% increase in myocardial triglyceride content and a 50% reduction in myocardial glycolytic flux rates [89].

In humans, plasma free fatty acid levels correlate with intramyocardial triglyceride levels [91]. This association is also evident in obese [91, 92], obese glucose intolerant [93] and diabetic [93, 94] individuals. Excessive intramyocardial triglyceride accumulation precedes the development of type-2 diabetes and tends to increase linearly with the degree of systemic insulin resistance [93]. Obese insulin resistant humans do not always have elevated serum free fatty acid levels but do appear to maintain higher rates of free fatty acid uptake, utilization and subsequent oxidation than lean controls [95].

5. The role of cytokines and chronic inflammation in insulin resistance

Obesity and insulin resistance is associated with chronic systemic inflammation caused by activation of the intrinsic immune systems in organs and the macrophages that infiltrate them [96]. The most prominent pro-inflammatory mediators involved in this inflammation are TNFα and IL-6 that originate from: 1) macrophages in adipose tissue and the liver [97], 2) the adipocytes themselves [97], and, 3) several other cytokine synthesising tissues in the body [97-99].

Elevated free fatty acids may increase pro-inflammatory cytokine expression and synthesis since studies inducing acute increases in plasma free fatty acids have observed activation of NFκB in skeletal muscle in humans [79] and increases hepatic TNFα, IL-1β and IL-6 and circulating monocyte chemotactic protein-1 (MCP-1) in rats [100, 101]. How elevated fatty acid cause NFκB activation is unknown but may involve DAG and PKC [102] or the Toll-like receptor 4 (TLR-4) [103]. MCP-1 is also known to regulate recruitment of macrophages to sites of inflammation and may be involved in the recruitment and differentiation of monocytes to macrophages that produce pro-inflammatory cytokines in conditions such as obesity and dyslipidaemia [97, 104].

TNFα causes insulin resistance by suppressing IRS-1 associated insulin signalling and glucose transport in skeletal muscle while IL-6 activates the phosphatase SHP-2 and Signal transducer and activator of transcription 3 (STAT3) causing increased expression of suppressor of cytokine signalling 3 (SOCS3) [105, 106]. IL-6 also activates several serine/threonine kinases such as JNK, p38 mitogen activated protein kinases and PKC-δ that contribute to reduced insulin sensitivity and glucose metabolism (Figure 4) [107, 108].

Information relating to the possible role of inflammation in the aetiology of myocardial insulin resistance is limited. A recent study however reported that high fat feeding caused increased myocardial macrophage infiltration and increased cytokine and SOCS levels in cardiomyocytes from these animals [109]. These changes were associated with reduced myocardial insulin sensitivity and glucose metabolism.
Figure 4. Proposed mechanism for inflammation induced insulin resistance in muscle. Cytokines from macrophages and myocytes activate their receptors and associated signalling pathways to increase serine (inhibitory) phosphorylation of IRS-1. IL-6 is known to activate the STAT3-SOCS3 pathways while TNFα activates JNK to phosphorylate IRS-1.

6. The role of the Renin-Angiotensin System (RAS) in insulin resistance

The authors [110] and others [111-115] have shown that the systemic and tissue renin-angiotensin systems (RAS) activity is increased in obesity. The role of increased RAS activity in metabolic and cardiovascular disease has been reviewed in detail [29, 116-118]. A key
observation linking the RAS system to insulin resistance was made when it became apparent that hypertensive patients treated with angiotensin converting enzyme (ACE) inhibitors or angiotensin (AT) receptor blockers have a reduced risk of developing insulin resistance and type-2 diabetes when compared to patients on other conventional anti-hypertensive therapy [119, 120]. Subsequent studies have corroborated these observations with RAS inhibition improving blood glucose management [121] and lowering risk of type-2 diabetes [122]. These data provided indirect evidence to suggest that the RAS (and particularly over-activation) contributes to insulin resistance and type-2 diabetes.

Several human and animal studies support a role for RAS over-activity in insulin resistance. Genetic abnormalities leading to over-activation of the RAS provides strong evidence for the involvement of the RAS in insulin resistance. In infants [123] and adults [124, 125] the DD genotype of the ACE I/D polymorphism is associated with glucose intolerance and insulin insensitivity. Similarly, AGTT174M polymorphisms are associated with metabolic syndrome in aboriginal Canadians [126].

As mentioned previously, pharmacological blockade of the RAS in clinical trials has provided the most compelling evidence for a role for RAS over-activity in metabolic abnormalities such as insulin resistance. The use of ACE inhibitors for antihypertensive therapy reduces the risk of developing type-2 diabetes by 14% [119]. Studies on animals support these observations with RAS inhibition improving insulin sensitivity in rat [127] and mice [128]. Genetic deletion of renin [129] or ACE [130] or one of the two AT receptors also appears to be effective in preventing or reducing insulin resistance in mice [131, 132].

Besides the evidence showing that inhibition of RAS activity may improve insulin sensitivity, several studies also provide direct evidence implicating over-activation of the RAS in the aetiology of insulin resistance. Chronic angiotensin II infusion causes insulin resistance in rats [133, 134] while the TG(mREN2)27 rat which suffers from chronic systemic RAS over-activation develops muscle and systemic insulin resistance [135]. The RAS induced insulin resistance in these animals is improved by renin inhibition or angiotensin receptor blockade [135, 136].

The mechanism for angiotensin II (Ang II) induced insulin resistance has received significant attention. Ang II adversely affects glucose metabolism and decreases its uptake and utilisation by interfering with insulin signalling [137]. In L6 myocytes Ang II suppresses insulin induced phosphorylation of the tyrosine residue on IRS-1. This was associated with decreased activation of PKB/Akt and GLUT4 translocation to the sarcolemma. These changes were all AT1 receptor, NADPH oxidase and NFκB dependent [138, 139]. Based on these observations it seems likely that Ang II activates NADPH oxidase and increases reactive oxygen species (ROS) generation through the angiotensin type 1 (AT1) receptor. ROS activate the NFκB to increase transcription of cytokines that include TNFα and IL-6. These cytokines increase SOCS3 expression which inhibits insulin signalling (Figure 5) [140]. In rats Ang II also reduces skeletal muscle mitochondrial content (possibly through increased ROS generation) which would be expected to reduce muscle glucose utilisation [141].
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Figure 5. Proposed mechanism for renin-angiotensin system over-activation induced insulin resistance. Angiotensin II activates NADPH oxidase to generate reactive oxygen species (ROS) which activate the translocation of NFkB to the nucleus. Here it causes the transcription, synthesis and release of cytokines (TNFα and IL-6). The binding of these cytokines to their sarcolemmal receptors induce serine kinases and SOC3 which inhibits IRS-1 tyrosine phosphorylation, insulin signalling and GLUT4 translocation.

Adipose tissue RAS over-activity may also contribute to systemic insulin resistance since Ang II from adipose tissue contributes to circulating Ang II levels. This was well demonstrated by a study investigating the effect of adipose tissue angiotensinogen (Agt) over-expression on systemic glucose tolerance and insulin resistance [142]. The over-expression of Agt in adipose tissue caused cardiac and skeletal insulin resistance and reduced muscle glucose uptake.

7. The role of adipocytokines in the aetiology of insulin resistance

Adipocytokines released from adipose tissue perform regulatory functions in energy and fluid balance and satiety and have been implicated in conditions such as obesity, dyslipidaemia, insulin resistance/diabetes and cardiovascular disease. Besides the two pro-inflammatory cytokines discussed previously (TNFα and IL-6) adipocytes secrete several well characterised adipocytokines that include: leptin, adiponectin, and resistin. Dysregulation of the synthesis and secretion of these peptides has been associated with, and implicated in, the aetiology of metabolic diseases such as insulin resistance and type-2 diabetes. A possible role for adipokines in the regulation of myocardial metabolism only emerged recently [143-145].
Leptin is synthesised by white adipose tissue and is involved in appetite control and energy expenditure. Although the absence of leptin leads to obesity and insulin resistance, most obese patients have elevated leptin levels but do not respond to the appetite suppressing and other effects of the peptide [146, 147]. Mutations of the leptin receptor (Ob-R) are associated with obesity in the db/db mouse [148] and the Zucker (fa/fa) rat [149] and leptin deficiency occurs in obese (ob/ob) mice [150] while the treatment of patients [151, 152] and animals [150] with recombinant leptin reduces body weight and improves serum lipid levels.

Serum triglyceride levels and blood glucose handling also improved in women with lipodystrophy and leptin deficiency indicating that leptin may alter lipid metabolism and prevent lipotoxicity [153]. Animal studies demonstrate that leptin promotes lipid oxidation. In rat adipocytes leptin reduces insulin’s lipogenic effect by: 1) inhibiting insulin binding to its receptor [154], 2) increasing adipose and non-adipose tissue β-oxidation, and, 3) decreasing adipose tissue triglyceride content without elevating circulating free fatty acids (Figure 6) [74]. This reduction in serum fatty acid levels will also counter the effect of insulin on lipogenesis [74, 154].

Figure 6. A simplified illustration to demonstrate the effects of adipocytokines on tissue insulin sensitivity and inflammation.
There is a strong association between leptin deficiency/resistance and lipotoxicity [155]. The lipid lowering effects of leptin in heart muscle was demonstrated in a study where 24 hour high fat feeding of mice was associated with cardiac lipid accumulation in animals with low leptin levels but not those with high plasma leptin levels [156]. Leptin administration decreases cardiac muscle lipotoxicity in a subsequent study by this group [157].

Leptin administration to the perfusate of isolated rat hearts perfused with palmitate and glucose significantly increased fatty acid oxidation and reduced intramyocardial triglyceride content without increasing cardiac work. This was accompanied by increased myocardial oxygen consumption and reduced cardiac efficiency [143]. The significance of leptin in metabolism is further highlighted in genetic models such as the leptin deficient $ob/ob$ mouse and the leptin resistant $db/db$ mouse that has a loss-of-function mutation on the leptin receptor. These animals are obese, insulin resistant and display excess intramyocardial lipid accumulation. They are also more prone to increased cardiomyocyte apoptosis and cardiac dysfunction than their control littermates [158-162].

Circulating adiponectin levels are reduced in obesity, insulin resistance and diabetes and correlate with the extent of insulin resistance and hyperinsulinaemia [163-165]. It is synthesised by adipocytes, skeletal muscle, heart muscle and endothelial cells [166] and is a key adipocytokine in the regulation of metabolism. It is considered to be an anti-diabetic, anti-inflammatory and anti-atherogenic agent with adiponectin deficient animals becoming glucose intolerant, insulin resistance and hyperleptinaemic [167, 168]. Studies utilising adiponectin replacement therapy have demonstrated its ability to decrease dyslipidaemia [169] and improve insulin sensitivity (Figure 6) [170-172].

Adiponectin acts via phosphorylation of 5’adenosine monophosphate-activated protein kinase (AMPK) to influence insulin sensitivity and fatty acid and glucose utilisation [172, 173]. Its action is mediated through the AdipoR1 and AdipoR2 receptors [170] that are both expressed in cardiac tissue [174]. Receptor activation is associated with modulation of AMPK, PI3K, p38 MAP kinase and extracellular signal-regulated kinase (Erk) 1/2 MAP kinase [175-177].

Resistin is secreted from white adipose tissue but is also expressed in other tissues [178]. It was given its name because it was originally shown to counter the effects of insulin by suppressing insulin signalling [179]. Over-expression of resistin is associated with dyslipidaemia and insulin resistance [180, 181] and inhibition of glucose uptake in cardiomyocytes [182]. In humans plasma resistin levels are closely correlated to insulin resistance irrespective of body weight [183]. However, these observations are not supported by two animal studies that found that resistin levels were not a good predictor of insulin resistance when corrected for body mass index (BMI) [184, 185]. In both high fat diet and genetic mutation induced obesity, resistin levels were closely associated with body weight with obese animals having significantly elevated resistin levels [179]. The exact role of resistin in insulin resistance is however poorly understood and unresolved.
8. Effects of myocardial insulin resistance on myocardial metabolism, mechanical function and tolerance to ischaemia and reperfusion

The heart utilises glucose, fatty acids and lactate as fuels for the production of ATP. Cardiac metabolism is under the control of several hormones with insulin being a key regulator of glucose, fatty acid and lactate metabolism. Changes in myocardial insulin sensitivity disrupt the hearts’ normal substrate metabolism and potentially decrease mechanical function and myocardial tolerance to ischaemia/reperfusion.

8.1. Myocardial metabolism

The heart is a dynamic organ, constantly requiring energy in the form of ATP in order to meet its homeostatic and contractile demands. This is achieved through a constant supply of oxidizable substrates from the circulation. The most important substrates utilized by the heart are: fatty acids, glucose and lactate. Although the adult heart is capable of oxidizing a variety of substrates, the majority of ATP (60-70%) generated by the heart originates from the oxidation of fatty acids [186, 187]. However, in the presence of elevated glucose and insulin levels as occurs immediately following a meal, 60-70% of ATP may be derived from glucose metabolism [188].

Circulating fatty acids are taken up by the heart either in their free form (as free fatty acids (FFAs)) bound to albumin, or they can be released from the triglyceride component of chylomicrons or very-low-density-lipoproteins (VLDL) [189]. The concentration of fatty acids present in blood greatly dictates their uptake and metabolism by the heart [190]. Under normal physiological conditions, long chain fatty acids (LCFAs) are the principal fatty acids oxidized by the heart [191]. The entry of LCFAs across the sarcolemma into the cytoplasm of the cardiomyocyte occurs through passive diffusion or membrane protein mediated transport, the latter accounting for the majority of fatty acid translocation to the cytosol [192]. This membrane protein mediated transport is facilitated by fatty acid translocase (FAT)/CD36, plasma membrane fatty acid binding protein (FABPpm) and fatty acid transport protein (FATP) [192]. Once inside the cell, non-esterified LCFAs are transported via cytoplasmic heart-type FABPs through the cytoplasm to the location where they will be utilized [193-195]. LCFAs are then esterified by acyl-CoA synthetase to form long chain fatty acyl-CoA’s (LCFA-CoA) [55]. LCFA-CoAs can be stored in intracellular lipid pools where they can be converted to additional lipid intermediates (triglycerides, diacylglycerol (DAG) or ceramide), or are transported to the mitochondria where they undergo β-oxidation.

Glucose enters the cardiomyocyte through either the basal uptake glucose transporter, GLUT1, or via the insulin dependent glucose transporter, GLUT4 [196]. GLUT4 is stored in cytoplasmic vesicles which are recruited to the sarcolemma in response to insulin stimulation or cardiac contraction. Glucose itself can also induce GLUT4 translocation with this and insulin stimulated translocation determining the glucose flux rate into the cardiomyocyte [197]. Inside the cell hexokinase converts glucose to glucose-6-phosphate which can be stored as glycogen (after conversion by glycogen synthase) or it can undergo
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Glycolysis to yield pyruvate and ATP. During adequate myocardial oxygen availability, pyruvate is transported into the mitochondria via a mitochondrial monocarboxylate transporter [198] and subsequently oxidized by pyruvate dehydrogenase (PDH) to produce acetyl-CoA (reviewed by Stanley et al. [199]). During anaerobic conditions as occurs during myocardial ischaemia, pyruvate may be converted to lactate.

The rate of glucose oxidation is also influenced by fatty acid β-oxidation rates since hexokinase, PFK and PDH activity are all inhibited by various products of fatty acid metabolism (for a review see Hue and Taegtmeyer [200]). There is a delicate interplay in the utilisation of these two myocardial substrates which is intricately related to their circulating levels. The common endpoint where glucose and fatty acid metabolism converge is the production of acetyl-CoA which enters the tricarboxylic acid/Krebs cycle where it is used to generate ATP during oxidative phosphorylation [187, 201]. Alternatively the acetyl-CoA can be utilised in non-oxidative pathways for the production of triglycerides, DAG and ceramide.

8.2. Impact of myocardial insulin resistance on myocardial metabolism

The early onset of insulin resistance in obesity may be a physiological response to increased lipid availability leading to increased lipid utilisation and a reciprocal reduction in glucose metabolism. Chronic dysregulation of glucose uptake and metabolism by dyslipidaemia and inflammation may however induce pathological changes in cardiac metabolism that compromise cardiac morphology and mechanical function.

High fat feeding of C57BL/6 mice induces myocardial insulin resistance within 10 days. This insulin resistance was associated with reduced myocardial glucose uptake, PKB/Akt activity and GLUT4 protein levels and preceded and occurred independently of systemic insulin resistance [202]. With myocardial insulin resistance, fatty acid oxidation rates are normal or elevated, while glucose oxidation rates are normally reduced both in the presence or absence of insulin stimulation [5, 44, 45, 203-205]. Although a limited number of studies have reported similar myocardial fatty acid and glucose oxidation rates in obese, insulin resistant animals when compared to lean controls, they have all found that insulin stimulated myocardial glycolytic flux rates remain suppressed with insulin resistance [89, 206]. In humans similar increases in myocardial fatty acid metabolism were reported in obese men and women. Gender however also played and important role in determining the impact of obesity of glucose and fatty acid uptake and utilization [207]. Women were less prone to obesity induced dysregulation of myocardial metabolism than their obese male counterparts. These gender based differences in myocardial metabolism in response to obesity may translate to differences in the development of obesity-related cardiovascular diseases.

8.3. Effect of insulin resistance on cardiac mechanical function

Increased lipid uptake and oxidation as seen with insulin resistance potentially leads to cellular lipid intermediate accumulation, excessive mitochondrial or peroxisomal ROS generation and functional derangement in the heart [71]. This is well demonstrated by a
study showing that cardiac specific PPARα over-expression which increases cardiac lipid oxidation causes metabolic derangements and leads to adverse structural and function changes in the heart [208].

Pre-diabetic (insulin resistant) obese Zucker rats display cardiac dysfunction [47]. These observations were corroborated in obese insulin resistant mice (ob/ob and db/db) that had increased myocardial lipid oxidation rates, decreased glucose oxidation rates and decreased cardiac efficiency. These changes were also associated with systolic dysfunction when compared to lean insulin sensitive littermates [45].

Although genetic models of obesity do not accurately resemble the phenotype of human obesity, the recent development of a number of models of diet-induced obesity have contributed to a better understanding of the impact of obesity and insulin resistance on myocardial function. High fat feeding induced insulin resistance in C57BL/6 mice also causes cardiac remodelling and systolic dysfunction [202]. The authors and other research groups have however also shown that rodent models of diet-induced obesity with insulin resistance have either normal [90, 203, 205, 209, 210] or compromised [110, 203, 204, 211, 212] cardiac mechanical function. It is currently not possible to conclusively attribute the cardiac dysfunction reported in these studies to myocardial insulin resistance since there are several studies that have reported normal cardiac function in animal models with insulin resistance [90, 203, 205, 209, 210].

Reduced cardiac efficiency possibly contributes to cardiac dysfunction in obesity, insulin resistance and diabetes [44, 45, 213]. Animals [44, 45, 162, 213] and humans [95] that are obese and insulin resistant or diabetic have increased myocardial oxygen consumption which reflects a decreased cardiac efficiency as determined by the myocardial work to myocardial oxygen consumption ratio [214]. Mitochondria isolated from obese insulin resistant mice have reduced oxidative capacity, and display fatty acid induced uncoupling of mitochondrial oxygen consumption and ATP production which is evident from the reduced ATP-to-O ratios [162, 213]. This data from human and rodent studies also implicate impaired mitochondrial energetics in the cardiac dysfunction associated with obesity and insulin resistance. Recent epidemiological evidence points to an important mediatory role for insulin resistance in the development of obesity related congestive heart failure [215].

8.4. Effect of dyslipidaemia and insulin resistance on myocardial tolerance to ischaemia/reperfusion

A key feature of myocardial ischaemia is the reduced oxygen and substrate availability that results in lower mitochondrial oxidative phosphorylation rates. Ischaemia essentially disrupts the tightly coupled ATP breakdown and re-synthesis equilibrium that exists during normoxia and leads to an ATP deficit. Cellular ATP becomes depleted with the extent of this depletion being dependent on the duration and severity of ischaemia [216].

Although oxidative metabolism is reduced during ischaemia, reperfusion after ischaemia is associated with an initial increase in glycolytic flux rate which quickly declines to normal levels [217]. Despite glycolysis only accounting for a small amount of the total ATP
production under aerobic conditions, glycolytically generated ATP becomes invaluable in the maintenance of cellular ion pump function and ion homeostasis and the reduction of myocardial damage during mild ischaemia [218]. While glycolytically produced ATP may aid in maintaining ion homeostasis during ischaemia, it is insufficient for the maintenance of myocardial contractile function [218]. Under conditions of severe ischaemia in the absence of glucose and oxygen, myocardial glycogen stores undergoing glycolysis do not only contribute to the ATP synthesised, but greatly increase cytosolic proton accumulation and a decline in intracellular pH [219]. Despite its potential adverse effect on pH, elevated glycogen levels at the onset of myocardial ischaemia may be important in maintaining tissue ATP levels since it has been associated with improved functional recovery after ischaemia [220].

Despite myocardial ischaemia decreasing mitochondrial substrate oxidation, fatty acid oxidation predominates during ischaemia and subsequent early reperfusion [221]. During early ischaemia there is a transient increase in anaerobic glycolysis while glucose oxidation decreases [199, 221-224]. Under these conditions normal or increased glucose uptake (under the influence of insulin) may be important for the delivery of glycolytic ATP to maintain ion homeostasis. Hearts from animal models of obesity and insulin resistance [211], isolated insulin resistance [225] and diabetes [226] have a reduced tolerance to ischaemia and reperfusion and suffer more severe ischaemia/reperfusion injury. Myocardial insulin resistance potentially decreases myocardial tolerance to ischaemia by decreasing glucose uptake, glycogen synthesis and glycolysis which all play a critical role in the delivery of ATP for cellular homeostasis in the ischaemic/reperfused heart.

Although fatty acids are predominantly oxidized by the ischaemic heart, the preference for fatty acid oxidation as occurs under dyslipidaemic conditions also has adverse effects on the ischaemic and reperfused heart. The mitochondrion generates 12% less ATP per oxygen molecule through the oxidation of fatty acids compared to glucose oxidation during normoxia [187]. Increased fatty acid oxidation consequently reduces cardiac efficiency during ischaemia and subsequent reperfusion. During reperfusion the glycolytic flux rate exceeds glucose oxidation rates which remains suppressed due to increased fatty acid oxidation during reperfusion [224, 227]. This fatty acid induced uncoupling of glucose oxidation from glycolysis results in an accumulation of hydrogen ions which can damage the heart and affect post ischaemic function [199, 228-230]. These detrimental effects of increased fatty acid β-oxidation during both ischaemia and reperfusion would be expected to be pronounced in dyslipidaemia (as occurs in obesity and high fructose feeding) and insulin resistance and exacerbate ischaemic injury.

Pharmacological inhibition of myocardial fatty acid oxidation prior to the onset of, or during reperfusion results in increased glucose oxidation and improved cardiac functional recovery following the ischaemic episode [224, 227]. Hearts from prediabetic obese Zucker rats have reduced GLUT4 expression, reduced glucose uptake and larger reductions in tissue ATP levels during low-flow ischaemia. These changes are associated with poorer post-ischaemic functional recoveries when compared to their lean control littermates [231]. Treating these rats with rosiglitazone (the insulin sensitizer) normalized myocardial total GLUT4 protein expression, myocardial ischaemic substrate metabolism and improved reperfusion functional recovery.
8.5. The effect of insulin resistance on myocardial pro-survival signalling and ischaemic tolerance

The ability of the heart to withstand injury during ischaemia and reperfusion is not only dependent on myocardial metabolism but also upon the expression and functionality of its intrinsic pro-survival signalling pathways. Investigations into cardioprotection with preconditioning and postconditioning has revealed common signalling elements that transduce protective stimuli and converge on mitochondrial targets [232-234]. These stimuli recruit paths comprising cell surface G-protein coupled receptors (GPCRs), signalling kinase networks (e.g. PI3K-Akt-eNOS, Erk1/2, PKC, p38-MAPK, Glycogen synthase kinase 3 beta (GSK3β)) that have been dubbed the Reperfusion Injury Salvage Kinases (RISKs), and mitochondrial components that may represent end-effectors. These end-effectors include KATP channels and the mitochondrial permeability transition pore - mPTP (Figure 7). Central to the RISK pathways is protein kinase B (PKB)/Akt which is not only key to myocardial insulin signalling [188] and physiological hypertrophy/remodelling [235] but is also considered a pro-survival/anti-apoptotic kinase in the context of myocardial ischaemia/reperfusion.

**Figure 7.** An illustration demonstrating the pivotal role of PKB/Akt in the RISK and insulin signalling pathways and the possible impact of dyslipidaemia and insulin resistance on these signalling pathways. Broken line represents the proposed mechanism linking insulin resistance with PKB/Akt inhibition/inactivation and Reperfusion Injury Salvage Kinase (RISK) pathway dysfunction.
Insulin regulates cardiac metabolism, growth and mitogen-activated protein kinase (MAPK) pathways through pivotal PKB/Akt. Dyslipidaemia induced insulin resistance which is characterized by PI3K/Akt dysregulation possibly also negatively influences the functionality of the RISK pathway in the heart during ischaemia/reperfusion.

Early experimental evidence has emerged to support a role for obesity with insulin resistance in RISK pathway dysfunction. Wagner and co-workers [236] have shown loss of preconditioning in a rat model of established metabolic syndrome. In the leptin-deficient (ob/ob) mouse cardiac benefit from postconditioning is impaired [237], while there is also evidence of failed preconditioning in obese insulin-resistant rats [238]. Failure of a variety of cardioprotective interventions involving multiple and varied triggers, implicates dysfunction of the signalling paths of the RISK pathway that are common to these interventions. This is also supported by the recent findings of Bouhidel and co-workers [237] who reported impaired phosphorylation of Akt, Erk1/2 and p70S6K1 in ob/ob mice while others [236] presented evidence of impaired Erk1/2 activation and failure to phosphorylate and inactivate GSK3β. Ineffective protection in obese insulin resistance rats is also associated with impaired activation of the mitochondrial KATP channel [238]. All early indications suggest that distinct changes in intrinsic cardioprotective signalling occur in myocardial insulin resistance.

9. Interventions and therapy for the treatment of insulin resistance

Compelling scientific evidence indicates that obesity and/or lipogenic diets that lead to dyslipidaemia promote insulin resistance. Besides the dyslipidaemia, abnormal RAS activity and perturbations in adipocytokine levels also contribute to tissue insulin insensitivity. The primary goal of therapy for the treatment of insulin resistance should therefore be to prevent or reduce obesity (adipose tissue expansion) and dyslipidaemia. In addition to normalising circulating lipid levels, weight loss would normalise adipose tissue content and its associated pro-inflammatory cytokine and adipocytokine levels and ultimately improve insulin resistance. Since there is a direct correlation between obesity and RAS over-activation, weight loss and/or RAS inhibition has the potential to attenuate the adverse effects of abnormal RAS activity on tissue insulin signalling.

9.1. Lifestyle changes: Physical activity and diet

Maintaining normal body weight or reducing body weight in overweight patients is the preferred approach for the prevention or treatment of the underlying causes of insulin resistance. Regular physical activity aimed at balancing caloric intake with caloric expenditure is recommended to maintain body weight. To reduce body weight caloric intake should be reduced and caloric expenditure increased until the desired body weight has been achieved. Current recommendations are to do 30 minutes moderate intensity exercise daily in order to maintain normal body weight and reduce the risk of developing medical conditions such as cancer, insulin resistance, diabetes and cardiovascular disease [239].

In addition to regular exercise to maintain normal body weight or promote weight loss, individuals with a genetic predisposition to obesity, insulin resistance and diabetes should
carefully manage their diet and reduce their intake of refined sugars, trans- and saturated fats and cholesterol and increase their consumption of grains, and fruit and vegetables [240]. Based on recent evidence provided by studies investigating the potential role of fructose in dyslipidaemia and metabolic diseases [24, 27, 41], it would also be prudent to avoid the overconsumption of fructose rich foods and beverages.

The larger the BMI loss achieved through exercise and/or dietary restriction, the larger the metabolic improvements that are achieved. Weight loss improves lipid profiles and blood glucose levels in metabolic syndrome patients [241] with a weight loss of more than 10% reversing metabolic disorders in two-thirds of metabolic syndrome patients studied [242]. These patients no longer met the criteria for metabolic syndrome. Lifestyle interventions also decreases the progression from insulin resistance to type-2 diabetes. In the US Diabetes Prevention Program, interventions aimed at reducing body weight by 7% succeeded in preventing progression from insulin resistance to type-2 diabetes by 58% [243]. In this study 38% of the patients with metabolic syndrome at entry into the study had a reversal of metabolic syndrome with body weight loss.

9.2. Drug therapy that improves insulin sensitivity

Although lifestyle changes should remain the therapy of choice for the reduction of body weight and normalisation of metabolic disorders, not all patients respond to lifestyle changes to the same extent. In many cases lifestyle changes fail to achieve the intended objective of adequate weight loss. Under these circumstances pharmacological interventions have to be considered. Several drugs have been developed to improve lipid profiles and insulin sensitivity/action but have been disappointing and have in some cases had adverse side effects.

9.2.1. Lipid lowering drugs

Dyslipidaemia which presents as elevated circulating triglycerides and LDL-cholesterol and low HDL-cholesterol can be treated with statins (3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors) that reduce levels of all forms of Apo B containing lipoproteins [244-247]. These drugs reduce the conversion of acetyl-CoA to mevalonate and the eventual synthesis of cholesterol in the liver by blocking HMG-CoA reductase. There are several studies that have demonstrated that statins (simvastatin and atorvastatin) improve plasma triglyceride and glycosylated haemoglobin in non insulin dependent diabetics [246]. Fluvastatin also improved lipid profiles and insulin resistance in nondiabetic dyslipidaemic patients. These researchers however concluded that the insulin sensitising effects of fluvastatin were not related to its triglyceride lowering effects [247].

Another class of lipid lowering drug that has achieved satisfactory results is the fibrates that activate peroxisome proliferator-activated receptor (PPARs) and facilitate lipid metabolism. In humans, fibrates lower circulating triglyceride and LDL-C levels [248, 249] and elevate HDL-C levels [249]. PPARα agonists possibly improve lipid profiles by increasing the synthesis of both apolipoprotein A-I [248] and A-II [250] which would assist in increasing HDL-cholesterol
while reducing apolipoprotein B which is a major lipoprotein constituent of LDL-cholesterol. PPARα agonists also increase hepatic mitochondrial β-oxidation which reduces hepatic free fatty acids that are an essential component of VLDL and LDL-cholesterol.

Since PPARα agonists have repeatedly been demonstrated to have both systemic and tissue specific insulin sensitizing effects [251-254] their potential for the treatment of insulin resistance and diabetes is encouraging. The insulin sensitising effects of the fibrates probably relate to their lipid lowering effects since a PPARα agonist significantly increases hepatic and skeletal muscle insulin receptor and IRS-1 tyrosine phosphorylation, while increasing IRS-associated PI3K activity in obese (ob/ob) mice [252]. These insulin sensitising effects were accompanied by reduced hepatic, skeletal muscle [252] and heart muscle [255] lipid accumulation.

Combination therapy using statins and fibrates has been an attractive possibility but the results have been disappointing. The fibrate gemfibrozil in combination with statins has been associated with increased risk of myopathy [256]. It has however been proposed that the adverse effects of gemfibrozil and statin combination therapy may be due to a pharmacological interaction between these two drugs and that other fenofibrates may be more suitable for combination therapy with statins [257].

9.2.2. Insulin sensitizers

The two most promising insulin sensitizers are metformin and the glitazones. Metformin decreases hepatic gluconeogenesis and triglyceride production which in turn enhances insulin sensitivity [258]. Metformin reduced the progression of insulin resistance (pre-diabetic) to type-2 diabetes in the Diabetes Prevention Program [243].

Thiazolidinediones (TZDs) are PPARγ agonists that regulate insulin sensitivity in the liver, muscle and adipose tissue by increasing fatty acid oxidation and decreasing fatty acid synthesis [258]. TZDs are also believed to have anti-inflammatory effects. Pioglitazone was used in the ACT-NOW study in which it improved HDL-cholesterol and triglyceride levels and reduced the incidence of type-2 diabetes by 78% in prediabetic patients followed up over 2 years [259]. The Pioglitazone In Prevention Of Diabetes (PIPOD) study demonstrated that pioglitazone reduced the incidence of diabetes in premenopausal women [260]. It similarly improves insulin sensitivity and reduces both blood FFA and triglycerides levels in obese non-diabetic patients [261]. The usefulness of pioglitazone for the management of insulin sensitivity is however limited since it promotes fluid retention which increases risk of heart failure in certain patient populations with cardiovascular disease. In the diabetes reduction assessment with ramipril and rosiglitazone medication (DREAM) trial, rosiglitazone showed potential in preventing diabetes but appeared to increase the risk of heart failure [262].

9.2.3. RAS inhibitors or AT receptor blockers

Obesity and high fat feeding increases both systemic and adipose tissue RAS activity [110, 112-115]. As discussed previously in this chapter, the most compelling evidence for a role
for the RAS in the aetiology of insulin resistance comes from studies using ACE inhibitors and AT receptor antagonists to control blood pressure. Both these therapies are associated with reduced risk of developing insulin resistance and type-2 diabetes in patients [119, 122, 263-266] and in rodent models of obesity and insulin resistance [127, 128]. Although these antihypertensives are not prescribed for the treatment of abnormal RAS activity, they potentially improve insulin sensitivity in a patient population that is at high risk of cardiovascular disease due to their hypertension.

9.2.4. Anti-inflammatory therapy

Several lines of evidence implicate chronic inflammation in the aetiology of insulin resistance. Obesity is associated with elevated circulating cytokines and C-reactive protein which can be normalised by weight loss [267]. Although no drugs are currently available to treat chronic systemic inflammation, the use of lipid lowering drugs have been associated with reduced C-reactive protein levels in patients [267-269]. These drugs are not prescribed to specifically reduce inflammation but may contribute to improved insulin sensitivity by improving dyslipidaemia and decreasing its stimulation of β-oxidation and ROS generation. Increase ROS generation potentially increase cytokine synthesis and release in certain organs (Figure 2).

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10. References

[1] Stefan, N., K. Kantartzis, and H.U. Haring, Causes and metabolic consequences of Fatty liver. Endocr Rev, 2008. 29(7): p. 939-60.
[2] Najjar, S.M., et al., Insulin acutely decreases hepatic fatty acid synthase activity. Cell Metab, 2005. 2(1): p. 43-53.
[3] Reaven, G.M., Banting lecture 1988. Role of insulin resistance in human disease. Diabetes, 1988. 37(12): p. 1595-607.
[4] Reaven, G.M., Pathophysiology of insulin resistance in human disease. Physiol Rev, 1995. 75(3): p. 473-86.
[5] Zhang, L., et al., Role of fatty acid uptake and fatty acid beta-oxidation in mediating insulin resistance in heart and skeletal muscle. Biochim Biophys Acta, 2010. 1801(1): p. 1-22.
[6] White, M.F. and C.R. Kahn, The insulin signaling system. J Biol Chem, 1994. 269(1): p. 1-4.
[7] Myers, M.G., Jr., et al., IRS-1 activates phosphatidylinositol 3'-kinase by associating with src homology 2 domains of p85. Proc Natl Acad Sci U S A, 1992. 89(21): p. 10350-4.
[8] Yonezawa, K., et al., Insulin-dependent formation of a complex containing an 85-kDa subunit of phosphatidylinositol 3-kinase and tyrosine-phosphorylated insulin receptor substrate 1. J Biol Chem, 1992. 267(36): p. 25958-65.

[9] Shepherd, P.R., D.J. Withers, and K. Siddle, Phosphoinositide 3-kinase: the key switch mechanism in insulin signalling. Biochem J, 1998. 333 (Pt 3): p. 471-90.

[10] Chang, L., S.H. Chiang, and A.R. Saltiel, Insulin signaling and the regulation of glucose transport. Mol Med, 2004. 10(7-12): p. 65-71.

[11] Alessi, D.R., et al., Mechanism of activation of protein kinase B by insulin and IGF-1. EMBO J, 1996. 15(23): p. 6541-51.

[12] Alessi, D.R. and P. Cohen, Mechanism of activation and function of protein kinase B. Curr Opin Genet Dev, 1998. 8(1): p. 55-62.

[13] Foran, P.G., et al., Protein kinase B stimulates the translocation of GLUT4 but not GLUT1 or transferrin receptors in 3T3-L1 adipocytes by a pathway involving SNAP-23, synaptobrevin-2, and/or cellubrevin. J Biol Chem, 1999. 274(40): p. 28087-95.

[14] Clarke, J.F., et al., Inhibition of the translocation of GLUT1 and GLUT4 in 3T3-L1 cells by the phosphatidylinositol 3-kinase inhibitor, wortmannin. Biochem J, 1994. 300 (Pt 3): p. 631-5.

[15] Summers, S.A., et al., Regulation of insulin-stimulated glucose transporter GLUT4 translocation and Akt kinase activity by ceramide. Mol Cell Biol, 1998. 18(9): p. 5457-64.

[16] Rider, M.H. and L. Hue, Activation of rat heart phosphofructokinase-2 by insulin in vivo. FEBS Lett, 1984. 176(2): p. 484-8.

[17] Hue, L. and M.H. Rider, Role of fructose 2,6-bisphosphate in the control of glycolysis in mammalian tissues. Biochem J, 1987. 245(2): p. 313-24.

[18] Hue, L., et al., Insulin and ischemia stimulate glycolysis by acting on the same targets through different and opposing signaling pathways. J Mol Cell Cardiol, 2002. 34(9): p. 1091-7.

[19] Luiken, J.J., et al., Insulin stimulates long-chain fatty acid utilization by rat cardiac myocytes through cellular redistribution of FAT/CD36. Diabetes, 2002. 51(10): p. 3113-9.

[20] Saddik, M., et al., Acetyl-CoA carboxylase regulation of fatty acid oxidation in the heart. J Biol Chem, 1993. 268(34): p. 25836-45.

[21] Kahn, S.E., R.L. Hull, and K.M. Utzschneider, Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature, 2006. 444(7121): p. 840-6.

[22] Rutledge, A.C. and K. Adeli, Fructose and the metabolic syndrome: pathophysiology and molecular mechanisms. Nutr Rev, 2007. 65(6 Pt 2): p. S13-23.

[23] Tappy, L. and K.A. Le, Metabolic effects of fructose and the worldwide increase in obesity. Physiol Rev, 2010. 90(1): p. 23-46.

[24] Tappy, L., et al., Fructose and metabolic diseases: new findings, new questions. Nutrition, 2010. 26(11-12): p. 1044-9.

[25] Boden, G., Obesity, insulin resistance and free fatty acids. Curr Opin Endocrinol Diabetes Obes, 2011. 18(2): p. 139-43.

[26] Kershaw, E.E. and J.S. Flier, Adipose tissue as an endocrine organ. J Clin Endocrinol Metab, 2004. 89(6): p. 2548-56.

[27] Dekker, M.J., et al., Fructose: a highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome. Am J Physiol Endocrinol Metab, 2010. 299(5): p. E685-94.
[28] Kannel, W.B., T. Gordon, and W.P. Castelli, *Obesity, lipids, and glucose intolerance. The Framingham Study*. Am J Clin Nutr, 1979. 32(6): p. 1238-45.

[29] Folli, F., et al., *Crosstalk between insulin and angiotensin II signalling systems*. Exp Clin Endocrinol Diabetes, 1999. 107(2): p. 133-9.

[30] Kalupahana, N.S. and N. Moustaid-Moussa, *The renin-angiotensin system: a link between obesity, inflammation and insulin resistance*. Obes Rev, 2012. 13(2): p. 136-49.

[31] Ryden, M. and P. Arner, *Tumour necrosis factor-alpha in human adipose tissue – from signalling mechanisms to clinical implications*. J Intern Med, 2007. 262(4): p. 431-8.

[32] Bizeau, M.E. and M.J. Pagliassotti, *Hepatic adaptations to sucrose and fructose*. Metabolism, 2005. 54(9): p. 1189-201.

[33] Stanhope, K.L. and P.J. Havel, *Fructose consumption: potential mechanisms for its effects to increase visceral adiposity and induce dyslipidemia and insulin resistance*. Curr Opin Lipidol, 2008. 19(1): p. 16-24.

[34] Faeh, D., et al., *Effect of fructose overfeeding and fish oil administration on hepatic de novo lipogenesis and insulin sensitivity in healthy men*. Diabetes, 2005. 54(7): p. 1907-13.

[35] Chong, M.F., B.A. Fielding, and K.N. Frayn, *Mechanisms for the acute effect of fructose on postprandial lipemia*. J Clin Nutr, 2007. 85(6): p. 1511-20.

[36] Matsuzaka, T., et al., *Insulin-independent induction of sterol regulatory element-binding protein-1c expression in the livers of streptozotocin-treated mice*. Diabetes, 2004. 53(3): p. 560-9.

[37] Nagai, Y., et al., *Amelioration of high fructose-induced metabolic derangements by activation of PPARalpha*. Am J Physiol Endocrinol Metab, 2002. 282(5): p. E1180-90.

[38] Adiels, M., et al., *Overproduction of large VLDL particles is driven by increased liver fat content in man*. Diabetologia, 2006. 49(4): p. 755-65.

[39] Stanhope, K.L., et al., *Twenty-four-hour endocrine and metabolic profiles following consumption of high-fructose corn syrup-, sucrose-, fructose-, and glucose-sweetened beverages with meals*. Am J Clin Nutr, 2008. 87(5): p. 1194-203.

[40] Taghibiglou, C., et al., *Mechanisms of hepatic very low density lipoprotein overproduction in insulin resistance. Evidence for enhanced lipoprotein assembly, reduced intracellular ApoB degradation, and increased microsomal triglyceride transfer protein in a fructose-fed hamster model*. J Biol Chem, 2000. 275(12): p. 8416-25.

[41] Le, K.A., et al., *Fructose overconsumption causes dyslipidemia and ectopic lipid deposition in healthy subjects with and without a family history of type 2 diabetes*. Am J Clin Nutr, 2009. 89(6): p. 1760-5.

[42] Wildman, R.P., *Healthy obesity*. Curr Opin Clin Nutr Metab Care, 2009. 12(4): p. 438-43.

[43] Fabbrini, E., Magkos, F.,Mohammed, B.S., Pietka, T., Abumrad, N.A., Patterson, B.W., Okunade, A., Klein, S., *Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity*. Proceedings of the National Academy of Sciences of the United States of America, 2009. 106 (36): p. 15430-15435.

[44] Mazumder, P.K., et al., *Impaired cardiac efficiency and increased fatty acid oxidation in insulin-resistant ob/ob mouse hearts*. Diabetes, 2004. 53(9): p. 2366-74.
[45] Buchanan, J., et al., Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. Endocrinology, 2005. 146(12): p. 5341-9.

[46] Luiken, J.J., et al., Increased rates of fatty acid uptake and plasmalemmal fatty acid transporters in obese Zucker rats. J Biol Chem, 2001. 276(44): p. 40567-73.

[47] Young, M.E., et al., Impaired long-chain fatty acid oxidation and contractile dysfunction in the obese Zucker rat heart. Diabetes, 2002. 51(8): p. 2587-95.

[48] Coort, S.I., et al., Increased FAT (fatty acid translocase)/CD36-mediated long-chain fatty acid uptake in cardiac myocytes from obese Zucker rats. Biochem Soc Trans, 2004. 32(Pt 1): p. 83-5.

[49] Thakker, G.D., et al., Effects of diet-induced obesity on inflammation and remodeling after myocardial infarction. Am J Physiol Heart Circ Physiol, 2006. 291(5): p. H2504-14.

[50] Unger, R.H., Lipotoxic diseases. Annu Rev Med, 2002. 53: p. 319-36.

[51] Chess, D.J. and W.C. Stanley. Role of diet and fuel overabundance in the development and progression of heart failure. Cardiovasc Res, 2008. 79(2): p. 269-78.

[52] Chiu, H.C., et al., A novel mouse model of lipotoxic cardiomyopathy. J Clin Invest, 2001. 107(7): p. 813-22.

[53] Carley, A.N., et al., Mechanisms responsible for enhanced fatty acid utilization by perfused hearts from type 2 diabetic db/db mice. Arch Physiol Biochem, 2007. 113(2): p. 65-75.

[54] Koonen, D.P., et al., Long-chain fatty acid uptake and FAT/CD36 translocation in heart and skeletal muscle. Biochim Biophys Acta, 2005. 1736(3): p. 163-80.

[55] Luiken, J.J., et al., Regulation of cardiac long-chain fatty acid and glucose uptake by translocation of substrate transporters. Pflugers Arch, 2004. 448(1): p. 1-15.

[56] Chabowski, A., et al., The subcellular compartmentation of fatty acid transporters is regulated differently by insulin and by AICAR. FEBS Lett, 2005. 579(11): p. 2428-32.

[57] van Herpen, N.A. and V.B. Schrauwen-Hinderling, Lipid accumulation in non-adipose tissue and lipotoxicity. Physiol Behav, 2008. 94(2): p. 231-41.

[58] Turinsky, J., D.M. O’Sullivan, and B.P. Bayly, 1,2-Diacylglycerol and ceramide levels in insulin-resistant tissues of the rat in vivo. J Biol Chem, 1990. 265(28): p. 16880-5.

[59] Ussher, J.R., et al., Inhibition of de novo ceramide synthesis reverses diet-induced insulin resistance and enhances whole-body oxygen consumption. Diabetes, 2010. 59(10): p. 2453-64.

[60] Yu, C., et al., Mechanism by which fatty acids inhibit insulin activation of insulin receptor substrate-1 (IRS-1)-associated phosphatidylinositol 3-kinase activity in muscle. J Biol Chem, 2002. 277(52): p. 50230-6.

[61] Jean-Baptiste, G., et al., Lysophosphatidic acid mediates pleiotropic responses in skeletal muscle cells. Biochem Biophys Res Commun, 2005. 335(4): p. 1155-62.

[62] Wang, X., et al., Insulin resistance accelerates muscle protein degradation: Activation of the ubiquitin-proteasome pathway by defects in muscle cell signaling. Endocrinology, 2006. 147(9): p. 4160-8.

[63] Schenk, S., M. Saberi, and J.M. Olefsky, Insulin sensitivity: modulation by nutrients and inflammation. J Clin Invest, 2008. 118(9): p. 2992-3002.

[64] Hannun, Y.A. and L.M. Obeid, The Ceramide-centric universe of lipid-mediated cell regulation: stress encounters of the lipid kind. J Biol Chem, 2002. 277(29): p. 25847-50.
Merrill, A.H., Jr. and D.D. Jones, An update of the enzymology and regulation of sphingomyelin metabolism. Biochim Biophys Acta, 1990. 1044(1): p. 1-12.

Kim, J.K., et al., PKC-theta knockout mice are protected from fat-induced insulin resistance. J Clin Invest, 2004. 114(6): p. 823-7.

Hajduch, E., et al., Ceramide impairs the insulin-dependent membrane recruitment of protein kinase B leading to a loss in downstream signalling in L6 skeletal muscle cells. Diabetologia, 2001. 44(2): p. 173-83.

Adams, J.M., 2nd, et al., Ceramide content is increased in skeletal muscle from obese insulin-resistant humans. Diabetes, 2004. 53(1): p. 25-31.

Summers, S.A., Ceramides in insulin resistance and lipotoxicity. Prog Lipid Res, 2006. 45(1): p. 42-72.

Holland, W.L., et al., Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. Cell Metab, 2007. 5(3): p. 167-79.

Zhou, Y.T., et al., Lipotoxic heart disease in obese rats: implications for human obesity. Proc Natl Acad Sci U S A, 2000. 97(4): p. 1784-9.

Hickson-Bick, D.L., L.M. Buja, and J.B. McMillin, Palmitate-mediated alterations in the fatty acid metabolism of rat neonatal cardiac myocytes. J Mol Cell Cardiol, 2000. 32(3): p. 511-9.

Katsuyama, K., et al., Role of nuclear factor-kappaB activation in cytokine- and sphingomyelinase-stimulated inducible nitric oxide synthase gene expression in vascular smooth muscle cells. Endocrinology, 1998. 139(11): p. 4506-12.

Shimabukuro, M., et al., Direct antidiabetic effect of leptin through triglyceride depletion of tissues. Proc Natl Acad Sci U S A, 1997. 94(9): p. 4637-41.

Ghafourifar, P., et al., Mitochondrial nitric-oxide synthase stimulation causes cytochrome c release from isolated mitochondria. Evidence for intramitochondrial peroxynitrite formation. J Biol Chem, 1999. 274(44): p. 31185-8.

Garcia-Ruiz, C., et al., Direct effect of ceramide on the mitochondrial electron transport chain leads to generation of reactive oxygen species. Role of mitochondrial glutathione. J Biol Chem, 1997. 272(17): p. 11369-77.

Heydrick, S.J., et al., Enhanced stimulation of diacylglycerol and lipid synthesis by insulin in denervated muscle. Altered protein kinase C activity and possible link to insulin resistance. Diabetes, 1991. 40(12): p. 1707-11.

Avignon, A., et al., Chronic activation of protein kinase C in soleus muscles and other tissues of insulin-resistant type II diabetic Goto-Kakizaki (GK), obese/aged, and obese/Zucker rats. A mechanism for inhibiting glycogen synthesis. Diabetes, 1996. 45(10): p. 1396-404.

Itani, S.I., et al., Lipid-induced insulin resistance in human muscle is associated with changes in diacylglycerol, protein kinase C, and IkappaB-alpha. Diabetes, 2002. 51(7): p. 2005-11.

Itani, S.I., et al., Involvement of protein kinase C in human skeletal muscle insulin resistance and obesity. Diabetes, 2000. 49(8): p. 1353-8.

Itani, S.I., et al., Increased protein kinase C theta in skeletal muscle of diabetic patients. Metabolism, 2001. 50(5): p. 553-7.

Sebastian, D., et al., CPT I overexpression protects L6E9 muscle cells from fatty acid-induced insulin resistance. Am J Physiol Endocrinol Metab, 2007. 292(3): p. E677-86.
[83] Virkamaki, A., et al., Intramyocellular lipid is associated with resistance to in vivo insulin actions on glucose uptake, antilipolysis, and early insulin signaling pathways in human skeletal muscle. Diabetes, 2001. 50(10): p. 2337-43.

[84] Manco, M., et al., Insulin resistance directly correlates with increased saturated fatty acids in skeletal muscle triglycerides. Metabolism, 2000. 49(2): p. 220-4.

[85] Sinha, R., et al., Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. Diabetes, 2002. 51(4): p. 1022-7.

[86] Boden, G., et al., Effects of acute changes of plasma free fatty acids on intramyocellular fat content and insulin resistance in healthy subjects. Diabetes, 2001. 50(7): p. 1612-7.

[87] Kelley, D.E., et al., Interaction between glucose and free fatty acid metabolism in human skeletal muscle. J Clin Invest, 1993. 92(1): p. 91-8.

[88] Griffin, M.E., et al., Free fatty acid-induced insulin resistance is associated with activation of protein kinase C theta and alterations in the insulin signaling cascade. Diabetes, 1999. 48(6): p. 1270-4.

[89] Atkinson, L.L., et al., Potential mechanisms and consequences of cardiac triacylglycerol accumulation in insulin-resistant rats. Am J Physiol Endocrinol Metab, 2003. 284(5): p. E923-30.

[90] Yan, J., et al., Increased glucose uptake and oxidation in mouse hearts prevent high fatty acid oxidation but cause cardiac dysfunction in diet-induced obesity. Circulation, 2009. 119(21): p. 2818-28.

[91] Kankaanpaa, M., et al., Myocardial triglyceride content and epicardial fat mass in human obesity: relationship to left ventricular function and serum free fatty acid levels. J Clin Endocrinol Metab, 2006. 91(11): p. 4689-95.

[92] Szczepaniak, L.S., et al., Myocardial triglycerides and systolic function in humans: in vivo evaluation by localized proton spectroscopy and cardiac imaging. Magn Reson Med, 2003. 49(3): p. 417-23.

[93] McGavock, J.M., et al., Cardiac steatosis in diabetes mellitus: a 1H-magnetic resonance spectroscopy study. Circulation, 2007. 116(10): p. 1170-5.

[94] Rijzewijk, L.J., et al., Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. J Am Coll Cardiol, 2008. 52(22): p. 1793-9.

[95] Peterson, L.R., et al., Effect of obesity and insulin resistance on myocardial substrate metabolism and efficiency in young women. Circulation, 2004. 109(18): p. 2191-6.

[96] Lazar, M.A., The humoral side of insulin resistance. Nat Med, 2006. 12(1): p. 43-4.

[97] Weisberg, S.P., et al., Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest, 2003. 112(12): p. 1796-808.

[98] Li, Z. and A.M. Diehl, Innate immunity in the liver. Curr Opin Gastroenterol, 2003. 19(6): p. 565-71.

[99] Kewalramani, G., P.J. Bilan, and A. Klip, Muscle insulin resistance: assault by lipids, cytokines and local macrophages. Curr Opin Clin Nutr Metab Care, 2010. 13(4): p. 382-90.

[100] Boden, G., et al., Free fatty acids produce insulin resistance and activate the proinflammatory nuclear factor-kappaB pathway in rat liver. Diabetes, 2005. 54(12): p. 3458-65.
[101] Boden, G., Fatty acid-induced inflammation and insulin resistance in skeletal muscle and liver. Curr Diab Rep, 2006. 6(3): p. 177-81.

[102] Gao, Z., et al., Inactivation of PKCtheta leads to increased susceptibility to obesity and dietary insulin resistance in mice. Am J Physiol Endocrinol Metab, 2007. 292(1): p. E84-91.

[103] Shi, H., et al., TLR4 links innate immunity and fatty acid-induced insulin resistance. J Clin Invest, 2006. 116(11): p. 3015-25.

[104] Kosteli, A., et al., Weight loss and lipolysis promote a dynamic immune response in murine adipose tissue. J Clin Invest, 2010. 120(10): p. 3466-79.

[105] Hotamisligil, G.S., N.S. Shargill, and B.M. Spiegelman, Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science, 1993. 259(5091): p. 87-91.

[106] Lebrun, P. and E. Van Obberghen, SOCS proteins causing trouble in insulin action. Acta Physiol (Oxf), 2008. 192(1): p. 29-36.

[107] Hirosumi, J., et al., A central role for JNK in obesity and insulin resistance. Nature, 2002. 420(6913): p. 333-6.

[108] Kim, H.J., et al., Differential effects of interleukin-6 and -10 on skeletal muscle and liver insulin action in vivo. Diabetes, 2004. 53(4): p. 1060-7.

[109] Ko, H.J., et al., Nutrient stress activates inflammation and reduces glucose metabolism by suppressing AMP-activated protein kinase in the heart. Diabetes, 2009. 58(11): p. 2536-46.

[110] du Toit, E.F., M. Nabben, and A. Lochner, A potential role for angiotensin II in obesity induced cardiac hypertrophy and ischaemic/reperfusion injury. Basic Res Cardiol, 2005. 100(4): p. 346-54.

[111] Dobrian, A.D., et al., Development of hypertension in a rat model of diet-induced obesity. Hypertension, 2000. 35(4): p. 1009-15.

[112] Engeli, S., et al., Weight loss and the renin-angiotensin-aldosterone system. Hypertension, 2005. 45(3): p. 356-62.

[113] Uckaya, G., et al., Plasma leptin levels strongly correlate with plasma renin activity in patients with essential hypertension. Horm Metab Res, 1999. 31(7): p. 435-8.

[114] Goossens, G.H., et al., Endocrine role of the renin-angiotensin system in human adipose tissue and muscle: effect of beta-adrenergic stimulation. Hypertension, 2007. 49(3): p. 542-7.

[115] Boustany, C.M., et al., Activation of the systemic and adipose renin-angiotensin system in rats with diet-induced obesity and hypertension. Am J Physiol Regul Integr Comp Physiol, 2004. 287(4): p. R943-9.

[116] Steckelings, U.M., et al., The evolving story of the RAAS in hypertension, diabetes and CV disease: moving from macrovascular to microvascular targets. Fundam Clin Pharmacol, 2009. 23(6): p. 693-703.

[117] Thatcher, S., et al., The adipose renin-angiotensin system: role in cardiovascular disease. Mol Cell Endocrinol, 2009. 302(2): p. 111-7.

[118] Yvan-Charvet, L. and A. Quignard-Boulange, Role of adipose tissue renin-angiotensin system in metabolic and inflammatory diseases associated with obesity. Kidney Int, 2011. 79(2): p. 162-8.

[119] Yusuf, S., et al., Ramipril and the development of diabetes. JAMA, 2001. 286(15): p. 1882-5.
[120] Vermes, E., et al., *Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies Of Left Ventricular Dysfunction (SOLVD).* Circulation, 2003. 107(9): p. 1291-6.

[121] Bosch, J., et al., *Effect of ramipril on the incidence of diabetes.* N Engl J Med, 2006. 355(15): p. 1551-62.

[122] Hansson, L., et al., *Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial.* Lancet, 1999. 353(9153): p. 611-6.

[123] Han, T., et al., *Relationship between angiotensin-converting enzyme gene insertion or deletion polymorphism and insulin sensitivity in healthy newborns.* Pediatrics, 2007. 119(6): p. 1089-94.

[124] Cong, N.D., et al., *The I/D polymorphism of angiotensin-converting enzyme gene but not the angiotensinogen gene is associated with insulin response to oral glucose in Japanese.* Proc Soc Exp Biol Med, 1999. 220(1): p. 46-51.

[125] Bonnet, F., et al., *Influence of the ACE gene insertion/deletion polymorphism on insulin sensitivity and impaired glucose tolerance in healthy subjects.* Diabetes Care, 2008. 31(4): p. 789-94.

[126] Pollex, R.L., et al., *Metabolic syndrome in aboriginal Canadians: prevalence and genetic associations.* Atherosclerosis, 2006. 184(1): p. 121-9.

[127] Henriksen, E.J., et al., *Selective angiotensin II receptor receptor antagonism reduces insulin resistance in obese Zucker rats.* Hypertension, 2001. 38(4): p. 884-90.

[128] Iwai, M., et al., *Direct renin inhibition improved insulin resistance and adipose tissue dysfunction in type 2 diabetic KK-A(y) mice.* J Hypertens, 2010. 28(7): p. 1471-81.

[129] Takahashi, N., et al., *Increased energy expenditure, dietary fat wasting, and resistance to diet-induced obesity in mice lacking renin.* Cell Metab, 2007. 6(6): p. 506-12.

[130] Jayasooriya, A.P., et al., *Mice lacking angiotensin-converting enzyme have increased energy expenditure, with reduced fat mass and improved glucose clearance.* Proc Natl Acad Sci U S A, 2008. 105(18): p. 6531-6.

[131] Kouyama, R., et al., *Attenuation of diet-induced weight gain and adiposity through increased energy expenditure in mice lacking angiotensin II type 1a receptor.* Endocrinology, 2005. 146(8): p. 3481-9.

[132] Yvan-Charvet, L., et al., *Deletion of the angiotensin type 2 receptor (AT2R) reduces adipose cell size and protects from diet-induced obesity and insulin resistance.* Diabetes, 2005. 54(4): p. 991-9.

[133] Ogihara, T., et al., *Angiotensin II-induced insulin resistance is associated with enhanced insulin signaling.* Hypertension, 2002. 40(6): p. 872-9.

[134] Ran, J., T. Hirano, and M. Adachi, *Chronic ANG II infusion increases plasma triglyceride level by stimulating hepatic triglyceride production in rats.* Am J Physiol Endocrinol Metab, 2004. 287(5): p. E955-61.

[135] Sloniger, J.A., et al., *Selective angiotensin II receptor antagonism enhances whole-body insulin sensitivity and muscle glucose transport in hypertensive TG(mREN2)27 rats.* Metabolism, 2005. 54(12): p. 1659-68.
Lastra, G., et al., Direct renin inhibition improves systemic insulin resistance and skeletal muscle glucose transport in a transgenic rodent model of tissue renin overexpression. Endocrinology, 2009. 150(6): p. 2561-8.

Richey, J.M., et al., Angiotensin II induces insulin resistance independent of changes in interstitial insulin. Am J Physiol, 1999. 277(5 Pt 1): p. E920-6.

Wei, Y., et al., Angiotensin II-induced NADPH oxidase activation impairs insulin signaling in skeletal muscle cells. J Biol Chem, 2006. 281(46): p. 35137-46.

Wei, Y., et al., Angiotensin II-induced skeletal muscle insulin resistance mediated by NF-kappaB activation via NADPH oxidase. Am J Physiol Endocrinol Metab, 2008. 294(2): p. E345-51.

Calegari, V.C., et al., Suppressor of cytokine signaling-3 Provides a novel interface in the cross-talk between angiotensin II and insulin signaling systems. Endocrinology, 2005. 146(2): p. 579-88.

Mitsuishi, M., et al., Angiotensin II reduces mitochondrial content in skeletal muscle and affects glycemic control. Diabetes, 2009. 58(3): p. 710-7.

Kalupahana, N.S., et al., Overproduction of angiotensinogen from adipose tissue induces adipose inflammation, glucose intolerance, and insulin resistance. Obesity (Silver Spring), 2012. 20(1): p. 48-56.

Atkinson, L.L., M.A. Fischer, and G.D. Lopaschuk, Leptin activates cardiac fatty acid oxidation independent of changes in the AMP-activated protein kinase-acetyl-CoA carboxylase-malonyl-CoA axis. J Biol Chem, 2002. 277(33): p. 29424-30.

Ding, G., et al., Adiponectin and its receptors are expressed in adult ventricular cardiomyocytes and upregulated by activation of peroxisome proliferator-activated receptor gamma. J Mol Cell Cardiol, 2007. 43(1): p. 73-84.

Palanivel, R., et al., Globular and full-length forms of adiponectin mediate specific changes in glucose and fatty acid uptake and metabolism in cardiomyocytes. Cardiovasc Res, 2007. 75(1): p. 148-57.

Buettner, C., et al., Leptin controls adipose tissue lipogenesis via central, STAT3-independent mechanisms. Nat Med, 2008. 14(6): p. 667-75.

Ren, J., Leptin and hyperleptinemia - from friend to foe for cardiovascular function. J Endocrinol, 2004. 181(1): p. 1-10.

Chua, S.C., Jr., et al., Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science, 1996. 271(5251): p. 994-6.

Takaya, K., et al., Molecular cloning of rat leptin receptor isoform complementary DNAs--identification of a missense mutation in Zucker fatty (fa/fa) rats. Biochem Biophys Res Commun, 1996. 225(1): p. 75-83.

Zhang, Y., et al., Positional cloning of the mouse obese gene and its human homologue. Nature, 1994. 372(6505): p. 425-32.

Montague, C.T., et al., Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature, 1997. 387(6636): p. 903-8.

Farooqi, I.S., et al., Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med, 1999. 341(12): p. 879-84.
[153] Oral, E.A., et al., Leptin-replacement therapy for lipodystrophy. N Engl J Med, 2002. 346(8): p. 570-8.
[154] Lago, F., et al., Adipokines as novel modulators of lipid metabolism. Trends Biochem Sci, 2009. 34(10): p. 500-10.
[155] Unger, R.H., Hyperleptinemia: protecting the heart from lipid overload. Hypertension, 2005. 45(6): p. 1031-4.
[156] Lee, Y., et al., Liporegulation in diet-induced obesity. The antisteatotic role of hyperleptinemia. J Biol Chem, 2001. 276(8): p. 5629-35.
[157] Lee, Y., et al., Hyperleptinemia prevents lipotoxic cardiomyopathy in acyl CoA synthase transgenic mice. Proc Natl Acad Sci U S A, 2004. 101(37): p. 13624-9.
[158] Christoffersen, C., et al., Cardiac lipid accumulation associated with diastolic dysfunction in obese mice. Endocrinology, 2003. 144(8): p. 3483-90.
[159] Barouch, L.A., et al., Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. Circ Res, 2006. 98(1): p. 119-24.
[160] Dong, F., et al., Impaired cardiac contractile function in ventricular myocytes from leptin-deficient ob/ob obese mice. J Endocrinol, 2006. 188(1): p. 25-36.
[161] Li, S.Y., et al., Cardiac contractile dysfunction in Lep/Lep obesity is accompanied by NADPH oxidase activation, oxidative modification of sarco(endo)plasmic reticulum Ca2+-ATPase and myosin heavy chain isozyme switch. Diabetologia, 2006. 49(6): p. 1434-46.
[162] Boudina, S. and E.D. Abel, Diabetic cardiomyopathy revisited. Circulation, 2007. 115(25): p. 3213-23.
[163] Arita, Y., et al., Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun, 1999. 257(1): p. 79-83.
[164] Weyer, C., et al., Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab, 2001. 86(5): p. 1930-5.
[165] Matsubara, M., S. Maruoka, and S. Katayose, Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. Eur J Endocrinol, 2002. 147(2): p. 173-80.
[166] Kadowaki, T. and T. Yamauchi, Adiponectin and adiponectin receptors. Endocr Rev, 2005. 26(3): p. 439-51.
[167] Kubota, N., et al., Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem, 2002. 277(29): p. 25863-6.
[168] Matsuda, M., et al., Role of adiponectin in preventing vascular stenosis. The missing link of adipo-vascular axis. J Biol Chem, 2002. 277(40): p. 37487-91.
[169] Xu, A., et al., Adiponectin ameliorates dyslipidemia induced by the human immunodeficiency virus protease inhibitor ritonavir in mice. Endocrinology, 2004. 145(2): p. 487-94.
[170] Yamauchi, T., et al., Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. J Biol Chem, 2003. 278(4): p. 2461-8.
[171] Yamauchi, T., et al., The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat Med, 2001. 7(8): p. 941-6.
[172] Yamauchi, T., et al., Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat Med, 2002. 8(11): p. 1288-95.
[173] Tomas, E., et al., Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. Proc Natl Acad Sci U S A, 2002. 99(25): p. 16309-13.

[174] Fujioka, D., et al., Role of adiponectin receptors in endothelin-induced cellular hypertrophy in cultured cardiomyocytes and their expression in infarcted heart. Am J Physiol Heart Circ Physiol, 2006. 290(6): p. H2409-16.

[175] Shibata, R., et al., Adiponectin-mediated modulation of hypertrophic signals in the heart. Nat Med, 2004. 10(12): p. 1384-9.

[176] Shibata, R., et al., Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. Nat Med, 2005. 11(10): p. 1096-103.

[177] Karmazyn, M., et al., Signalling mechanisms underlying the metabolic and other effects of adipokines on the heart. Cardiovasc Res, 2008. 79(2): p. 279-86.

[178] Adeghate, E., An update on the biology and physiology of resistin. Cell Mol Life Sci, 2004. 61(19-20): p. 2485-96.

[179] Kusminski, C.M., P.G. McTernan, and S. Kumar, Role of resistin in obesity, insulin resistance and Type II diabetes. Clin Sci (Lond), 2005. 109(3): p. 243-56.

[180] Rajala, M.W., et al., Regulation of resistin expression and circulating levels in obesity, diabetes, and fasting. Diabetes, 2004. 53(7): p. 1671-9.

[181] Sato, N., et al., Adenovirus-mediated high expression of resistin causes dyslipidemia in mice. Endocrinology, 2005. 146(1): p. 273-9.

[182] Graveleau, C., et al., Mouse and human resistins impair glucose transport in primary mouse cardiomyocytes, and oligomerization is required for this biological action. J Biol Chem, 2005. 280(36): p. 31679-85.

[183] Silha, J.V., et al., Plasma resistin, adiponectin and leptin levels in lean and obese subjects: correlations with insulin resistance. Eur J Endocrinol, 2003. 149(4): p. 331-5.

[184] Youn, B.S., et al., Plasma resistin concentrations measured by enzyme-linked immunosorbent assay using a newly developed monoclonal antibody are elevated in individuals with type 2 diabetes mellitus. J Clin Endocrinol Metab, 2004. 89(1): p. 150-6.

[185] Rea, R. and R. Donnelly, Resistin: an adipocyte-derived hormone. Has it a role in diabetes and obesity? Diabetes Obes Metab, 2004. 6(3): p. 163-70.

[186] Zierler, K.L., Fatty acids as substrates for heart and skeletal muscle. Circ Res, 1976. 38(6): p. 459-63.

[187] Opie, L.H., The Heart; Physiology, from Cell to Circulation. 3rd Edition, 1998, Raven Press: Philadelphia, NY. p. Chapter 11, pp295-342.

[188] Bertrand, L., et al., Insulin signalling in the heart. Cardiovasc Res, 2008. 79(2): p. 238-48.

[189] van der Vusse, G.J., M. van Bilsen, and J.F. Glatz, Cardiac fatty acid uptake and transport in health and disease. Cardiovasc Res, 2000. 45(2): p. 279-93.

[190] Scott, J.C., L.J. Finkelstein, and J.J. Spitzer, Myocardial removal of free fatty acids under normal pathological conditions. Am J Physiol, 1962. 203: p. 482-6.

[191] Coort, S.L., et al., Cardiac substrate uptake and metabolism in obesity and type-2 diabetes: role of sarcolemmal substrate transporters. Mol Cell Biochem, 2007. 299(1-2): p. 5-18.

[192] Luiken, J.J., et al., Uptake and metabolism of palmitate by isolated cardiac myocytes from adult rats: involvement of sarcolemmal proteins. J Lipid Res, 1997. 38(4): p. 745-58.
[193] Fournier, N., M. Geoffroy, and J. Deshusses, Purification and characterization of a long chain, fatty-acid-binding protein supplying the mitochondrial beta-oxidative system in the heart. Biochim Biophys Acta, 1978. 533(2): p. 457-64.

[194] Vork, M.M., J.F. Glatz, and G.J. Van Der Vusse, On the mechanism of long chain fatty acid transport in cardiomyocytes as facilitated by cytoplasmic fatty acid-binding protein. J Theor Biol, 1993. 160(2): p. 207-22.

[195] Schaap, F.G., et al., Impaired long-chain fatty acid utilization by cardiac myocytes isolated from mice lacking the heart-type fatty acid binding protein gene. Circ Res, 1999. 85(4): p. 329-37.

[196] Kraegen, E.W., et al., Glucose transporters and in vivo glucose uptake in skeletal and cardiac muscle: fasting, insulin stimulation and immunosolation studies of GLUT1 and GLUT4. Biochem J, 1993. 295 (Pt 1): p. 287-93.

[197] Zaninetti, D., R. Greco-Perotto, and B. Jeanrenaud, Heart glucose transport and transporters in rat heart: regulation by insulin, workload and glucose. Diabetologia, 1988. 31(2): p. 108-13.

[198] Halestrap, A.P. and N.T. Price, The proton-linked monocarboxylate transporter (MCT) family: structure, function and regulation. Biochem J, 1999. 343 Pt 2: p. 281-99.

[199] Stanley, W.C., et al., Regulation of myocardial carbohydrate metabolism under normal and ischaemic conditions. Potential for pharmacological interventions. Cardiovasc Res, 1997. 33(2): p. 243-57.

[200] Hue, L. and H. Taegtmeyer, The Randle cycle revisited: a new head for an old hat. Am J Physiol Endocrinol Metab, 2009. 297(3): p. E578-91.

[201] Depre, C., J.L. Vanoverschelde, and H. Taegtmeyer, Glucose for the heart. Circulation, 1999. 99(4): p. 578-88.

[202] Park, S.Y., et al., Cardiac-specific overexpression of peroxisome proliferator-activated receptor-alpha causes insulin resistance in heart and liver. Diabetes, 2005. 54(9): p. 2514-24.

[203] Wilson, C.R., et al., Western diet, but not high fat diet, causes derangements of fatty acid metabolism and contractile dysfunction in the heart of Wistar rats. Biochem J, 2007. 406(3): p. 457-67.

[204] Aasum, E., et al., Fenofibrate modulates cardiac and hepatic metabolism and increases ischemic tolerance in diet-induced obese mice. J Mol Cell Cardiol, 2008. 44(1): p. 201-9.

[205] Wright, J.J., et al., Mechanisms for increased myocardial fatty acid utilization following short-term high-fat feeding. Cardiovasc Res, 2009. 82(2): p. 351-60.

[206] Lopaschuk, G.D. and J.C. Russell, Myocardial function and energy substrate metabolism in the insulin-resistant JCR:LA corpulent rat. J Appl Physiol, 1991. 71(4): p. 1302-8.

[207] Peterson, L.R., et al., Impact of gender on the myocardial metabolic response to obesity. JACC Cardiovasc Imaging, 2008. 1(4): p. 424-33.

[208] Finck, B.N., et al., The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. J Clin Invest, 2002. 109(1): p. 121-30.

[209] Carroll, J.F., W.J. Zenebe, and T.B. Strange, Cardiovascular function in a rat model of diet-induced obesity. Hypertension, 2006. 48(1): p. 65-72.

[210] Maarman, G., et al., Effect of Chronic CPT-1 Inhibition on Myocardial Ischemia-Reperfusion Injury (I/R) in a Model of Diet-Induced Obesity. Cardiovasc Drugs Ther, 2012.
[211] du Toit, E.F., et al., Myocardial susceptibility to ischemic-reperfusion injury in a prediabetic model of dietary-induced obesity. Am J Physiol Heart Circ Physiol, 2008. 294(5): p. H2336-43.

[212] Ouwen, D.M., et al., Cardiac contractile dysfunction in insulin-resistant rats fed a high-fat diet is associated with elevated CD36-mediated fatty acid uptake and esterification. Diabetologia, 2007. 50(9): p. 1938-48.

[213] Boudina, S., et al., Reduced mitochondrial oxidative capacity and increased mitochondrial uncoupling impair myocardial energetics in obesity. Circulation, 2005. 112(17): p. 2686-95.

[214] How, O.J., et al., Increased myocardial oxygen consumption reduces cardiac efficiency in diabetic mice. Diabetes, 2006. 55(2): p. 466-73.

[215] Ingelsson, E., et al., Insulin resistance and risk of congestive heart failure. JAMA, 2005. 294(3): p. 334-41.

[216] Puri, P.S., et al., Alterations in energy metabolism and ultrastructure upon reperfusion of the ischemic myocardium after coronary occlusion. Am J Cardiol, 1975. 36(2): p. 234-43.

[217] Opie, L.H., Effects of regional ischemia on metabolism of glucose and fatty acids. Relative rates of aerobic and anaerobic energy production during myocardial infarction and comparison with effects of anoxia. Circ Res, 1976. 38(Suppl 1): p. 152-74.

[218] Opie, L.H., The Heart; Physiology, from Cell to Circulation. 4th Edition, 2004, Lippincott Williams & Wilkins: Philadelphia, PA. p. Chapter 11, pp330-333; Chapter 17, p533.

[219] Garlick, P.B., G.K. Radda, and P.J. Seeley, Studies of acidosis in the ischaemic heart by phosphorus nuclear magnetic resonance. Biochem J, 1979. 184(3): p. 547-54.

[220] Van Rooyen, J., J. McCarthy, and L.H. Opie, Increased glycolysis during ischaemia mediates the protective effect of glucose and insulin in the isolated rat heart despite the presence of cardiodepressant exogenous substrates. Cardiovasc J S Afr, 2002. 13(3): p. 103-9.

[221] Stanley, W.C., Changes in cardiac metabolism: a critical step from stable angina to ischaemic cardiomyopathy. Eur Heart J, 2001. 3((Supplement O)): p. O2-O7.

[222] Liedtke, A.J., Alterations of carbohydrate and lipid metabolism in the acutely ischemic heart. Prog Cardiovasc Dis, 1981. 23(5): p. 321-36.

[223] Liedtke, A.J., et al., Changes in substrate metabolism and effects of excess fatty acids in reperfused myocardium. Circ Res, 1988. 62(3): p. 535-42.

[224] Lopaschuk, G.D., et al., Glucose and palmitate oxidation in isolated working rat hearts reperfused after a period of transient global ischemia. Circ Res, 1990. 66(2): p. 546-53.

[225] Morel, S., et al., Insulin resistance modifies plasma fatty acid distribution and decreases cardiac tolerance to in vivo ischaemia/reperfusion in rats. Clin Exp Pharmacol Physiol, 2003. 30(7): p. 446-51.

[226] Aasum, E., et al., Age-dependent changes in metabolism, contractile function, and ischemic sensitivity in hearts from db/db mice. Diabetes, 2003. 52(2): p. 434-41.

[227] Lopaschuk, G.D., R.B. Wambolt, and R.L. Barr, An imbalance between glycolysis and glucose oxidation is a possible explanation for the detrimental effects of high levels of fatty acids during aerobic reperfusion of ischemic hearts. J Pharmacol Exp Ther, 1993. 264(1): p. 135-44.

[228] Liu, Q., et al., High levels of fatty acids delay the recovery of intracellular pH and cardiac efficiency in post-ischemic hearts by inhibiting glucose oxidation. J Am Coll Cardiol, 2002. 39(4): p. 718-25.
[229] Liu, B., et al., Cardiac efficiency is improved after ischemia by altering both the source and fate of protons. Circ Res, 1996. 79(5): p. 940-8.

[230] Orchard, C.H. and J.C. Kentish, Effects of changes of pH on the contractile function of cardiac muscle. Am J Physiol, 1990. 258(6 Pt 1): p. C967-81.

[231] Sidell, R.J., et al., Thiazolidinedione treatment normalizes insulin resistance and ischemic injury in the zucker Fatty rat heart. Diabetes, 2002. 51(4): p. 1110-7.

[232] Downey, J.M., A.M. Davis, and M.V. Cohen, Signaling pathways in ischemic preconditioning. Heart Fail Rev, 2007. 12(3-4): p. 181-8.

[233] Halestrap, A.P., S.J. Clarke, and I. Khaliulin, The role of mitochondria in protection of the heart by preconditioning. Biochim Biophys Acta, 2007. 1767(8): p. 1007-31.

[234] Hausenloy, D.J. and D.M. Yellon, Preconditioning and postconditioning: underlying mechanisms and clinical application. Atherosclerosis, 2009. 204(2): p. 334-41.

[235] Bernardo, B.C., et al., Molecular distinction between physiological and pathological cardiac hypertrophy: experimental findings and therapeutic strategies. Pharmacol Ther, 2010. 128(1): p. 191-227.

[236] Wagner, C., et al., Cardioprotection by postconditioning is lost in WOKW rats with metabolic syndrome: role of glycogen synthase kinase β. J Cardiovasc Pharmacol, 2008. 52(5): p. 430-7.

[237] Bouhidel, O., et al., Myocardial ischemic postconditioning against ischemia-reperfusion is impaired in ob/ob mice. Am J Physiol Heart Circ Physiol, 2008. 295(4): p. H1580-6.

[238] Katakam, P.V., et al., Myocardial preconditioning against ischemia-reperfusion injury is abolished in Zucker obese rats with insulin resistance. Am J Physiol Regul Integr Comp Physiol, 2007. 292(2): p. R920-6.

[239] Thompson, P.D., et al., Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation, 2003. 107(24): p. 3109-16.

[240] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation, 2002. 106: p. 3143-21.

[241] Phelan, S., et al., Impact of weight loss on the metabolic syndrome. Int J Obes (Lond), 2007. 31(9): p. 1442-8.

[242] Muzio, F., et al., Long-term effects of low-calorie diet on the metabolic syndrome in obese nondiabetic patients. Diabetes Care, 2005. 28(6): p. 1485-6.

[243] Orchard, T.J., et al., The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. Ann Intern Med, 2005. 142(8): p. 611-9.

[244] Ballantyne, C.M., et al., Influence of low high-density lipoprotein cholesterol and elevated triglyceride on coronary heart disease events and response to simvastatin therapy in 4S. Circulation, 2001. 104(25): p. 3046-51.
Pyorala, K., et al., *Reduction of cardiovascular events by simvastatin in nondiabetic coronary heart disease patients with and without the metabolic syndrome: subgroup analyses of the Scandinavian Simvastatin Survival Study (4S).* Diabetes Care, 2004. 27(7): p. 1735-40.

Paolisso, G., et al., *Effects of simvastatin and atorvastatin administration on insulin resistance and respiratory quotient in aged dyslipidemic non-insulin dependent diabetic patients.* Atherosclerosis, 2000. 150(1): p. 121-7.

Sonmez A, B.Y., Kilic M, Saglam K, Buluku F and Kocar IH., *Fluvastatin improves insulin resistance in nondiabetic dyslipidemic patients.* Endocrine, 2003. 22(2): p. 151-154.

Malmendier, C.L. and C. Delcroix, *Effects of fenofibrate on high and low density lipoprotein metabolism in heterozygous familial hypercholesterolemia.* Atherosclerosis, 1985. 55(2): p. 161-9.

Robins, S.J., et al., *Relation of gemfibrozil treatment and lipid levels with major coronary events: VA-HIT: a randomized controlled trial.* JAMA, 2001. 285(12): p. 1585-91.

Vu-Dac, N., et al., *Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor.* J Clin Invest, 1995. 96(2): p. 741-50.

Guerre-Millo, M., et al., *Peroxisome proliferator-activated receptor alpha activators improve insulin sensitivity and reduce adiposity.* J Biol Chem, 2000. 275(22): p. 16638-42.

Ide, T., et al., *Enhancement of insulin signaling through inhibition of tissue lipid accumulation by activation of peroxisome proliferator-activated receptor (PPAR) alpha in obese mice.* Med Sci Monit, 2004. 10(10): p. BR388-95.

Bergeron, R., et al., *Peroxisome proliferator-activated receptor (PPAR)-alpha agonism prevents the onset of type 2 diabetes in Zucker diabetic fatty rats: A comparison with PPAR gamma agonism.* Endocrinology, 2006. 147(9): p. 4252-62.

Tsunoda, M., et al., *A novel PPARalpha agonist ameliorates insulin resistance in dogs fed a high-fat diet.* Am J Physiol Endocrinol Metab, 2008. 294(5): p. E833-40.

Forcheron, F., et al., *Diabetic cardiomyopathy: effects of fenofibrate and metformin in an experimental model—the Zucker diabetic rat.* Cardiovasc Diabetol, 2009. 8: p. 16.

Chang, J.T., et al., *Rhabdomyolysis with HMG-CoA reductase inhibitors and gemfibrozil combination therapy.* Pharmacoepidemiol Drug Saf, 2004. 13(7): p. 417-26.

van Puijenbroek, E.P., et al., *Possible increased risk of rhabdomyolysis during concomitant use of simvastatin and gemfibrozil.* J Intern Med, 1996. 240(6): p. 403-4.

Moscatiello, S., et al., *Managing the combination of nonalcoholic fatty liver disease and metabolic syndrome.* Expert Opin Pharmacother, 2011. 12(17): p. 2657-72.

DeFronzo, R.A., et al., *Pioglitazone for diabetes prevention in impaired glucose tolerance.* N Engl J Med, 2011. 364(12): p. 1104-15.

Xiang, A.H., et al., *Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes.* Diabetes, 2006. 55(2): p. 517-22.

Campia, U., L.A. Matuskey, and J.A. Panza, *Peroxisome proliferator-activated receptor-gamma activation with pioglitazone improves endothelium-dependent dilation in nondiabetic patients with major cardiovascular risk factors.* Circulation, 2006. 113(6): p. 867-75.

Dagenais, G.R., et al., *Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the
Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. Diabetes Care, 2008. 31(5): p. 1007-14.

[263] Fogari, R., et al., Comparative effects of lisinopril and losartan on insulin sensitivity in the treatment of non diabetic hypertensive patients. Br J Clin Pharmacol, 1998. 46(5): p. 467-71.

[264] Yavuz, D., et al., Effects of ACE inhibition and AT1-receptor antagonism on endothelial function and insulin sensitivity in essential hypertensive patients. J Renin Angiotensin Aldosterone Syst, 2003. 4(3): p. 197-203.

[265] Aksnes, T.A., et al., Improved insulin sensitivity with the angiotensin II-receptor blocker losartan in patients with hypertension and other cardiovascular risk factors. J Hum Hypertens, 2006. 20(11): p. 860-6.

[266] Jin, H.M. and Y. Pan, Angiotensin type-1 receptor blockade with losartan increases insulin sensitivity and improves glucose homeostasis in subjects with type 2 diabetes and nephropathy. Nephrol Dial Transplant, 2007. 22(7): p. 1943-9.

[267] van Dielen, F.M., et al., Macrophage inhibitory factor, plasminogen activator inhibitor-1, other acute phase proteins, and inflammatory mediators normalize as a result of weight loss in morbidly obese subjects treated with gastric restrictive surgery. J Clin Endocrinol Metab, 2004. 89(8): p. 4062-8.

[268] Jialal, I., et al., Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive C-reactive protein levels. Circulation, 2001. 103(15): p. 1933-5.

[269] Nesto, R., C-reactive protein, its role in inflammation, Type 2 diabetes and cardiovascular disease, and the effects of insulin-sensitizing treatment with thiazolidinediones. Diabet Med, 2004. 21(8): p. 810-7.