REVIEW

Obesity and diabetes: lipids, ‘nowhere to run to’

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ABSTRACT

Although specific pathogenic entities contributing to diabetic risk, such as central adiposity, ectopic fat accumulation, hyperlipidaemia and inflammation, are well-characterized, the response of cellular systems to such insults are less well understood. This short review highlights the effect of increasing fat mass on ectopic fat accumulation, the role of triacylglycerols (triglycerides) in Type 2 diabetes mellitus and cardiovascular disease pathogenesis, and selected current therapeutic strategies used to ameliorate these risk factors.

INTRODUCTION

Obesity, diabetes and CVD (cardiovascular disease) are recognized as part of a rising global epidemic; however, there are regions of the world where the concomitant health implications have yet to be fully acknowledged. Although few studies have focussed on these countries, the global study REACH (Reduction in Atherothrombotic Risk in the Context of an Global Evaluation of Thrombolysis in Myocardial Infarction; http://www.escardio.org/about/press/press-releases/congress-06/Pages/reach-international-study.aspx) assessed data from 68 000 patients in 44 countries and exposed significant variation in the potential burden of disease. Despite the WHO (World Health Organization) identifying obesity as “the most blatantly visible, yet most neglected public health problem” [1], weight gain has historically been associated with wealth and prosperity in many traditional communities. This belief, coupled with the shift from fibre-rich foods to a more Western diet, has undoubtedly contributed to the current health crisis facing many at-risk populations. For example, Musaiger [2] observed that, within the last four decades, daily per capita fat in the Saudi diet increased by 143.3 %, with clear indications that this would continue to rise. These circumstances are not unique and are reflected in many other regions around the world.

At present however, many regions worldwide lack sufficient reliable data as to the current health status of the population, and they will probably bear the burden of obesity and associated diseases in the future [3]. The International Obesity Taskforce estimates that, worldwide, more than 312 million adults are obese [4] and the incidence of diabetes is projected to rise by 32 % in Europe and 72 % in the U.S.A. by 2030. However, the most dramatic projected increases in diabetes incidence (> 150 %) are predicted in the Middle East, Southeast Asia, India, Sub-Saharan Africa and Latin America [5,6]. Additionally, the cardiovascular complications of obesity and diabetes risk overwhelming countries that are both unprepared in terms of management and decisive prevention strategies.

The present review examines the impact of fat localization, the inter-relationship between lipid accumulation and metabolism, and the potential diabetic and CVD risk.

Key words: cardiovascular disease, fatty acid, obesity, triacylglycerol, Type 2 diabetes.

Abbreviations: AMPK, AMP-activated protein kinase; apoB, apolipoprotein B; ASC, acyl-CoA synthetase; CPT-1, carnitine palmitoyltransferase-1; CRP, C-reactive protein; CVD, cardiovascular disease; FA, fatty acid; GGPP, geranylgeranyl PPi; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; IMTG, intramyocellular triacylglycerol; IRS, insulin receptor substrate; LCFA, long-chain FA; LDL, low-density lipoprotein; NEFA, non-esterified FA; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PPAR, peroxisome-proliferator-activated receptor; TAG, triacylglycerol; T2DM, Type 2 diabetes mellitus; TNF-α, tumour necrosis factor-α; TZD, thiazolidinedione.

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CONTRIBUTION OF CENTRAL ADIPOCYTE TO DIABETIC AND CARDIOVASCULAR RISK

The anatomical location of adipose accumulation is fundamental to the metabolic risk profile predictive of CVD and T2DM (Type 2 diabetes mellitus). In particular, increased abdominal adiposity is generally associated with high circulating TAGs [triacylglycerols (triglycerides)], low HDL (high-density lipoprotein)-cholesterol and high plasma concentrations of apoB (apolipoprotein B)-containing lipoproteins. These lipid abnormalities are the metabolic consequences of inequities in energy metabolism, impaired glucose tolerance, insulin resistance and inflammation; all of which contribute to pathophysiology within the cardiovascular system.

Central (or ‘android’) obesity in women correlates with a higher incidence of glucose intolerance and high fasting plasma TAGs relative to women with a predominantly lower-body fat (‘gynoid’) distribution [7]. This offers an important marker for potential metabolic complications. In addition to lipid abnormalities associated with the abdominal depot, there is increased hyperlipolytic activity in omental (visceral) adipose tissue relative to abdominal subcutaneous adipose tissue, which might represent differences in receptor expression and adipokine secretion between subcutaneous and omental adipocytes. Studies have shown that adipokines, such as leptin [8], are secreted more abundantly in subcutaneous adipocytes. Studies have shown that adipokines, such as leptin [8], are secreted more abundantly in subcutaneous adipocytes, whereas adiponectin, IL-1β, IL-8 and PAI-1 (plasminogen-activator inhibitor-1) are more abundant in omental adipose tissue [9]. However, caution is indicated as subcutaneous adipose fat can comprise as much as 80% of total adipose tissue mass with omental adiposity only comprising 6–20% of adipose tissue mass [10]. As such, changes in distribution, as well as alteration in circulating factors related to risk profile, can have multifactorial influences on adipose tissue depots, which in turn can influence adipokine metabolism. In anatomical terms, omental adipose tissue drains directly into the hepatic portal vein and further studies have suggested [11] that such exposure of the liver to high concentrations of metabolites and adipokines released from omental adipocytes may increase cardio-metabolic risk [12–15]. Further studies have also addressed the risk of accumulating abdominal subcutaneous adipose tissue [16–19] and all conclude that central obesity remains a reliable predictor of cardiovascular disease profiles [20–23].

ECTOTIC FAT ACCUMULATION

Ultimately, failure of adipocytes to appropriately buffer the plasma FA (fatty acid) concentration can result in disturbances in the otherwise tightly regulated lipid content of non-adipocyte cells. This may result in cellular dysfunction, apoptosis and consequent pleiotropic pathogenic sequelae. Although white adipose tissue is pivotal as a homoeostatic mechanism regulating FA concentration, the FA oxidation capacity of adipocytes is barely 10% that of skeletal muscle, and this percentage does not alter significantly in obesity or insulin resistance [24]. The mechanisms involved in lipid accumulation in non-adipocytes have yet to be fully clarified; however, on a simplistic level, when dysregulation of FA uptake occurs and cellular de novo lipogenesis outweights FA oxidation, the result is an increase in cellular lipid storage. If it is assumed that lipid accumulation in non-adipocytes is an acquired pathogenic state, this suggests three areas of potential therapeutic intervention, as described by Baker et al. [25]: (i) reduction of lipid uptake by non-adipocytes, either directly or via a reduction in circulating lipid concentration; (ii) up-regulation of β-oxidation of lipids in non-adipocytes; and (iii) down-regulation of lipogenesis in non-adipocytes. However, there is also speculation [26] that a phenotype transformation of the white adipocyte to acquire the oxidative capacity of a brown adipocyte would reduce FA release into the bloodstream, thereby increasing cellular buffering capacity; particularly during the post-prandial onslaught.

Undoubtedly, adipocytes specifically evolved with the potential to store a significant quantity of TAGs to create an ample supply of energy, particularly as storage in non-specialist cells was not tenable due to unavoidable pathogenic consequences. The crucial mechanism that directs TAGs towards storage in adipocytes rather than other cell types is complex and compelling arguments are proposed by Unger and co-workers [27,28]. In essence, the work by Unger and co-workers has highlighted the role of peptides secreted by adipocytes, specifically leptin and, to a lesser degree, adiponectin, which are responsible for maintaining non-adipocyte lipid homoeostasis. Indeed, where normal leptin homoeostasis is dysfunctional, intracellular TAG dysregulation follows; however, others have proposed a lipid overflow model [29] whereby lipid only accumulates in non-adipocyte cells when adipocyte capacity has been exceeded and, furthermore, this model incorporates the observed similarities in ectopic lipid deposition and consequent insulin resistance observed in lipodystrophy and obesity [30,31]. In lipodystrophy, there is insufficient adipose tissue available to buffer the post-prandial lipid influx whereas, in obesity, the hypertrophic adipocytes become refractory to further lipid uptake. There is, however, considerable experimental evidence to support a role for leptin in the regulation of non-adipocyte lipid accumulation [32–36]. Such regulation initially appeared to be influenced via increased FA oxidation, stimulated by a leptin-induced up-regulation of AMPK (AMP-activated protein kinase) [37]. Notably, a similar role has been suggested for adiponectin [38], but the evidence for this is rather less compelling. It has also been proposed that a combination of leptin-stimulated AMPK and PI3K (phosphoinositide 3-kinase) signalling...
is implicated in thermogenic substrate cycling between *de novo* lipogenesis and lipid oxidation which protects skeletal muscle from excess TAG accumulation [39]. A more recent investigation [40] has comprehensively illustrated the effect of central leptin on key enzymes in the liver and adipose tissue, and the subsequent tissue-specific effect on limiting fat mass and ectopic lipid accumulation. It would appear, therefore, that while the regulation of non-adipocyte TAG storage may be multifactorial, adequate and ‘healthy’ adipose tissue is essential for maintenance of physiological concentrations.

### ACCUMULATION OF LIPID IN MUSCLE

It is widely accepted that intracellular, and specifically IMTG (intramyocellular TAG) correlates well with both tissue and whole-body insulin resistance [18,41,42], although the relationship is complex. Contrasting findings have been reported with the use of fenofibrate and rosiglitazone on IMTG in Zucker diabetic rats, although both PPAR (peroxisome-proliferator-activated receptor) agonists improved insulin resistance [43], thus highlighting a need for further exploration. Over 40 years ago, Randle et al. [44–46] first proposed a model of FA-induced insulin resistance in skeletal muscle and, in 1992, McGarry [47] first suggested the link between lipid metabolism and pathogenesis of T2DM. Current theories now focus on activation of PKC (protein kinase C) isoforms by FA metabolites, particularly DAG (diacylglycerol) [48], leading to the serine/threonine phosphorylation of IRS (insulin receptor substrate) [49] and their subsequent failure to activate PI3K (Figure 1). Elevated intracellular TAG concentrations in insulin-sensitive tissues such as skeletal muscle and liver can blunt the cellular response to insulin stimulation and the subsequent metabolic dysfunction leading to T2DM. Furthermore, chronic low-grade inflammation is similarly associated with insulin resistance and T2DM, with the most reliable marker being CRP (C-reactive protein), which has also been shown to induce phosphorylation of IRS-1 on two separate residues (Ser307 and Ser612) in L6 myocytes [50]. Increased phosphorylation in this manner ultimately inhibits the insulin-signalling pathway via JNK (c-Jun N-terminal kinase) and ERK1/2 (extracellular-signal-regulated kinase 1/2), and eventually impairs insulin-stimulated glucose uptake, GLUT4 (glucose transporter 4) translocation and glycogen synthesis, as mediated by the IRS-1/PI3K/protein kinase B (also known as Akt)/GSK-3 (glycogen synthase kinase-3) pathway.

Although IMTG has been correlated closely with insulin resistance in many subject groups, endurance-trained athletes exhibit high levels of IMTG and yet are often extremely insulin sensitive [51]. One explanation for this paradox is an increased myocyte oxidative capacity in these athletes; an augmented capacity which may reduce IMTG peroxidation and ultimately reduce expression of TNF-α (tumour necrosis factor-α) [52,53]. Although relating only to one group, these studies suggest it is not simply the accumulation of TAG which is responsible for insulin resistance in skeletal muscle, but that, under certain physiological conditions, the lipotoxic effects of IMTG can be circumvented. Further investigations have indicated that the explanation could

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**Figure 1** Ectopic FA accumulation, leading to the activation of PKC isoforms, and raised CRP levels due to chronic inflammation are both responsible for selective phosphorylation of the IRSs

This increased phosphorylation of the serine and threonine residues ultimately inhibits activation of PI3K and therefore the PIP3 cascade. This Figure is reproduced and adapted from [25], Baker, A. R., Creely, S. J., McTernan, P. G. and Kumar, S. (2007) Epicardial and intramyocardial adipose tissue: the enemy within. Immunol. Endocr. Metab. Agents Med. Chem. 7, 143–148, with permission © Bentham Science Publishers Ltd. Abbreviations are indicated in the text.
lie with PPARδ activation, which rodent studies have shown is a key feature of skeletal muscle FA oxidation [54]. Moreover, there may be a direct connection between PPARδ activation and elevated skeletal muscle fibre type 1 composition (with a concomitant increase in FA oxidation), which is precisely the response following physical exercise and increased running endurance [55]; however, these studies were more ambivalent regarding the effects of PPARδ activation on insulin sensitivity.

**ACCUMULATION OF LIPID IN LIVER**

Accumulation of lipid in the liver is well correlated with hepatic insulin resistance in both T2DM and in non-diabetic individuals [56,57] with impaired insulin-mediated suppression of hepatic glucose production in the post-prandial (i.e. hyperglycaemic, hyperinsulinaemic) state. Lipid deposition in the liver leads to NAFLD (non-alcoholic fatty liver disease), which is associated with insulin resistance status [58], and this may subsequently develop into NASH (non-alcoholic steatohepatitis). As well as insulin resistance and cellular dysfunction, dysregulation of lipid content in non-adipocytes can result in lipid-induced apoptosis (lipoapoptosis). TAG itself may not be directly involved in this mechanism and has, in fact, been considered to be a protective agent [59]. However, ceramides, which are known initiators of the apoptotic cascade [60], may be important in lipoapoptosis as it is the formation and accumulation of these lipid species which seems to be central to induced lipoapoptosis [27,61]. Although TAGs are generally considered inert, it is their hydrolysis to fatty acyl-CoA that provides an amplified substrate for ceramide synthesis. Ceramide up-regulates iNOS (inducible NO synthase) expression and, subsequently, NO production. This leads to an increase in intracellular peroxynitrite which is considered a candidate for lipoapoptosis [62]. Although the ceramide pathway appears to be a significant destructive route, other pathways independent of ceramide, such as lipid peroxidation, have also been implicated in the lipoapoptotic cascade [59,63].

Hepatocytes and myocytes have the most efficient mechanisms for clearing surplus TAGs: the liver exports TAG in the form of VLDLs [very-LDLs (low-density lipoproteins)] and myocytes have the capacity to increase TAG oxidation through exercise. However, pancreatic β-cells can perform neither of these mechanisms and are therefore more susceptible to lipid overload and cell death [64]. Previous studies have correlated lipopoptosis in obese rat pancreatic β-cells [61,65–67], identifying an increase in de novo synthesis of ceramide resulting directly from a profusion of non-oxidized FAs. It has thus been proposed that a similar pathology could exist in cardiomyocyte steatosis leading to loss of cardiac function in humans.

**ACCUMULATION OF LIPID IN CARDIOMYOCYTES**

Evidence strongly suggests a causal link between cardiomyocyte steatosis and cardiac dysfunction in obesity. This may be a result of cardiac lipoapoptosis which is preventable by reducing cardiac lipids [63]. CVD is strongly associated with intracellular lipid accumulation in the heart and discrepancies between FA uptake and utilization are thought to lead to lipotoxic cardiomyopathies.

Cardiomyocytes rely on β-oxidation of LCFAs (long-chain FAs) to generate ATP as the cells have no mechanism for de novo synthesis or storage of this substrate. Under normal physiological conditions, serum concentrations of NEFAs (non-esterified FAs; ‘free’ FAs) are insufficient (in the nanomolar range) so cardiomyocytes have evolved an efficient import mechanism to satisfy all levels of energy demand. Several important proteins are involved in the transmembrane uptake of LCFA, including FATP1 (FA transport protein 1) and long-chain ASC1 (acyl-CoA synthetase 1). During the early phase of CVD, myocardial metabolism can switch from LCFA oxidation to glucose as a substrate and, although this may be beneficial for the cell initially, the adaptive function eventually leads towards lipotoxicity and so contributes to cellular dysfunction. In some models of obesity and T2DM it is proposed [68] that high serum NEFA levels promote LCFA import in excess of normal cellular capacity, thereby overriding the regulated transmembrane transport mechanism which could initiate diabetic cardiomyopathies. Studies using a transgenic mouse model expressing long-chain ASC in the heart (MHC-ACS) have shown marked TAG accumulation in cardiomyocytes which were toxic to these cells and initiated apoptosis [68,69]. This excess of TAG in non-adipose tissue (steatosis) expands the intracellular pool of fatty acyl-CoA thereby increasing substrate availability for oxidative metabolic pathways and ceramide synthesis [64]. However, these surplus non-oxidized FAs enter pathways of non-oxidative metabolism. The central importance of the PI3K pathway is once again highlighted as impaired phosphorylation, due to obesity and diabetes, leads to a decrease in the vasodilatory and anti-inflammatory benefits of insulin. Consequently, the likelihood of vascular inflammation and endothelial dysfunction associated with CVD is increased.

**ADIPOCYTE INFILTRATION INTO TISSUES**

As well as accumulation of lipid in non-adipocytes, obesity, T2DM and CVD can lead to an increase in the volume of non-classical adipose depots, such as epicardial adipose tissue, and adipocyte ‘infiltration’ into other tissues. The effects of such increases may be exerted in two ways: first, there are potential physical effects and
secondly, there are potential paracrine and endocrine effects.

The epicardial surface of the human heart is covered, to a variable degree, by a layer of adipose tissue [70]. This epicardial fat has a high capacity for NEFA release and is implicated as a source of this preferred metabolite for the myocardium [71]. It is also a source of a number of pro-inflammatory and pro-atherogenic proteins [72,73]. The lack of any fascia-like structure between the adipose and myocardial layers results in a poorly defined boundary between the two tissues and isolated ‘islands’ of adipocytes can be detected within the myocardium itself (Figure 2), although the origin of these cells has not been established. Mesenchymal stem cells are common progenitors of myocytes and adipocytes, and it has been observed in the myometrium that replenishment of smooth muscle can be hijacked by adipogenesis when β-catenin is conditionally deleted [74]. This suggests the possibility that inter-myocytic adipocytes may arise from the differentiation of precursor cells, normally destined to replenish myocytes, through a change in cell-fate decision signals. Another possibility is raised by the suggestion of transdifferentiation of mature myocytes into adipocytes, as in a case of familial dilated cardiomyopathy described by d’Amati et al. [75]. One potential source of these isolated adipocytes is the epicardial adipose tissue, although little is known about the ability of mature adipocytes, preadipocytes or the putative ‘adipophage’ [76] to infiltrate other tissues directly. An increase in epicardial adipose tissue, and the development of inter-myocytic adipocytes, may inevitably lead to increased non-contractile mass and greater work for the myocardium. This may, in turn, lead to hypertrophy and eventually heart failure. There is also substantial evidence linking NEFAs and lipomatous hypertrophy with arrhythmias [77,78].

Given the well-established association between obesity, T2DM and heart failure [79,80], it could be envisaged that these additional adipocytes are exerting a negative effect on heart function. As well as the physical effects of extraneous adipocytes there are also potential paracrine effects. Adipocytes and non-adipocytes in adipose tissue secrete a plethora of adipokines which include pro-inflammatory, anti-inflammatory [81] and

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Figure 2  Histological analysis of the heart and epicardial fat
Histological analysis of the left (A) and right (B) atrium of the myocardium showing multiple inter-myocytic adipocyte cells (denoted by a honeycomb appearance) as well as discrete inter-myocytic cells (C) within the myocardium. (D) Normal heart tissue from a non-obese subject. A, B and D, magnification ×4; C, magnification ×10.
pro-atherogenic [82] peptides, as well as proteins known to induce insulin resistance [83] and reduce myocyte contractility [84,85]. Combined with the accumulation of IMTG leading to insulin resistance and therefore reduced glucose utilization in the myocardium, the potential effect of the fatty heart is one of multiple synergistic insults to myocardial function and metabolism. However, the potential risks associated with an increase in epicardial adipose tissue mass may not be clear cut, as studies by Chaowalit et al. [86] were unable to correlate epicardial adipose tissue thickness with elevated risk of CVD in subjects undergoing echocardiography and coronary angiopathy, whereas age was a significant factor in increasing tissue accumulation.

THERAPEUTICS

Ectopic fat in muscle, liver and the heart have significant effects on the pathogenesis of both diabetes and CVD. Adipocytes normally have a finite storage capacity so, consequently, exposure to excess FAs leads to the deposition of lipid in non-adipocytes which has a significant impact on pathogenesis. However, drugs that increase the lipid storage ability and proliferation capacity of adipocytes, thereby moderating abnormal deposition, may ultimately help to mitigate this problem (Figure 3).

**PPAR agonists**

An important group of drugs are the TZDs (thiazolidinediones) which are PPARγ agonists, and include rosiglitazone and pioglitazone. PPARγ is a nuclear transcription factor found in a large number of tissues but highly expressed in liver and adipose tissue [88]. One of the principal effects of the PPARγ agonists is their ability to potentially regulate the formation of new small adipocytes from pre-adipocytes [89] and to induce apoptosis of larger lipid-rich adipocytes [90]. This effect occurs mainly in subcutaneous abdominal adipose tissue rather than the visceral depot [91]. Although this leads to the paradox of weight gain with a reduction in insulin resistance and blood glucose [56,92], one benefit of this redistribution of adiposity is that TAGs move from visceral sources to the subcutaneous depot. This reduces the exposure of the
liver to lipid and results in a reduction in abnormal storage and the deleterious effects on insulin signalling.

In clinical studies, rosiglitazone has been shown to reduce intrahepatic lipid significantly over a short period of treatment [93], and other studies have demonstrated that, not only does pioglitazone reduce intrahepatic and intramyocellular lipid [94], but this reduction strongly correlates with the ability of insulin to suppress endogenous glucose production. In addition, pioglitazone inversely correlates with a rise in adiponectin concentrations [56,95]. However, work on PPARγ-knockout (FKOy) mice by He et al. [96] has shown that targeted knockout in adipose tissue results in higher NEFA levels and hypocellular adipose tissue. This leads to reduced adipose tissue lipid storage and increased ectopic deposition due to the fundamental role of PPARγ in adipogenesis [89]. As a result the mice were more susceptible to hepatic steatosis and hyperinsulinemia/insulin resistance when exposed to a high-fat diet. The insulin resistance in the liver could, however, be reversed by TZD treatment despite no effect on the plasma NEFA levels. In addition, the fat PPARγ-deficient mice failed to develop muscle insulin resistance, despite a decrease in adiponectin, indicating that additional adipose-derived factors may also be involved in driving systemic insulin sensitivity.

Intramyocellular lipid and its direct relationship to insulin resistance [41,97,98] is also affected by therapeutic treatments. First, weight loss has been shown to reduce certain lipid metabolites such as palmitate-CoA and stearate-CoA, which in turn reverses the inhibition on insulin signalling via PI13 (protease inhibitor 13) and the PIP3 (phosphatidylinositol 3,4,5-trisphosphate) cascade, thereby increasing insulin action [99]; however, these results have been partially contradicted by another study showing no overall effect following weight loss on total LCFA-CoA concentrations [100], which is possibly explained by the relative pathogenicity and, indeed, the comparative changes of lipid factors included in the studies [101]. Further findings have shown that glitazone treatment redistributes lipid from the intracellular to the extracellular compartments in patients [93], and increases oxidation of lipid within the mitochondria of myocytes. The net effect is an increase in insulin sensitivity and a reduction in the inhibitory effect of FAs on the action of insulin.

The PPARγ agonists, a class including the anti-lipid fibrates, have some beneficial effects on ectopic fat. In initial studies, fenofibrate were noted to reduce the intensity of muscle TAG signal [102] as well as increasing the hepatic expression of CPT-1 (carnitine palmitoyltransferase-1), an important enzyme in the pathway of long-chain lipid oxidation. These studies have been supported by work in rodents showing that LCFA are reduced by a novel PPARγ agonist in comparison with pioglitazone. Exogenous PPARγ agonists are also known to reduce TNF-α-induced activation of NF-κB (nuclear factor κB), a transcription factor which integrates inflammation and atherosclerosis [103], which may suggest a route for its apparent effects on insulin resistance, although this has yet to be established [102,104]. Experiments with combined PPARα and PPARγ agonists, such as ragaglitazar, have shown that this combination reduces circulatory lipid and increases TAG turnover in the liver [105]. This also corresponds to an effect on histological fatty liver with a marked reduction in liver TAG in high-fat-fed rats compared with PPARγ agonists alone [106]. Inhibition of CPT-1 has been shown in vivo to increase intramyocellular lipid and promote insulin resistance [107], suggesting that the up-regulation of this enzyme may present an attractive drug target. Conversely, partial CPT-1 inhibitors have a beneficial effect on myocardial function and are a recognized therapy for angina [108].

Statin therapy

Lipid abnormalities play an important role in the development of CVD by the preponderance of circulating LDL-cholesterol which, together with TAG-rich lipoprotein particles and low levels of HDL, forms a potent atherogenic combination. This profile strongly predisposes lipid accumulation in the arterial wall and the formation of atherosclerotic plaques [109]. Currently the American Diabetes Association has identified LDL as the major priority for lipid-lowering strategies; the optimal level has been identified as 2.6 mmol/l (100 mg/dl). The current therapeutic tools for lipid-lowering are statins [HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors], which are a class of hypo-lipidaemic agents that lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase; this being the rate-limiting enzyme in the mevalonate pathway of cholesterol synthesis. Inhibition of HMG-CoA reductase in the liver also stimulates LDL receptors which, in turn, reduce circulating LDL-cholesterol by increased clearance. Statins differ in their lipid-lowering efficacy and in their ability to help patients achieve their lipid goals. Berne et al. [110] evaluated the lipid-lowering abilities of rosuvastatin and atorvastatin in patients with T2DM. They observed that, although rosuvastatin was significantly more effective in achieving 2003 European LDL-cholesterol goals (< 2.5 mmol/l) than atorvastatin, atorvastatin may have another possible therapeutic advantage as a vascular antioxidant in patients with diabetes. These antioxidant effects are possibly mediated through inhibition of Rac-1 via a reduction in GGPP (geranylgeranyl PP), which could be a novel mechanism for the action of statins against oxidative stress induced by diabetes. As such, this provides a further potential pharmacological tool for attenuating the complications of diabetes. Several other studies [111–116] have identified statins as beneficial to patients with diabetes. The 5 year CARE (Cholesterol and Recurrent
Events) trial investigated whether the lipid-lowering effect of pravastatin successfully reduced recurrent cardiovascular events [115]. The results certainly suggest that patients with diabetes and patients without diabetes with impaired fasting glucose were less likely to experience recurrent coronary events with pravastatin treatment compared with placebo administration [117]. Similarly, the MRC (Medical Research Council)/BHF (British Heart Foundation) Heart Protection Study provided compelling evidence that simvastatin is equally effective in reducing the incidence of a primary major vascular event in patients with diabetes irrespective of cholesterol status. Comprehensive interpretation of these major studies concludes that the introduction of statin therapy to existing treatments safely achieves significant additional benefit for high-risk patients against a wide range of cardiovascular events. Most importantly, there was no evidence of adverse effects on cancer incidence or other significant non-vascular disease which might reduce its popularity as a preventative treatment strategy.

There is, undoubtedly, a comprehensive armoury of pharmacological agents specifically targeting the pathogenic metabolic consequences of lipid overload, but these should not overshadow the potential positive therapeutic contribution of lifestyle intervention [118]. Investigation of factors such as weight loss, exercise and fish oil supplements ([119], but see [120]) are revealing valid alternative strategies for maintaining homoeostatic mechanisms before drug intervention becomes inevitable (Table 1).

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**SUMMARY**

The action of circulating lipids and the tissue-specific effects of lipid metabolism in the pathogenesis of CVD and diabetes are substantial. Within this, there is a clear need to understand the role of adipocytes and the accumulation of ectopic lipid within tissues such as the liver and heart, as has been achieved with muscle. Furthermore, although strategies are available to reduce the pathogenic qualities of adipocytes, many of these therapeutic agents also have complex actions within the cellular system which require further evaluation as to their beneficial effects in the long term.

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