

REVIEW

MECHANISMS IN ENDOCRINOLOGY

Non-alcoholic fatty liver disease in common endocrine disorders

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease spanning from simple benign steatosis to steatohepatitis with fibrosis and scarring that can eventually lead to cirrhosis. Its prevalence is rising rapidly and is developing into the leading indication for liver transplantation worldwide. Abnormalities in endocrine axes have been associated with NAFLD, including hypogonadism, hypothyroidism, GH deficiency and hypercortisolaemia. In some instances, correction of the endocrine defects has been shown to have a beneficial impact. While in patients with type 2 diabetes the association with NAFLD is well established and recognised, there is a more limited appreciation of the condition among common endocrine diseases presenting with hormonal excess or deficiency. In this review, we examine the published data that have suggested a mechanistic link between endocrine abnormalities and NAFLD and summarise the clinical data endorsing these observations.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) exists as a disease spectrum from the accumulation of lipid within hepatocytes (steatosis) to inflammation of the liver (non-alcoholic steatohepatitis (NASH)) to scarring of the liver (fibrosis) and finally to cirrhosis (1). The prevalence of simple hepatic steatosis in the general population may be as high as 50%, although these studies have varied in terms of the diagnostic criteria and the populations examined (2). The gold standard for diagnosis remains liver biopsy, and 20–50% of healthy individuals assessed for live partial liver donation have biopsy-proven hepatic steatosis (3, 4). In obese cohorts undergoing bariatric surgery, the prevalence of biopsy confirmed that steatosis may be as high as 91 and 37% for NASH (5).

The impact of simple steatosis on mortality is contentious (6, 7) and may reflect differing definitions, observation intervals and the diagnostic methods used to determine the presence of NAFLD. Cardiovascular mortality is increased in NASH cirrhosis even when compared with cirrhosis caused by other aetiologies (8) and is also associated with a 5-year cumulative incidence of hepatocellular carcinoma of 11.3% (9).

NAFLD is often seen in patients with endocrinopathies (10, 11), and it is possible that these observations may shed light onto the aetiological mechanisms underpinning the pathogenesis of NAFLD. Perhaps more importantly, this is a condition that has been

overlooked by some endocrinologists and therefore the aim of this review is to not only examine the association and possible causal relationship between endocrinopathies and the development of NAFLD but also raise awareness within the endocrine community.

Pathogenesis of NAFLD

The pathogenesis of NAFLD has been reviewed extensively elsewhere and is discussed briefly below (12, 13, 14). Lipid accumulation within the liver represents an equilibrium between synthesis and utilisation. Fatty acids within the liver typically undergo one of the three metabolic pathways: β -oxidation, storage as triglycerides (TGs) or further processing for secretion as lipoproteins. Lipidomic analysis of liver biopsies from NAFLD and NASH patients has shown that while free fatty acids (FFAs) are unchanged, levels of diacylglycerols and triacylglycerols are increased with elevated saturated fatty acid composition (15). Isotope studies on patients with NAFLD undergoing liver biopsy had dissected the relative contribution of the metabolic pathways that contribute to lipid accumulation within the liver; 59% were derived from re-esterification of circulating FFAs, 26.1% from *de novo* lipogenesis and 14.9% from dietary fatty acids (16).

The increased lipid flux through the liver and dysfunctional lipid metabolism results in intracellular

stress and apoptosis and consequent liver damage (17). Insulin-resistant adipose tissue with uncontrolled lipolysis resulting in enhanced FFA delivery to the liver has been postulated to be central in driving the pathogenesis of NAFLD. Adipose tissue insulin resistance (IR) has been shown to correlate with severity of liver biopsy findings in NASH (18). The low-grade inflammatory phenotype that is associated with obesity and IR may be important, and adipose tissue tumour necrosis factor α (TNF α) and circulating interleukin 6 are associated with IR and circulating FFA levels (19) and both are increased in patients with NAFLD and NASH (20, 21). In addition, adiponectin, which is produced by mature adipocytes and is known to have an anti-inflammatory action as well as being associated with insulin sensitisation, is decreased in patients with NASH (22).

In summary, the pathogenesis underpinning NAFLD is complex and relies upon crosstalk between the liver and adipose tissues. A three-hit hypothesis has been proposed (14, 23); the first hit involves the accumulation of lipid by the mechanisms described above. The second hit is the initiation of an inflammatory response and the triggers to this are still to be clearly defined, but the cell death that is associated with this is the hallmark of progressive disease. Finally, there is emerging evidence to suggest that the third hit is a defective repair and regenerative response (24). It is entirely plausible that endocrine abnormalities with hormonal deficiencies and excess may contribute to any one of these 'hits' and therefore may be implicated in the pathogenesis of NAFLD. In this review, we will examine both the mechanistic and the clinical data that have led to the implication of endocrine axes in the pathogenesis of NAFLD.

Hormonal axes and the development of NAFLD

Androgens

There is emerging data implicating androgens in the pathogenesis of NAFLD that is of relevance to hypogonadal men, those on testosterone replacement as well as the hypogonadism associated with obesity. In addition, circulating and tissue-specific androgen excess in the context of polycystic ovary syndrome (PCOS) may be important in its association with NAFLD.

Having entered the cell, androgens bind to the androgen receptor (AR) and translocate to the nucleus to modulate gene transcription. Mice with liver-specific deletion of the AR develop a greater degree of hepatic steatosis in comparison with obese controls (25). Translational studies have endorsed these findings and have demonstrated an association between hepatic steatosis and low serum testosterone levels (26, 27). In a retrospective cross-sectional study of 495 men, 251 were identified with NAFLD using abdominal ultrasound scanning and the absence of an alternative aetiology; serum testosterone concentrations were

lower in this group (1.4 vs 1.7 pmol/l). Serum testosterone levels were subsequently divided into quintiles and using multiple logistic regression to take account of confounding variables including age, smoking, diabetes, exercise, body mass index (BMI), triglycerides (TGs), high-density lipoproteins (HDL), homeostatic model assessment- insulin resistance (HOMA-IR), C-reactive protein (CRP) and visceral adipose tissue, the lowest quintile of testosterone concentrations (0–1.1 pmol/l) had an odds ratio of 4.52 (2.09–9.80) for the presence of NAFLD (26). In a further retrospective cohort study including 1912 men, hepatic steatosis was also associated with lower serum testosterone levels (14.2 vs 17.2 nmol/l) (27). When patients were divided into quintiles according to serum testosterone and adjusting for the above confounders, low serum testosterone remained associated with hepatic steatosis. Visceral adiposity is a significant risk factor for the development of fibrosis associated with NAFLD (28). A single, 8-year longitudinal study has shown an inverse correlation between serum testosterone and increased BMI and waist circumference (29), suggesting that changes in circulating androgens over time may alter the risk of development of NAFLD.

While there are mechanistic data from preclinical models and observational data linking testosterone levels and NAFLD, there are emerging interventional data. Testosterone replacement in hypogonadal men causes a significant reduction in weight, BMI, waist circumference and circulating TNF α (30). In obese men with obstructive sleep apnoea, testosterone treatment reduced liver fat as measured by computed tomography (CT) without a reduction in BMI or weight (31). Although deranged liver enzymes are poorly predictive of steatohepatitis, testosterone administration has also been shown to decrease alanine transaminase (ALT) and aspartate transaminase (32).

Polycystic ovarian syndrome

PCOS is a complex condition characterised by IR and androgen excess (33, 34). The prevalence of NAFLD within cohorts of obese PCOS patients is elevated and may be as high as 70% (35). Free androgens, IR and NAFLD prevalence are higher in obese patients with PCOS compared with obese, BMI-matched controls, suggesting that PCOS rather than obesity and its associated features is crucial in the development of NAFLD (35). The relative contribution of IR vs androgen excess has been explored in other studies, but the data remain conflicting. In PCOS patients with and without NAFLD, it is IR rather than androgen excess that correlates most closely with the presence of NAFLD (36). Furthermore, in lean patients with PCOS and IR, there was no increase in NAFLD compared with controls (37). In contrast, in a further study in which patients with PCOS matched for obesity and IR with control subjects, hepatic steatosis was associated with higher

circulating androgen levels (38). It is therefore likely that a combination of elevated androgens, obesity and IR contribute to the development of NAFLD in PCOS. The difficulty in teasing out the relationship is augmented by our lack of understanding of the pathogenesis of PCOS and it is inconceivable that this is identical in all patients bearing in mind the variety of clinical presentations associated with the diagnosis of PCOS.

Metformin has been widely used in the symptomatic treatment of patients with PCOS in an attempt to restore insulin sensitivity (39). It has also been used to treat patients with NAFLD with and without diabetes (40). Treating patients with PCOS and NAFLD with metformin improves both insulin sensitivity and liver enzymes. These improvements are associated with a reduction in measures of IR and in the free androgen index (41). Importantly, weight loss through lifestyle modification, which often forms the mainstay of current treatment approaches, results in liver biopsy-proven improvements in NASH in patients with PCOS (42).

The contrasting effects of testosterone deficiency in men contributing to the development of NAFLD with the potential contribution of androgen excess in women with PCOS raises the potential for a 'physiological window' for testosterone (43). However, this needs to be further explored in larger populations of both men and women.

Oestrogens

Preclinical data suggest that oestrogens may protect against the development of NAFLD. Oestradiol (E_2)-treated oophorectomised mice fed a high-fat diet have improved insulin sensitivity, reduced hepatic steatosis and increased export of hepatic TGs in comparison with vehicle-treated animals. In mice lacking the oestrogen receptor, these protective effects were not seen (44). Male aromatase knockout mice that are unable to convert androgens to oestrogens develop hepatic steatosis driven by increased *de novo* lipogenesis and fatty acid uptake. Oestrogen replacement protects against this, suggesting a crucial role for aromatase (45). In addition, antagonising oestrogen action using tamoxifen drives hepatic steatosis (46). Importantly, oestrogen receptor expression and activation vary across the female reproductive cycle and this has been implicated in coordinating hepatic lipid metabolism (47).

These preclinical data are endorsed by clinical observations, suggesting that E_2 may protect men from the development of NAFLD. In a large cross-sectional study in men, low E_2 was associated with the presence of hepatic steatosis (48). Furthermore, tamoxifen when used as an adjuvant chemotherapeutic agent in patients with breast cancer is known to be associated with NAFLD (49).

Postmenopausal women are at an increased risk of developing NAFLD, but whether this relates to the accumulation of metabolic risk factors and the ageing process rather than oestrogen deficiency is less clear

(50). There is emerging evidence to suggest that hormone replacement therapy (HRT) may protect against NAFLD (51), but improvements in cardiovascular risk in postmenopausal patients may be secondary to changes in lipid profile (52). Contrasting with these data, in a double-blind randomised control trial using insulin–euglycaemic clamps, HRT reduced insulin sensitivity in postmenopausal non-diabetic women, with no benefit in body composition (53).

GH and insulin-like growth factor 1

GH and insulin-like growth factor 1 (IGF1) are important for growth and development but are also of ongoing metabolic significance in adult life. GH is secreted by the anterior pituitary under the control of GH-releasing hormone from the hypothalamus and stimulates the hepatic production of IGF1. Both GH and IGF1 are believed to be important in the regulation of hepatic lipid metabolism (54).

The exact mechanisms by which GH and IGF1 deficiency contribute to liver steatosis and fibrosis are not fully understood. Animal models of GH deficiency develop hepatic steatosis and fibrosis that are ameliorated by the administration of GH or IGF1 (55). Alterations in reactive oxygen species and improved mitochondrial function have been suggested as underpinning mechanisms.

In a large cross-sectional study including 1667 patients diagnosed with NAFLD and 5479 controls, random GH levels were lower in the NAFLD group (0.02 vs 0.11 ng/ml) (56). GH levels were negatively correlated with other features of the metabolic syndrome and the NAFLD cohort was significantly older. However, GH levels were negatively associated with NAFLD, independent of age, gender, BMI, waist circumference, mean arterial pressure, ALT, gamma-glutamyl transpeptidase (GGT), lipid profile and fasting plasma glucose. In a smaller study of 160 obese patients, liver biopsy demonstrating NASH with a fibrosis score of ≥ 2 was associated with a GH level of < 0.45 ng/ml (57). Conversely, a smaller study of 55 patients with NAFLD found no association between grade of fibrosis and GH concentrations. Perhaps unsurprisingly, as IGF1 is predominantly produced by the liver, there was a negative correlation between IGF1 and fibrosis stage (58) and low levels of circulating IGF1 in patients with NAFLD has been replicated in other studies (59). Using dynamic tests, peak levels of GH and IGF1 are reduced in patients with NAFLD (60), and in patients with pituitary disease, GH deficiency appears to be associated with increased hepatic lipid content (61).

While the cross-sectional observational data are largely consistent, the interventional data are more controversial. In a series of 69 patients with hypopituitarism in whom GH was not replaced, the prevalence of NAFLD on ultrasound scanning was 77 vs 12% of controls (11). The introduction of GH replacement

reduced liver enzyme concentrations and in the five patients who underwent paired biopsies before and after GH replacement, 6–12 months of treatment improved histological findings (11). A further case report has also identified histological improvement in NAFLD following GH replacement therapy (62). Conversely, in a separate study in patients with GHD, GH replacement decreased subcutaneous and visceral but not hepatic fat (63). The causes of GHD in this study were variable and GH was typically not an isolated deficiency and therefore differences in other hormonal replacement regimes may be important.

To date, there is almost no published cross-sectional or interventional data in patients with acromegaly that have specifically examined the prevalence or progression of NAFLD. However, untreated acromegaly is associated with raised serum TGs (64) and IR and a high visceral adiposity index (65). Perhaps unexpectedly, a single study has shown that co-treatment of acromegaly with a somatostatin analogue and the GH receptor antagonist, pegvisomant, increases intrahepatic lipid (66), but further studies are clearly warranted.

Glucocorticoids

Glucocorticoids (GCs) are produced by the adrenal gland under the control of pituitary ACTH secretion. In addition, they are metabolised at a pre-receptor level by the isoforms of 11 β -hydroxysteroid dehydrogenase (11 β -HSD) and the A-ring reductases (5 α - and 5 β -reductase (5 α R, 5 β R)). 11 β -HSD2 inactivates cortisol to cortisone that is subsequently regenerated by 11 β -HSD1 in key metabolic target tissues including adipose tissue and liver. In contrast, cortisol is cleared and inactivated by both 5 α R and 5 β R.

The actions of GCs upon lipid metabolism in the liver are complex. While in isolation they decrease lipogenesis, in combination with insulin they act synergistically to increase lipid accumulation (67). They also have profound effects on adipose tissue to drive lipolysis as well as adipocyte differentiation. It is their lipolytic action that may well be responsible for enhanced FFA delivery to the liver that may fuel the NAFLD phenotype. Liver-specific disruption of the GC receptor ameliorates lipid accumulation in rodent models (68). In addition, pre-receptor regulation of GC action can also regulate hepatic phenotype. Genetic knockdown of 11 β -HSD1 (69) as well as pharmacological inhibition (70) decreases hepatic steatosis. Interestingly, this may not reflect changes in hepatic GC availability as liver-specific 11 β -HSD1 deletion does not impact significantly on metabolic phenotype and this may point to a more crucial role of GC metabolism within adipose tissue (71). The role of the A-ring reductases has been less well explored, although there is some evidence to suggest that deletion of 5 α R type 1 increases the risk of development of hepatic steatosis (72).

Patients with Cushing's syndrome do develop NAFLD, although this has not been explored in large series. The prevalence of hepatic steatosis measured by liver/spleen attenuation on CT scanning was 20% in a cohort of 50 patients with Cushing's syndrome (73). Importantly, patients with NAFLD do not have 'mild Cushing's syndrome', although abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis have been described including increase in urinary free cortisol concentrations and a reduction in dexamethasone suppression of plasma cortisol (74, 75). Work from our own group has shown that GC metabolism differs between patients with simple steatosis and NASH. In patients with uncomplicated steatosis, 5 α R activity is increased and 11 β -HSD1 decreased while in those with NASH, the activity of 11 β -HSD1 was increased. This suggests that in simple steatosis, the increased clearance of cortisol may represent a protective response to try to limit lipid accumulation, while in NASH, the opposite effect might be aimed at limiting hepatic inflammation (76). The increase in urinary 5 α -reduced GC metabolites has been shown in a further study in patients with NAFLD and NASH; however, hepatic expression of 11 β -HSD1 mRNA was similar in patients and those with normal liver on biopsy (77). An additional study has also demonstrated increased 5 β R activity with increasing hepatic fat (78). Although selective 11 β -HSD1 inhibitors have not been studied in the context of hepatic steatosis, in patients with diabetes, they caused modest improvement in glycaemic control and weight loss and improved lipid profiles (79, 80).

Thyroid

The thyroid hormones, triiodothyronine and thyroxine, are secreted by the follicular cells of the thyroid gland under the control of TSH from the anterior pituitary, which is itself regulated by TRH from the hypothalamus. Thyroid receptor α (THR α) is ubiquitously expressed; THR β is more restricted; however, it is expressed in the liver (81). Thyroid hormones are key regulators of metabolic phenotype, but the demonstration of a clear causal mechanism between thyroid dysfunction and NAFLD has not been established.

Hypothyroidism decreases liver uptake of FFA derived from TGs (82) and is associated with a reduction in adipose tissue lipolysis (83). In addition, TR α knockout mice are protected from hepatic steatosis and peripheral IR (84). Recent work has shown the importance of thyroid hormones for the intrahepatic metabolism of lipids including fatty acid β -oxidation and delivery of fatty acids to mitochondria (85). Conversely, hyperthyroidism promotes adipose tissue lipolysis (86) and hepatic lipogenesis (87).

Overt hypothyroidism has been associated with the development of NAFLD (88). The prevalence of NAFLD, as diagnosed by ultrasound and the exclusion of other causes of hepatic steatosis, in patients with treated

hypothyroidism was 30.2% compared with 19.5% in the control population (10). When adjusted for key determinants of NAFLD risk including age, gender, BMI, hypertension and diabetes, treated hypothyroidism remained predictive (odds ratio 1.38 (1.17–1.62)). The data with respect to subclinical hypothyroidism are more variable with some studies identifying it as an independent risk factor for the presence of hepatic steatosis after correcting for confounding variables (89). However, other studies have failed to confirm this (88).

The reciprocal relationship also appears to hold true. The prevalence of hypothyroidism among a cohort of 246 patients with biopsy-proven NAFLD was 21 vs 9.5% in 430 age-, gender-, race- and BMI-matched controls (90). In addition, the prevalence of hypothyroidism in patients with NASH is higher than those with more benign disease (90, 91). There are currently no published studies that have examined NAFLD in the context of hyperthyroidism.

Pharmacological correction of hypothyroidism is metabolically beneficial, and in a single case report, correction of profound hypothyroidism improved lipid profile and hepatic steatosis, as measured by magnetic resonance spectroscopy (MRS) (92). Administration of thyroid hormones to euthyroid patients is detrimental; however, targeted manipulation of thyroid hormone action could have potential benefits. Endorsing this concept, a hepatic selective TR β agonist reduces hepatic steatosis and circulating FFA and TG levels (93), although at present there are no published clinical data.

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP1) is principally secreted from the L-cells of the small intestine as a cleavage product of proglucagon. It is crucially important in the incretin effect whereby the insulin secretory response is greater following oral rather than parenteral glucose loading. GLP1 has many beneficial metabolic effects including enhanced glucose-dependent insulin secretion, decreased β -cell apoptosis, delayed gastric emptying and decreased appetite (94).

The administration of GLP agonists reduces hepatic steatosis and decreases serum glucose, IR and markers of oxidative stress in rodent models (95, 96), decreasing the expression of lipogenic genes including SREBP-1c and SCD1 and increasing those involved in β -oxidation including PPAR α (95, 97).

There are only very limited clinical data available examining the effect of GLP1 agonists on NAFLD. As part of studies powered to detect changes in glycaemic control in patients with type 2 diabetes and NAFLD, they caused a reduction in intrahepatic lipid as measured by MRS in addition to reductions in body weight and improved glycaemic control (98). In a separate analysis of type 2 diabetic patients treated with Liraglutide, there was a dose-dependent but non-significant improvement in hepatic steatosis,

measured by liver–spleen attenuation ratio as well as improvements in abnormal liver function tests (99). In an open-label study, a small cohort of patients with biopsy-proven NAFLD and diabetes were treated with exenatide, 3/8 had a histological improvement after 28 weeks of treatment (100).

Prolactin

Prolactin is released from the pituitary under the negative feedback of dopamine. Prolactin is also secreted from adipose tissue where regulatory effects upon insulin signalling and adipogenesis have been demonstrated (101). In diet-induced obesity and genetic models of obesity, administration of the dopamine agonist bromocriptine improves hepatic steatosis and markers of mitochondrial oxidative stress; however, prolactin levels were not measured in this study (102).

Despite the evidence to suggest that dopamine agonist treatment may have a beneficial effect on metabolic phenotype causing modest improvement in lipid profiles and in some studies (but not all) body weight and insulin sensitivity, the impact on the incidence and progression of NAFLD has not been examined (103, 104, 105).

Vitamin D

There is an increasing body of evidence supporting a role for vitamin D in the control of metabolic phenotype. In rats fed a western diet, vitamin D depletion exacerbated histological features of NASH as well as increasing markers of oxidative stress and IR (106). Vitamin D depletion is also associated with increased inflammation (107) and phototherapy to restore vitamin D levels reduced hepatic TG accumulation and improved markers of inflammation and fibrosis (107).

In a study of 6567 men who underwent abdominal US and measurement of vitamin D levels, there was a significant association between NAFLD and low vitamin D (108). The lowest tertiles of vitamin D were associated with NAFLD even after adjustment for the presence of other features of the metabolic syndrome. Similar observations have been made in smaller studies; however, in addition, there is some evidence to suggest that vitamin D levels correlate with the stage of fibrosis on liver biopsy (109). Therapeutic interventional trials have not been published.

Insulin

The association between NAFLD and type 2 diabetes is well established and has been reviewed extensively elsewhere (110, 111). Diabetes is an independent risk factor for NAFLD, and in a large cohort of ~170 000 patients with diabetes, the incidence of NAFLD was 18.13/10 000 person years compared with 9.55 in ~650 000 control subjects (112). The converse

relationship is also true. In a 4-year longitudinal study, the proportion of incident diabetes in those with steatosis and an abnormal ALT was 11.8% compared with 3.5% in the control group (113). Furthermore, glycaemic control is worse in patients with type 2 diabetes and coexistent NAFLD (114), and there is an increased rate of complications including coronary and cerebrovascular events (114), diabetic nephropathy (115) and death (116). In patients with type 1 diabetes, NAFLD is associated with higher rates of diabetic nephropathy and cardiovascular disease (117, 118). The prevalence of ultrasound-diagnosed NAFLD in type 1 diabetes is ~50% (117, 119).

Some of the therapeutic options licensed for the treatment of diabetes have shown some benefit in NAFLD in those patients with diabetes. The data for the use of metformin in NAFLD in non-diabetic individuals are conflicting and it is not currently recommended for the treatment of NAFLD in those patients (120). There is some data showing an improvement in liver biopsy findings following thiazolidinedione treatment in non-diabetic patients with NASH. Despite this, there are limited long-term data regarding the safety of the use of thiazolidinediones in diabetic patients with NASH (120).

In physiological conditions, insulin suppresses lipolysis and glucose production and promotes lipogenesis as well as glucose uptake, utilisation and storage (121). In the hyperinsulinaemic, insulin-resistant state, as seen in NAFLD, this tight homeostatic control of lipid and carbohydrate is partially lost. IR is associated with uncontrolled adipose tissue lipolysis as well as increased hepatic expression of fatty acid transporter proteins required for fatty acid uptake into the liver (122). Furthermore, obesity and IR are associated with increased re-esterification of fatty acids (123). Consequently, IR results in increased lipid flux into the liver and results in increased cases of hepatic steatosis (112). In addition to the re-esterification of fatty acids, ~25% of the lipid content within the liver of patients with NAFLD is derived from *de novo* lipogenesis (16). Although insulin promotes lipogenesis, it is clear that systemic IR is also associated with increased hepatic lipogenesis (124). This idea of 'selective' IR whereby insulin fails to suppress hepatic gluconeogenesis while promoting hepatic lipogenesis has been discussed previously but the mechanisms underpinning this are not yet fully elucidated (125). In addition, IR has also been implicated in driving increased β -oxidation and oxidative stress, which is central to the development of NASH (126).

Hyperinsulinaemia and IR are widely accepted as central to the pathogenesis of NAFLD in the context of type 2 diabetes. There are currently few data examining the relationship between type 1 diabetes mellitus and NAFLD (127). Decreased insulin concentrations in the portal circulation may be important; however, the emerging evidence to suggest a component of IR in

patients with type 1 diabetes (128) may implicate similar mechanisms to those observed in type 2 diabetes.

Conclusion

The rising prevalence of NAFLD is undoubtedly fuelled by the epidemic of obesity, type 2 diabetes and IR. However, it is clear that many common endocrine diseases are associated with the development and progression of NAFLD. It is important that the clinical endocrinologist recognises the presence of the condition and its potentially devastating consequences, albeit over a prolonged period of time. It is not only the realisation that NAFLD is associated with common endocrine diseases that is important but also the realisation that inappropriate over or under replacement of many hormonal therapies has the potential to exacerbate the condition. Understanding the hormonal regulation of NAFLD may well lead to advances in its treatment, and hormonal interventions may offer a therapeutic advance, and in the future, therapies targeted to the liver, or perhaps adipose tissue, may offer to avoid the potential for the adverse systemic effects.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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