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Studies on nutrition, body composition and bone mineralization in healthy 8-yr-olds in an urban Swedish community

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VIEW ARTICLE

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Abstract:

ESSENCE OF ARTICLE

“Saturated fat and intake of full fat milk were inversely associated with BMI.”

ARTICLE

Background: The incidence of welfare diseases including overweight in childhood is increasing worldwide. The results from a study of healthy pre-school children showed that in a population with well educated parents 17% of the children were overweight or obese at the age of 4 years. Gender differences in metabolic profiles and correlations between food intake and anthropometry motivated a follow-up study at the age of 8 years. Aim: The aim of the study was to investigate nutritional intake, bone mineralization and metabolic markers in a group of healthy 8-year-olds and relate these parameters to body composition, growth, socio-economic variables, physical activity and health. Subjects & Methods: Ninety-two, previously examined children, accepted participation and an additional 28 children were included. A 24-hour dietary recall was performed. Questionnaires on food choice, health, physical activity and socioeconomic variables were used. Anthropometry was measured and bone mineralization and body composition were assessed by dual energy x-ray absorptiometry. Blood samples were obtained for analysis of metabolic markers. Results: The population was representative of that in Sweden except that more parents held a university degree. Seventeen % of the children were overweight. Glucose, HOMA-index and leptin differed by gender despite no difference in anthropometry. Leptin was the best marker for overweight. Serum concentration of vitamin D was low (<75 nmol/L) in 62% of the children. Food choice was similar to that at 4 years of age suggesting that food habits were established at an early age. Children who consumed fat fish once a week or

more had higher concentrations of n-3 serum phospholipid fatty acids and a lower n-6/n-3 ratio. Intake of saturated fat was negatively associated to anthropometry and children who consumed full fat milk regularly had a lower BMI compared to those who seldom or never drank milk. With the exception for the intake of milk and soft drinks no socioeconomic influences were seen on the children's nutritional intake. Bone mass differed by gender and weight and larger bones were found in boys and overweight children. Physical activity was associated with the bone mass in the hip of both boys and girls. Serum phospholipid fatty acid pattern was associated with bone mineralization. Conclusions: BMI correlated strongly to fat mass and leptin was the best marker of overweight and fat mass in 8-year-olds. Food choice was similar to that at 4 years of age. An intake of fat fish once a week was associated with higher serum concentrations of n-3 fatty acids. Saturated fat and intake of full fat milk were inversely associated with BMI. Serum phospholipid fatty acids were associated with bone mineralisation. The results for metabolic markers may provide preliminary reference intervals in healthy children.

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Yoshikawa I, Nagato M, Yamasaki M, Kume K, Otsuki M.

Long-term treatment with proton pump inhibitor is associated with undesired weight gain.

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ESSENCE OF ARTICLE

“Patients with GERD showed increases in BW (baseline: 56.4 +/- 10.4 kg, end: 58.6 +/- 10.8 kg, mean +/- SD, P < 0.0001) and BMI (baseline: 23.1 +/- 3.1 kg/m², end: 24.0 +/- 3.1 kg/m², P < 0.001), but no such changes were noted in the control group.”

ARTICLE

AIM: To examine the effects of long-term proton pump inhibitor (PPI) therapy on body weight (BW) and body mass index (BMI) in patients with gastroesophageal reflux disease (GERD). METHODS: The subjects were 52 patients with GERD and 58 sex- and age-matched healthy controls. GERD patients were treated with PPI for a mean of 2.2 years (range, 0.8-5.7 years), and also advised on lifestyle modifications (e.g. selective diet, weight management). BW, BMI and other parameters were measured at baseline and end of study. RESULTS: Twenty-four GERD patients were treated daily with 10 mg omeprazole, 12 with 20 mg omeprazole, 8 with 10 mg rabeprazole, 5 with 15 mg lansoprazole, and 3 patients with 30 mg lansoprazole. At baseline, there were no differences in BW and BMI between reflux patients and controls. Patients with GERD showed increases in BW (baseline: 56.4 +/- 10.4 kg, end:

58.6 +/- 10.8 kg, mean +/- SD, P < 0.0001) and BMI (baseline: 23.1 +/- 3.1 kg/m², end: 24.0 +/- 3.1 kg/m², P < 0.001), but no such changes were noted in the control group. Mean BW increased by 3.5 kg (6.2% of baseline) in 37 (71%) reflux patients but decreased in only 6 (12%) patients during treatment. CONCLUSION: Long-term PPI treatment was associated with BW gain in patients with GERD. Reflux patients receiving PPI should be encouraged to manage BW through lifestyle modifications.

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Paper

A Nexus of Progression of Chronic Kidney Disease: Charcoal, Tryptophan and Profibrotic Cytokines

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Key Words

- Indoxyl sulfate
- Uremic toxins
- AST-120

ESSENCE OF ARTICLE

"A novel charcoal compound, AST-120, has been used for over a decade in Japan to prevent progression of CKD....."

Enteric capsules containing *Bifidobacterium longum* have been shown to prevent progression of CKD in a preliminary study."

ARTICLE

Abstract

Fibrosis plays a role in the pathogenesis of progressive chronic kidney disease (CKD). The inhibition of the renin-angiotensin system, which promotes fibrosis, has become the standard of care in the treatment of patients with CKD. A novel charcoal compound, AST-120, has been used for over a decade in Japan to prevent progression of CKD. It is thought that the oral administration of AST-120 blocks the intestinal absorption of tryptophan-derived indole. This prevents the hepatic conversion of indole to indoxyl sulfate (IS). IS has been shown to stimulate the production

of profibrotic cytokines such as transforming growth factor-beta. AST-120 lowers IS in a dose dependent fashion and does not change the creatinine appearance rate in the urine. Enteric capsules containing *Bifidobacterium longum* have been shown to prevent progression of CKD in a preliminary study. These findings suggest that prospective clinical trials be undertaken to determine if these other potential methods of inhibiting fibrosis are useful in slowing progressive CKD.

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From Current Opinion in Gastroenterology

Recent Advances in Nonalcoholic Fatty Liver Disease

Victoria Greenfield; Onpan Cheung; Arun J. Sanyal

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Abstract and Introduction

Abstract

ESSENCE OF ARTICLE

“Considerable new information on the role of insulin resistance, cytokines and adipose tissue in the genesis of NAFLD has been clarified. The clinical presentation and natural history of the disease have been outlined. Several noninvasive diagnostic tools are currently in development. Of the treatments studied, pioglitazone and bariatric surgery have been the most beneficial, although they are limited by several problems related to both safety and efficacy. While many therapies have been studied, it is anticipated that the role of thiazolidinediones, metformin and vitamin E will be resolved in a definitive manner in the near future”

ARTICLE

Purpose of Review: The purpose of this review is to summarize recent advances in defining the clinical features, pathophysiology, natural history, and treatment of nonalcoholic fatty liver disease.

Recent Findings: Nonalcoholic fatty liver disease is present in approximately 30% of the US population. A histologic grading and staging system has been developed and validated. Nonalcoholic fatty liver disease increases the risk of developing the metabolic syndrome. The presence and severity of nonalcoholic fatty liver disease correlates with the severity of obesity, fat distribution, age, and presence of other features of the metabolic syndrome. Fifteen to 20% of subjects with nonalcoholic steatohepatitis develop cirrhosis. Hepatic steatosis is associated with an increase in both free fatty acid delivery to the liver for re-esterification and increased de-novo lipogenesis. Several mechanisms of hepatocyte injury and death including free fatty acid toxicity, increased free cholesterol, cytokine-mediated injury and activation of the unfolded protein response have been defined. While many therapeutic targets have been identified and pilot studies performed, a definitive treatment for nonalcoholic steatohepatitis remains to be established.

Summary: Nonalcoholic fatty liver disease is a widely prevalent disease that is critically linked to insulin resistance and the metabolic syndrome. While much new information on the pathogenesis and natural history of nonalcoholic steatohepatitis is available, an effective therapy remains to be established.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disorder in developing countries. The demographics of the condition mirror those of the metabolic syndrome, which is characterized by obesity, diabetes

mellitus, hypertension and dyslipidemia, with obesity and insulin resistance being the most commonly associated conditions. Many of the risk factors for NAFLD are well defined, but the underlying pathogenesis is not well understood. At present, therapy is aimed at correcting the risk factors, but there are no proven therapies at this point.

Epidemiology

It is now clear that that NAFLD is the most common cause of chronic liver disease in North America. In a large population-based study, in which hepatic steatosis was assessed by magnetic resonance spectroscopy,[1] a third of the population was found to have hepatic steatosis. Interestingly, this was not distributed evenly among ethnic groups with the prevalence of hepatic steatosis in Hispanics at 45%, Caucasians 33% and African Americans 24%. NAFLD is also considered to be the most common cause of persistently elevated liver enzymes, which is present in about 7% of the general population, once viral causes have been excluded.[2] In other studies, it has been shown that the complete histologic spectrum of NAFLD can frequently exist despite normal liver enzymes.[3] It is also appreciated that, in those with normal serum aminotransferase levels, the liver enzymes are higher in those with a higher body mass index.[2,4] This has led to the notion that the currently accepted upper limits of normal for these enzymes may need to be revised.

An important development in the epidemiology of NAFLD is the close relationship between this condition and the features of the metabolic syndrome. While this association has been recognized for over two decades,[5,6] recent studies have shown that the greater the number of features of the metabolic syndrome, the greater the likelihood of having nonalcoholic steatohepatitis (NASH) the progressive form of NAFLD.[7] On the other hand, the presence of NAFLD, as assessed by elevated liver enzymes, was found to be a very strong and independent predictor of the development of metabolic syndrome.[8] The presence of NAFLD is also independently associated with endothelial dysfunction, carotid plaque prevalence and intimal thickness, and ischemic changes on routine ECGs.[9–12] These data indicate that NAFLD is part of a systemic condition that is metabolic syndrome and that the presence of NAFLD worsens the outcomes of the metabolic syndrome.

Pathology and Pathogenesis

The phenotype of NAFLD is characterized by the changes in liver histology. These include hepatic steatosis, inflammation, hepatocyte injury as exemplified by cytologic ballooning and Mallory's hyaline and fibrosis. The NASH clinical research network has developed a grading and staging system of NASH.[13] The NAFLD activity score (NAS) is a method for histologic grading of disease activity and includes the steatosis, cytologic ballooning and inflammation grades. At this time, this is mainly a research tool. While this system has been validated with respect to its reproducibility, its ability to predict long-term outcomes remains to be fully validated. Considerable advanced have been made in recent years in the understanding of the individual histologic features of NAFLD.

Insulin Resistance

It is now well established that insulin resistance is the principal pathophysiologic driver of NAFLD. Insulin resistance is a clinical syndrome defined by impaired metabolic clearance of glucose. In reality, it is associated with a complex set of changes that affect virtually every aspect of cellular and bodily function. Insulin resistance has been associated with obesity, hypertension, diabetes, hypertriglyceridemia, low HDL-cholesterol, hyperuricemia, hyperferritinemia, NAFLD, polycystic ovary syndrome, atherosclerotic heart disease and several types of cancer, for example breast, colon and pancreas.

Recent studies have focused on the role of adipose tissue in the early events leading to insulin resistance (Fig. 1). Adipocytes vary in size; larger adipocytes have greater metabolic activity.[14] In addition to these cells, there are mesenchymal cells, vascular endothelial cells and macrophages in white adipose tissue.[15] The number of CD14+ macrophages in white adipose tissue are directly related to adipose tissue mass (BMI) and are maximal in visceral adipose tissue.[16] In animal studies,[17] weight gain is associated with the appearance of macrophages within

adipose tissue. These changes predate the development of insulin resistance and its attendant metabolic abnormalities.[18] The adipose tissue macrophages are the source of the majority of tumor necrosis factor (TNF)- α produced while adipocytes secrete most of the leptin and half of the interleukin (IL)-6 in adipose tissue.[16] Thus, the appearance of macrophages and elaboration of pro-inflammatory cytokines is a sentinel event in the development of the metabolic syndrome in obesity.

Figure 1. Relationship between obesity, inflammation and insulin resistance

The mechanisms by which macrophage infiltration and activation in white adipose tissue occurs remain to be fully defined. It is currently unclear whether these are solely bone marrow derived macrophages or if adipocytes have trans-differentiated into a macrophage phenotype.[19,20] It has been hypothesized that adipose tissue and the innate immune system are linked by leptin, which decreases during caloric restriction to increase food intake and diminish caloric expenditure by its effects on thyroxine, the reproductive system and innate immunity.[21–23] Leptin deficiency leads to apoptosis of mononuclear cells while leptin promotes proliferation of such cells.[24] Obesity and the metabolic syndrome are associated with high leptin levels, which may drive the innate immune system and inflammation.[21] The role of gut flora and interactions between dietary constituents, gut bacteria and the intestinal epithelium in activation of the innate immune system is an active and exciting area of current investigation.

The principal biologic consequences of the activation of adipocytes in adipose tissue are mediated by the production of adipocytokines. A growing number of adipocytokines that have been recognized (Table 1) have either pro-inflammatory or anti-inflammatory effects. These effects are mediated by alteration of endothelial adhesiveness and permeability, leukocyte migration, adherence and chemotaxis, and endothelial injury. The cytokines produce these effects either directly or indirectly by producing oxidant stress-mediated endothelial injury and induction of pro-inflammatory products at their site of action. In the insulin-resistant state, the profile of cytokines produced is predominantly pro-inflammatory, pro-thrombotic and pro-fibrogenic. The principal metabolic effect of these cytokines is a relatively greater activity of hormone sensitive lipase at any given level of plasma insulin. This results in a net increase in peripheral lipolysis and release of free fatty acids (FFA) into the circulation. FFA impairs insulin signaling in striated muscle and thus decreases the metabolic clearance of glucose. The pancreas responds to the increased glucose and free fatty acids by increasing insulin secretion. Over time, sustained overproduction of insulin induces injury of islet β cells, causing a failure to produce enough insulin to maintain euglycemia and resulting in diabetes.[25]

Table 1. Adipocytokines and their known Effects on Inflammation

Development of Steatosis

Hepatic steatosis represents a balance between lipid synthesis and import on one hand and metabolism and export on the other (Fig. 2). A detailed lipidomic analysis of NAFLD has been recently published.[26•] This study confirmed that hepatic triglyceride accumulation is the hallmark of NAFLD. Importantly, there were also highly significant increases in diacylglycerol (DAG), a highly metabolically active molecule. The increase in DAG–triglyceride ratio in both fatty liver and NASH suggests increased activity of diacylglycerol acyl transferase (DGAT). This leptin-sensitive enzyme moves toxic FFA into a relatively metabolically inert neutral triglyceride storage form and its increased activity may serve a protective function. Indeed, knockout of DGAT II function leads to improved steatosis but more severe lipotoxicity.[27,28] Recent studies, utilizing incorporation of labeled precursors, have also identified increased de-novo lipogenesis (DNL) in very obese subjects with NAFLD.[29] DNL is mediated by enzymes under the transcriptional regulation of sterol regulatory element binding protein-1c (SREBP-1c), which is upregulated by insulin and is likely to be activated by hyperinsulinemia.[30] DNL is also increased by activation of

the cannabinoid receptors on hepatocytes;[31] activation of these pathways has been implicated in the pathogenesis of hepatic steatosis.[31,32]

Figure 2. Interactions between key factors involved in the development of hepatic steatosis

Inflammation

Activation of the innate immune system plays an important role in both the development of the metabolic syndrome and in the sustenance of a systemic pro-inflammatory, profibrogenic state. Fatty acids of the n3 (linolenic acid-derived), n6 (linoleic acid-derived) and n9 (oleic acid-derived) types all have immunomodulatory effects. n-3 Polyunsaturated fatty acids (PUFAs) inhibit lymphocyte proliferation, neutrophil chemotaxis and secretion of IL-1 and TNF- α . [33] Oxidized PUFAs can cause lipid peroxidation and alteration of membrane phospholipid composition. [34,35] The resultant changes in membrane fluidity and eicosanoid production along with the direct effects of lipids on gene expression modulate the activity of transcriptional factors and expression of cell surface molecules such as histocompatibility antigens. [36] Sterols may further modulate the innate immune system via the orphan nuclear receptor liver X receptor (LXR). [37] LXR-mediated gene expression is important for macrophage survival and expression of cytokines for example vascular endothelial growth factor. [38,39] Within the liver, the products of hepatocyte injury and cytokine milieu combine to promote inflammation. The role of chemokines in the genesis of hepatic inflammation has not been studied yet.

Hepatocyte Injury

It has been believed that increased FFA delivery to the liver induces lipotoxicity and thus hepatocyte injury. [40] A recent study, [26] however, found that the hepatic FFA levels do not rise in NAFL or NASH. This does not preclude the possibility that exposure to high circulating FFA may cause hepatotoxicity. Several other mechanisms for hepatotoxicity have also been found to be present in NASH. These include oxidative stress, depletion of n-3 polyunsaturated fatty acids, unfolded protein response and TNF- α mediated cytotoxicity. [26,41–43] Mitochondrial injury is also often present in subjects with NASH and is likely to play a role in the genesis of liver injury and cell death in NASH. [32,42]

Fibrosis

NASH is characterized by sinusoidal fibrosis, which is mediated by activated hepatic stellate cells (HSCs). HSCs are activated by a variety of pro-inflammatory cytokines. Upon activation, they are driven to produce a collagenous matrix, a process stimulated by leptin and insulin. [44,45] The development of fibrosis represents a balance between matrix production and turnover. Matrix production is also further modulated by HSC apoptosis, which can be affected by cannabinoid receptor activation as well. [46]

Clinical Features

The development of NASH has been associated with several medications including tamoxifen. There is also a case report of raloxifene induced NASH. [47] In this case report the patient had acute transaminitis after taking the medication and resolution of the transaminitis after discontinuation. Liver biopsy after discontinuation of the medication was consistent with NASH. The patient did, however, have a family history of cryptogenic cirrhosis and personal risk factors for the development of NASH. Most subjects with NASH, however, have features of the metabolic syndrome.

Most patients are asymptomatic although some complain of vague right upper quadrant pain, fatigue, and occasionally hepatomegaly. The most common presentation is the incidental identification of elevated

transaminases. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are two to five times the upper limit of normal with the AST: ALT ratio usually below one, in contrast to alcoholic liver disease, although the ratio tends to increase as the degree of fibrosis increases. A recent study[48] evaluated the relationship between fat distribution and the hepatic histology in NAFLD. It confirmed the importance of abdominal obesity as a marker of both steatosis and the grade of the disease. Interestingly, about 28% of subjects had increased dorso-cervical fat, which correlated strongly with histologic severity. This raises the possibility of subtle abnormalities in the pituitary–adrenal axis, which may play a role in the genesis of NASH.

The severity of liver disease is also greater in Hispanic subjects and milder in African Americans than in Caucasian subjects.[1,49] In children, the fibrosis and inflammation are often portal-based in contrast to patterns seen in adults.[50]

Diagnostic Studies

A liver biopsy remains the gold standard for the diagnosis, grading and staging of NASH. Fatty liver can be identified on ultrasound as hyperechoic liver, and on computed tomography as low-density hepatic parenchyma but current imaging modalities are unable to distinguish NAFLD from NASH. Biopsy features typically include ballooning degeneration of hepatocytes, Mallory bodies and fibrosis. Because of the anticipated growth in incidence of fatty liver disease and the invasive nature and sampling variability associated with biopsies, other diagnostic strategies are being pursued. Non-invasive tests such as the FibroTest and SteatoTest have previously been developed to predict patients with fibrosis and steatosis respectively.[51] Last year Poynard et al. [52] expanded on this to develop a NASH test that combined 13 parameters to assess the likelihood of the presence of NASH. The NASH test was able to detect NASH with 71% sensitivity and 94% specificity. Their diagnostic utility for identification, grading and staging of NASH remain to be independently validated. Circulating level of cytokeratin-18, a marker of apoptosis, has also been found to correlate with the likelihood of having NASH.[53] This too now awaits independent validation.

Natural History

Fatty liver disease has been considered a benign disease with few long-term sequelae. In fact patients with NAFLD had the same life expectancy as the general population and a low risk of end stage liver disease. A study published in 2005[54] found that among patients with NAFLD fibrosis progressed in 37%, remained stable in 34%, and regressed in 29% of subjects (Table 2). They also noted that low initial fibrosis score, high BMI, and diabetes were associated with progression. Interestingly, 3–5% of subjects with fatty liver were noted to develop cirrhosis. In another excellent study,[55•] 15% of subjects with NASH progressed to cirrhosis over a 10–15-year timeframe. Importantly, this study also confirmed both increased cardiovascular and liver-related mortality in subjects with NASH. In this study, however, most of the excess mortality was seen in subjects with NASH rather than with fatty liver. Compared to alcoholic steatohepatitis, NASH progresses to cirrhosis less frequently and has better long-term survival.[56] Among patients with evidence of steatohepatitis on initial biopsy, 22% progressed to cirrhosis or liver-related mortality while only 4% of patients with steatosis alone progressed to the same endpoints.[57,58]

Table 2. Changes in Fibrosis Stage Over Time in Subjects with Nonalcoholic Steatohepatitis

Once cirrhosis develops, subjects with NASH decompensate at the rate of 4% annually.[59•] This was noted to be somewhat lower than in subjects with cirrhosis due to hepatitis C virus (HCV). This difference was mainly due to a lower rate of development of ascites. Once the Child-Pugh class progressed to class B, the mortality rates between subjects with NASH and HCV were identical. The 10-year risk of development of hepatocellular cancer in cirrhosis due to NASH is about 10%.[55•] This too was noted to be lower than that seen in a control group of subjects with hepatitis C.

The development of cirrhosis is associated with a loss of steatosis and other features of NASH; when all such features are lost, subjects are often categorized as cryptogenic cirrhosis. A higher rate of hepatocellular cancer has been reported in those with cryptogenic cirrhosis than that reported for cirrhosis with features of NASH. This may reflect different propensities for development of cancer at different stages of the disease.

Following liver transplantation, hepatic steatosis recurs almost universally within 3–4 years.[60,61] Many such patients develop steatosis and steatohepatitis sequentially. Recurrent cirrhosis and graft loss has been reported in some individuals with recurrent post-orthotopic liver transplant (OLT) NASH. The vast majority of subjects, however, have 5–10-year graft loss rates comparable to the general population of subjects undergoing OLT.[61]

Treatment

There is currently no approved therapy for NASH. The focus of therapy is therefore to attack the risk factors or protect the liver from harmful factors such as TNF- α . The mainstay of treatment is weight management. The overall efficacy of caloric restriction for the treatment of NAFLD was determined to be 61% based on two studies of liver histology before and after caloric restriction for 261–365 days.[62] A pilot study[63] also suggested benefit with orlistat. Overall about 60% efficacy rates are also noted in subjects undergoing bariatric surgery (Table 3).[64–68] Importantly, a beneficial effect on insulin resistance and liver histology was seen with gastric bypass but not with abdominal liposuction.[69]

Table 3. Studies on Efficacy of Bariatric Surgery in the Improvement of Histologic Features

Two studies have reported outcomes of subjects with NASH with cirrhosis undergoing Roux-en-Y proximal gastric bypass. In the first,[70] two of 14 subjects died after surgery; of the remaining subjects nine underwent a follow-up biopsy and reversal of cirrhosis was seen in eight of nine cases. In another larger study with 91 subjects,[71] there were three early and seven late deaths. Six of the seven late deaths were due to liver failure. Unfortunately, no histological follow-up data are available for the remaining subjects. At this time, the use of bariatric surgery for the treatment of NASH remains experimental.

Several small pilot trials have evaluated the role of insulin sensitizers for the treatment of NASH. The data from studies using metformin have been somewhat discrepant with some studies showing improvement in steatosis while others failing to demonstrate histological improvement.[72–74] A large randomized clinical trial of metformin in children with NASH is currently underway. In contrast to metformin, all of the studies using thiazolidinediones have shown improvement in insulin sensitivity and liver histology. Several small studies also noted an improvement in hepatic fibrosis. In an important and well done trial of pioglitazone in subjects with impaired glucose tolerance or diabetes and NASH, there was significant improvement in liver histology.[75] Unfortunately, this study was underpowered and therefore the results are not definitive. A large definitive trial of pioglitazone in nondiabetic subjects with NASH has been completed by the National Institutes of Health (NIH) NASH Clinical Research Network and the results are awaited.

The excitement about 'glitazones' has to be tempered by recent data suggesting an increased risk of cardiovascular 'events' in subjects receiving rosiglitazone.[76] While there is considerable controversy related to the validity of these reports,[77–79] it is also worth noting that all thiazolidinediones may not be similar with respect to their effects on the lipid profile. Pioglitazone has beneficial effects on the dyslipidemia associated with the metabolic syndrome.[80] Pioglitazone, however, has been associated with an increased risk of heart failure.[81] Surprisingly, the overall mortality and risk of cardiovascular events is decreased with the use of this drug despite the increase in heart failure. Also, all glitazones are associated with an increased risk of osteopenia and fractures especially involving distal limbs in elderly women.[82] Finally, it was recently demonstrated that while the weight gain during

pioglitazone therapy does not reverse after drug discontinuation, the improvement in liver histology reverses to its baseline state.[75]

While vitamin E, an antioxidant, has been reported to reduce liver enzyme levels, there are only minimal histologic data associated with its use. In one pilot study comparing vitamin E (400 IU/day) versus vitamin E and pioglitazone,[83] there was improvement in hepatic steatosis and some improvement in inflammation but no improvement in cytologic ballooning or fibrosis. A large definitive phase III trial of vitamin E for NASH in nondiabetic subjects by the NIH NASH Clinical Research Network has finished enrollment and the results are awaited. Another controversial report has noted a mild but statistically significant increase in all cause mortality in subjects taking vitamin E as a health supplement.[84]

TNF- α is considered to play an important role in the pathogenesis of NASH. Two small studies have evaluated the role of pentoxifylline, which inhibits TNF- α . Both studies noted an improvement in liver enzymes.[85] In one study, however, there was a considerable drop out due to nausea and gastrointestinal adverse effects. The role of this drug and other anti-TNF- α strategies remain to be fully explored.

Several other drugs have been studied in very small pilot trials. These include studies using angiotensin receptor blockers such as losartan, betaine, s-adenosyl methionine, n-3 polyunsaturated fatty acids, hypolipidemic drugs such as fibrates, gemfibrozil, and statins among others. None of these studies are powered adequately to provide either proof of concept that they are definitely effective. Moreover, the potential for publication bias has to be considered when evaluating small positive pilot trials with a great risk of type 1 statistical error. The role of cannabinoid receptor antagonists, which effectively improve insulin resistance, for the treatment of NASH has not been defined.

Conclusion

Considerable new information on the role of insulin resistance, cytokines and adipose tissue in the genesis of NAFLD has been clarified. The clinical presentation and natural history of the disease have been outlined. Several noninvasive diagnostic tools are currently in development. Of the treatments studied, pioglitazone and bariatric surgery have been the most beneficial, although they are limited by several problems related to both safety and efficacy. While many therapies have been studied, it is anticipated that the role of thiazolidinediones, metformin and vitamin E will be resolved in a definitive manner in the near future.

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Table 1. Adipocytokines and their known Effects on Inflammation

Table 2. Changes in Fibrosis Stage Over Time in Subjects with Nonalcoholic Steatohepatitis

Table 3. Studies on Efficacy of Bariatric Surgery in the Improvement of Histologic Features

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AASLD: NASH Patients Perk Up with Vitamin E

By John Gever, Senior Editor, MedPage Today

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Reviewed by Robert Jasmer, MD; Associate Clinical Professor of Medicine, University of California, San Francisco and

Dorothy Caputo, MA, RN, BC-ADM, CDE, Nurse Planner

BOSTON -- Vitamin E and, potentially, pioglitazone (Actos) may become the first effective treatments for non-alcoholic steatohepatitis (NASH), a researcher said here.

About 43% of NASH patients in a randomized, placebo-controlled trial met the study's primary endpoint -- a composite of improved liver function, decreased ballooning, and stabilization of fibrosis -- after about two years of vitamin E treatment, compared with less than 20% of patients on placebo ($P < 0.001$), according to Arun Sanyal, MD, of Virginia Commonwealth University in Richmond.

Some 35% of patients assigned to pioglitazone in the 247-patient trial met the same criteria ($P < 0.04$ versus placebo), Sanyal reported.

Despite the apparent significance, pioglitazone failed to meet the primary endpoint because the trial design stipulated a P value of 0.025 or less relative to placebo, he said.

Action Points

- Explain to interested patients that NASH is a serious, chronic liver disease that often leads to cirrhosis.

- Note that this study was published as an abstract and presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

He said the main reason for the failure appeared to be a fluke of the randomization -- substantially more patients in the pioglitazone group had no ballooning at baseline, and therefore could not show a decrease with treatment.

The data showed that, for most of the individual measures of NASH disease activity, pioglitazone was approximately as effective as vitamin E, Sanyal said, with both agents superior to placebo.

Still, he said, the key finding was that vitamin E was clearly an effective treatment for active NASH.

There is currently no approved approved therapy for NASH.

The two agents were chosen for the study because earlier research suggested that both insulin resistance and oxidative damage are involved in NASH.

Patients were included in the trial if they had biopsy-proven NASH in previous six months, with a Non-Alcoholic Fatty Liver Disease Score of at least 5 with definite or probable steatohepatitis, or a score of 4 if steatohepatitis was agreed on by two of three pathologists.

Exclusion criteria included diabetes, cirrhosis or other liver diseases, prior bariatric surgery, or a recent history of drug therapy for NASH.

Patients were randomized to receive placebo, 30 mg/day of pioglitazone, or 800 IU/day of vitamin E, in the form of rrr α -tocopherol for 96 weeks, at which point a liver biopsy was obtained. Other outcomes were measured at week 120.

Just over half of both the vitamin E and pioglitazone groups showed resolution of NASH, Sanyal said, compared with about 25% of the placebo group ($P < 0.01$ for both active-treatment groups versus placebo).

About 55% of vitamin E patients showed improvement in steatosis, as did some 70% of those taking pioglitazone. In the placebo group, 30% improved.

About the same proportion of each group showed worsening of steatosis during the study, from 15% to 20%.

Most other outcomes also showed improvement with both agents relative to placebo, including:

- Lobular inflammation
- Severity of ballooning
- Proportion of patients with improved ballooning
- Alanine aminotransferase levels

However, there were only weak, nonsignificant trends toward improvement of fibrosis with either vitamin E or pioglitazone. About 40% of both groups showed improvement, as did more than 30% of the placebo group. Fibrosis worsened in roughly 20% of all three groups.

As expected, pioglitazone had two effects not seen with the other treatments. Patients on the drug showed significant weight gain -- about 5 kg on average during the study, compared with less than 1 kg for placebo and vitamin E -- and a lessening of insulin resistance as measured by HOMA-IR scores.

No drug-related adverse events were seen in the trial (weight gain was excluded), and other events were spread evenly among groups.

Sanyal pointed out that the trial was not powered to assess safety issues. He said they would need to be addressed in future studies.

Scott Friedman, MD, president of AASLD and a hepatologist at Mount Sinai School of Medicine in New York City, said the study was among the most important reported at this year's meeting.

"This should resurrect our efforts to use antioxidants for NASH," he said.

However, he cautioned that over-the-counter vitamin E supplements may not have the same effect seen in the trial. He noted that quality of commercial supplements is largely unregulated and may vary from one product to another.

The study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases. Pioglitazone was provided by Takeda. Vitamin E was provided by Pharmavite.

Sanyal reported relationships with Takeda, Salix, Ikaria, Astellas, Pfizer, Gilead, Vertex, Exalenz, Bayer, Onyx, Amylin, sanofi-aventis, and Intercept.

Friedman reported relationships with Exalenz, sanofi-aventis, Axcan, Angion, Intercept, 7TM, Stromedix, and Celera.

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Pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis: PIVENS trial design.

Chalasani NP, Sanyal AJ, Kowdley KV, Robuck PR, Hoofnagle J, Kleiner DE, Unalp A, Tonascia J; NASH CRN Research Group.

Indiana University School of Medicine, Indianapolis, IN, United States

ESSENCE OF ARTICLE

” PIVENS is conducted to test the hypotheses that treatment with pioglitazone, a thiazolidinedione insulin sensitizer, or vitamin E, a naturally available antioxidant, will lead to improvement in hepatic histology in non-diabetic adults with biopsy proven NASH. DESIGN”

ARTICLE

BACKGROUND: Non-alcoholic steatohepatitis (NASH) is a common liver disease associated with obesity and diabetes. NASH is a progressive disorder that can lead to cirrhosis and liver failure. Insulin resistance and oxidative stress are thought to play important roles in its pathogenesis. There is no definitive treatment for NASH.

OBJECTIVES: PIVENS is conducted to test the hypotheses that treatment with pioglitazone, a thiazolidinedione insulin sensitizer, or vitamin E, a naturally available antioxidant, will lead to improvement in hepatic histology in non-diabetic adults with biopsy proven NASH. **DESIGN:** PIVENS is a randomized, multicenter, double-masked, placebo-controlled trial to evaluate whether 96 weeks of treatment with pioglitazone or vitamin E improves hepatic histology in non-diabetic adults with NASH compared to treatment with placebo. Before and post-treatment liver biopsies are read centrally in a masked fashion for an assessment of steatohepatitis and a NAFLD Activity Score (NAS) consisting of steatosis, lobular inflammation, and hepatocyte ballooning. The primary outcome measure is defined as either an improvement in NAS by 2 or more in at least two NAS features, or a post-treatment NAS of 3 or less, and improvement in hepatocyte ballooning by 1 or more, and no worsening of fibrosis. **METHODS:** PIVENS enrollment started in January 2005 and ended in January 2007 with 247 patients randomized to receive either pioglitazone (30 mg q.d.), vitamin E (800 IU q.d.), or placebo for 96 weeks. Participants will be followed for an additional 24 weeks after stopping the treatment. The study protocol incorporates the use of several validated

questionnaires and specimen banking. This protocol was approved by all participating center Institutional Review Boards (IRBs) and an independent Data and Safety Monitoring Board (DSMB) which was established for monitoring the accumulated interim data as the trial progresses to ensure patient safety and to review efficacy as well as the quality of data collection and overall study management. (ClinicalTrials.gov number, NCT00063622).

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