been shown to decrease levels of adiponectin.[5] Thus, a combination of increased TNF-α and decreased adiponectin leads to severe insulin resistance, which in turn leads to NAFLD. Various treatments for NAFLD (e.g., weight loss or use of drugs such as thiazolidinediones) serve to increase adiponectin levels.[5,6]

Adams and associates,[1] in their discussion of the inflammatory and fibrotic mediators of NAFLD, suggest that adiponectin promotes liver fibrosis in NAFLD, but the evidence indicates that the opposite is true. Some clarification seems warranted.

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References

1. Adams LA, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. *CMAJ* 2005;172(7):899-905.
2. Kelley DE, McKolanis TM, Hegazi RA, Kuller LH, Kalhan SC. Fatty liver in type 2 diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. *Am J Physiol Endocrinol Metab* 2003;285:E906-16.
3. Misra A, Garg A. Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature. *Medicine (Baltimore)* 2003;82:129-46.
4. Kern PA, Di Gregorio GB, Lu T, Rassouli N, Ranganathan G. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. *Diabetes* 2003;52:1779-85.
5. Bruun JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, et al. Regulation of adiponectin by adipose tissue-derived cytokines: in vivo and in vitro investigations in humans. *Am J Physiol Endocrinol Metab* 2003;285:E527-33.
6. Yu JG, Javorschi S, Hevener AL, Kruszynska YT, Norman RA, Sinha M, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. *Diabetes* 2002;51:2968-74.

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Leon Adams and associates[1] provide an excellent and up-to-date review of NAFLD in adults,[1] but they do not discuss the condition in children. Childhood NAFLD has been reported globally since our first large clinical series from the Hospital for Sick Children in Toronto was published in 2000.[2] In part this recent reporting reflects the increasing prevalence of obesity in childhood.[3,4] NAFLD is typically diagnosed in children 12–14 years old, but serious liver disease associated with NAFLD has been reported in children as young as 5 years of age.[5,6]

In adults NAFLD must be differentiated from alcoholic liver disease, but in children NAFLD must be distinguished from various rare metabolic disorders that cause fatty liver (such as Wilson disease). The typical child suffers from overnutrition, is asymptomatic or has vague abdominal pain, and may have abnormal results on liver biochemistry testing. As in adults, an important feature of childhood NAFLD is hyperinsulinemia associated with relative insulin resistance, as shown by clinical studies using the homeostasis model of insulin resistance.[5] Whether oxidative damage to the liver is prominent in childhood NAFLD is now being investigated.

NAFLD in adults can progress to cirrhosis with chronic liver failure requiring liver transplantation or to hepatocellular carcinoma, but the long-term outcome for children with NAFLD is unknown. Cirrhosis has been reported in a few children.[6] Although simple steatosis (hepatic fat accumulation without inflammation and fibrosis) carries a benign prognosis in adults, the long-term outcome for children with simple steatosis is uncertain. Current treatment strategies in NAFLD are aimed at eliminating or reducing the risk factors associated with NAFLD: they involve weight loss and increased physical activity. Few pediatric data are available regarding pharmacologic interventions such as vitamin E, ursodiol and metformin.[7-9] Well-designed prospective studies in children are urgently needed to determine the best overall medical management.

Childhood NAFLD may be the hepatic manifestation of the metabolic dysregulation leading to type 2 diabetes, hypertension and cardiovascular disease. Given that childhood NAFLD is highly prevalent — estimated at 3% to 10% of obese children — we need to intervene now so as to avoid cirrhosis, as well as these other diseases, in the current generation of children.

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References

1. Adams LA, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. *CMAJ* 2005;172(7):899-905.
2. Rashid M, Roberts EA. Nonalcoholic steatohepatitis in children. *J Pediatr Gastroenterol Nutr* 2000;30:48-53.
3. Canning PM, Courage ML, Frizzell LM. Prevalence of overweight and obesity in a provincial population of Canadian preschool children. *CMAJ* 2004:171(3):240-2.
4. Janssen I, Katzmarzyk PT, Boyce WF, Vereecken C, Mulvihill C, Roberts C, et al; Health Behaviour in School-Aged Children Obesity Working Group. Comparison of overweight and obesity prevalence in school-aged youth from 34 countries and their relationships with physical activity and dietary patterns. *Obesity Rev* 2005;6:123-32.
5. Schwimmer JB, Deutsch R, Rauch JB, Behling C, Newbury R, Lavine JE. Obesity, insulin resistance and other clinicopathological correlates of pediatric nonalcoholic fatty liver disease. *J Pediatr* 2003;143:500-5.
6. Roberts EA. Non-alcoholic fatty liver disease (NAFLD) in children. *Front Biosci* 2005;10:2306-18. Available: www.bioscience.org/ (by subscription or purchase).
7. Lavine JE. Vitamin E treatment of nonalcoholic steatohepatitis in children: a pilot study. *J Pediatr* 2000;136:734-8.
8. Vajro P, Franzese A, Valerio G, Iannucci MP, Aragione N. Lack of efficacy of ursodeoxycholic acid for the treatment of liver abnormalities in obese children. *J Pediatr* 2000;136:739-43.
9. Schwimmer JB, Middleton MS, Deutsch R, Lavine JE. A phase 2 clinical trial of metformin as a treatment for non-diabetic paediatric non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2005;31:871-9.

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[The authors respond:]

As Pankaj Madan points out, adiponectin is an insulin-sensitizing hormone secreted by adipose tissue; its levels are lower among people with central obesity, which is a common characteristic of patients with NAFLD. Our review[1] incorrectly stated that leptin and adiponectin promote liver fibrogenesis in animal models, where it should have stated that leptin and adiponectin affect fibrogenesis in animal models.

Adiponectin may protect against NAFLD by multiple mechanisms. In animal models of NAFLD, adiponectin supplementation improves hepatic steatosis by increasing hepatic free fatty acid oxidation.[2] Correspondingly, in human cross-sectional studies, serum adiponectin is inversely correlated with degree of hepatic steatosis.[3,4] Furthermore, experimental liver injury and fibrosis, which are enhanced in adiponectin knock-out mice, are ameliorated by adiponectin supplementation.[5–7] Consistent with this observation is the finding that the hepatic expression of adiponectin is lower among patients with nonalcoholic steatohepatitis than among those with steatosis.[8] However, serum adiponectin levels do not appear to correlate with fibrosis, nor are they consistently associated with degree of necroinflammation.[3,4] Thus although an increasing body of evidence from in-vitro and animal studies supports the "hepatoprotective" effect of adiponectin, the exact role in the pathogenesis of human NAFLD requires further investigation and is eagerly awaited.

Diana Mager and Eve Roberts correctly point out that NAFLD is being increasingly recognized among children. As stated in our article, the prevalence of this condition among school children (4–12 years of age), as detected by ultrasonography, is 2.6%,[9] increasing to 22.5% among obese children. Unfortunately, space limitations prevented us from discussing this important issue further in the original review. The significance of this common liver condition among children remains to be determined, and thus the need for specific treatment aimed at preventing progression to cirrhosis is unknown, particularly as we are unable to accurately identify those who will experience liver-related complications. Intuitively, we might expect a greater risk of advanced hepatic fibrosis with a longer duration of "hepatic fat exposure" from childhood, which would place these subjects at risk for liver disease later in life. Clearly, further research on this important topic is needed. It is important, however, to recognize that the metabolic conditions frequently accompanying pediatric (and adult) NAFLD place these patients at risk of complications such as cardiovascular disease (and perhaps cirrhosis), and intervention is therefore essential.

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References

1. Adams LA, Angulo P, Lindor KD. Nonalcoholic fatty liver disease. *CMAJ* 2005;172(7):899-905.
2. Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest* 2003;112:91-100.
3. Bugianesi E, Pagotto U, Manini R, Vanni E, Gastaldelli A, De Iasio R, et al. Plasma adiponectin in nonalcoholic fatty liver is related to hepatic insulin resistance and hepatic fat content, not to liver disease severity. *J Clin Endocrinol Metab* 2005;90:3498-504.
4. Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology* 2004;40:46-54.
5. Sennello JA, Fayad R, Morris AM, Eckel RH, Asilmaz E, Montez J, et al. Regulation of T cell-mediated hepatic inflammation by adiponectin and leptin. *Endocrinology* 2005;146:2157-64.
6. Masaki T, Chiba S, Tatsukawa H, Yasuda T, Noguchi H, Seike M, et al. Adiponectin protects LPS-induced liver injury through modulation of TNF-alpha in KK-Ay obese mice. *Hepatology* 2004;40:177-84.
7. Kamada Y, Tamura S, Kiso S, Matsumoto H, Saji Y, Yoshida Y, et al. Enhanced carbon tetrachloride-induced liver fibrosis in mice lacking adiponectin. *Gastroenterology* 2003;125:1796-807.
8. Kaser S, Moschen A, Cayon A, Kaser A, Crespo J, Pons-Romero F, et al. Adiponectin and its receptors in non-alcoholic steatohepatitis. *Gut* 2005;54:117-21.
9. Tominaga K, Kurata JH, Chen YK, Fujimoto E, Miyagawa S, Abe I, et al. Prevalence of fatty liver in Japanese children and relationship to obesity. An epidemiological ultrasonographic survey. *Dig Dis Sci* 1995;40:2002-9.

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Corrections

An error in the recent obituary of Dr. William Tatlow[1] was pointed out to us, as follows, by Dr. Joseph Stratford, a long-time friend and colleague of the late Dr. Tatlow. "[A]ll is fine until you come to the point where it says 'out for his morning *job* when he fell.' [I]t is true that Bill had continued working, reading EEGs, and he was a consultant for certain pharmaceutical companies, so in a sense he did have a 'job,' but that morning, out at Hudson, he was out for his morning *jog* when he fell." We apologize for our mistake.

Reference

1. Deaths. *CMAJ* 2005;173(3):323.

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The following information was mistakenly omitted from a recent article.[1] Steven Grover has conducted research supported by Pfizer, Bristol-Myers Squibb, Aventis and AstraZeneca. He has received consulting fees from Pfizer and AstraZeneca and speaker fees from Pfizer, Oryx and Aventis. He owns stock in Pfizer, Merck, Bristol-Myers Squibb and Kos.

Reference

1. Hemmelgarn BR, Grover S, Feldman RD, for the Canadian Hypertension Education Program. Applying the 2005 Canadian Hypertension Education Program recommendations: 2. Assessing and reducing global atherosclerotic risk among hypertensive patients. *CMAJ* 2005;173(6):593-5.

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