Waist circumference correlates with liver fibrosis in children with non-alcoholic steatohepatitis

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ABSTRACT

Objective: Waist circumference is widely accepted as a risk factor for cardiovascular disease and metabolic syndrome. Non-alcoholic fatty liver disease (NAFLD) is a feature of the metabolic syndrome. A contribution of metabolic syndrome, and especially of waist circumference, to liver fibrosis in children with NAFLD is strongly suspected.

Design: Cross-sectional study.

Setting: Department of Hepatogastroenterology and Nutrition, Paediatric Hospital "Bambino Gesù", Rome, Italy.

Patients: 197 consecutive Caucasian children with NAFLD (136 males and 61 females) aged 3–19 years.

Main outcome measures: Multivariable logistic regression models were used to examine the contribution of gender, age, body mass index (BMI) and metabolic syndrome components (waist circumference, high-density lipoprotein (HDL)-cholesterol, triglycerides, blood pressure and glucose) to the odds of liver fibrosis as detected by liver biopsy.

Results: 92% of the children had BMI $\geqslant 85^{th}$ percentile and 84% had a waist $\geqslant 90^{th}$ percentile for gender and age. Ten per cent of the children had metabolic syndrome and 67% had liver fibrosis, mostly of low degree. At multivariable analysis, waist was the only metabolic syndrome component to be associated with liver fibrosis. This was seen both when the components of the metabolic syndrome were coded as dichotomous (odds ratio (OR) = 2.40; 95% confidence interval (CI), 1.04 to 5.54) and continuous (OR = 2.07; 95% CI, 1.43 to 2.98 for a 5 cm increase). In the latter case, age was also associated with the outcome (OR = 0.70; 95% CI, 0.55 to 0.89 for a 1 year increase).

Conclusions: Abdominal rather than generalised obesity contributes to liver fibrosis in children with NAFLD. Waist is also the only component of the metabolic syndrome to be associated with fibrosis in these children. Therefore, the presence of abdominal obesity is an additional criterion for the selection of children and adolescents who should undergo extensive investigation, including liver biopsy.

Paralleling childhood obesity, non-alcoholic fatty liver disease (NAFLD) is a growing problem in Westernised countries and is rapidly becoming one of the most important chronic liver diseases in children.[1] NAFLD is strongly associated with the metabolic syndrome, single co-morbidities defining this syndrome, and, of course, type 2 diabetes.[2]

Liver biopsy is required to distinguish simple steatosis from necro-inflammation (non-alcoholic steatohepatitis, which is termed NASH), to stage the degree of fibrosis and to rule out competing diagnoses.[3 4] Staging the degree of fibrosis is of particular interest since fibrosis may be associated with progressive liver injury. In addition to the cost, liver biopsy is not without risk, including haemorrhaging and even death.[5] Additional concerns may be raised with children and adolescents so that it seems more difficult to propose liver biopsy in the paediatric setting.

There is, therefore, a recognised need for non-invasive tests to screen or diagnose subjects with NAFLD at risk of liver fibrosis. Laboratory parameters and combinations of laboratory and clinical parameters have been proposed for this purpose.[6 7] Because metabolic syndrome is a risk factor for fibrosis in adults with NAFLD,[8] it is possible that it or some of its components may be used to predict fibrosis also in children with NAFLD.

The aim of the present study was to evaluate the relationship between the metabolic syndrome, especially abdominal obesity as detected by waist circumference, and liver fibrosis, in young patients with NAFLD. Our main hypothesis was that, besides overall obesity (as detected by body mass index and by a direct measure of body fat), abdominal obesity (as detected by waist circumference) might be a risk factor for liver fibrosis in children with NAFLD.

PATIENTS AND METHODS

Patients

One hundred and ninety-seven Caucasian children (3–19 years) with NAFLD were consecutively enrolled into the study at the Hepatogastroenterology and Nutrition Unit of the "Bambino Gesù" Paediatric Hospital (Rome, Italy) between January 2003 and September 2007. The study sample comprises two series previously reported by our group.[2 9–12] Criteria for suspecting NAFLD were: (1) serum aminotransferases persistently elevated and/or fluctuating between normal and high levels (with at least two high levels during the 6 months prior to the enrolment); (2) diffusely echogenic liver at ultrasonography; (3) absence of alcohol intake; and (4) absence of hepatic virus infection or known liver disease, parenteral nutrition and drugs of any kind.[2] The final diagnosis of NAFLD and NASH was obtained by liver biopsy in all cases. The nature and purpose of the study were carefully explained to the children's guardians who gave their written consent.

Anthropometry

Weight and height were measured using standard procedures.[13] The z-score of body mass index (BMI) was calculated using United States reference values

Table 1 Measurements of the 197 children with non-alcoholic fatty liver disease (NAFLD)

	Males (n = 136)				Females (n = 61)				Mann–Whitney test
Measurement	Median	IQR	Min	Max	Median	IQR	Min	Max	p Value
Age (years)	12.3	3.2	4.7	19.1	11.9	4.0	3.3	18.2	0.446
Weight (kg)	63.4	26.7	19.4	107.0	55.6	32.0	14.0	128.0	0.084
Height (m)	1.53	0.17	0.99	1.87	1.47	0.23	0.86	1.87	0.050
BMI (kg/m^2)	26.0	6.0	16.5	40.7	26.0	6.9	15.2	38.3	0.554
z-BMI (SDS)	1.9	0.7	0.6	4.1	1.8	0.8	−1.7	2.9	0.319
Waist (cm)	92	11	60	110	91	17	60	110	0.396
Body fat (kg)	15.8	9.8	2.2	41.8	15.2	12.6	2.8	49.1	0.297
Per cent body fat	26.1	8.8	11.1	64.5	26.5	8.1	9.5	49.7	0.997
ALT (U/l)	67	43	10	388	63	39	18	407	0.431
AST (U/l)	44	22	16	164	43	24	19	187	0.476
GGT (U/l)	21	18	10	130	18	11	10	104	0.003
Cholesterol (mg/dl)	164	45	75	243	151	42	90	250	0.105
HDL-cholesterol (mg/dl)	48	23	21	70	33	23	11	71	0.071
Triglycerides (mg/dl)	83	56	24	424	90	48	28	351	0.464
Systolic BP (mm Hg)	108	20	80	161	110	22	90	161	0.264
Diastolic BP (mm Hg)	70	10	50	84	69	10	50	84	0.649
Glucose (mg/dl)	81	12	52	138	79	10	56	138	0.088
Insulin (μU/ml)	11.7	11.1	3.0	79.0	12.0	6.1	3.5	32.5	0.634
HOMA-IR	2.5	2.2	0.5	16.0	2.2	1.4	0.7	6.3	0.432

ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BP, blood pressure; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment-insulin resistance; IQR, inter-quartile range; max., maximum; min., minimum; SDS, standard deviation score; z-BMI, z-score of BMI.

and is given as standard deviation score (SDS).[14] Overweight was defined as BMI ⩾85th (1.036 SDS) and <95th (1.645 SDS) percentiles, and obesity as a value of BMI ⩾95th (1.645 SDS) percentile for gender and age. Waist circumference was measured at the highest point of the iliac crest with a standing subject.[15] A large waist was defined as waist ⩾90th percentile for age and gender using US reference values.[16]

Body composition

Total body fat was measured by dual-energy *x* ray absorptiometry using a QDR-1500 densitometer (Hologic, Waltmann, MA, USA) in the pencil beam mode with enhanced whole body analysis (software version 5.67).[17] The per cent body fat was calculated as (total body fat/body weight)×100, where body fat and body weight are in kilograms.

Laboratory assessment

Fasting glucose, triglycerides, cholesterol and high-density lipoprotein (HDL)-cholesterol were measured using standard laboratory methods. Insulin was measured by radioimmunoassay (MYRIA Technogenetics, Milan, Italy) with a lower limit of sensitivity of 0.3 μU/ml and an inter-assay coefficient of variation ranging from 2.9 to 4.8%. Impaired fasting glucose or diabetes was defined as fasting glucose ⩾100 mg/dl;[18] hypertriglyceridaemia as fasting triglycerides ⩾150 mg/dl;[18] low HDL-cholesterol as fasting HDL <40 mg/dl in subjects <16 years of age and <40 mg/dl in males or <50 mg/dl in females aged ⩾16 years.[18] A value of >3.0 for the homeostasis model assessment-insulin resistance (HOMA-IR) was taken as a surrogate measure of insulin resistance.[1 19]

Blood pressure

After a 5 min rest, blood pressure was measured with an aneroid sphygmomanometer (Taylor Instruments, Asheville, NC, USA) equipped with a cuff appropriate for arm size.[20] Three measurements were performed and the average of the last two measurements was taken as the measure of blood pressure. Hypertension was defined as a value of systolic blood pressure ⩾130 mm Hg or diastolic blood pressure ⩾85 mm Hg.[18]

Metabolic syndrome

Metabolic syndrome was defined as three or more of the following: large waist, low HDL-cholesterol, hyper-triglyceridaemia, hypertension and impaired fasting glucose or diabetes.[18 21]

Liver histology

Biopsies were performed and processed as described elsewhere.[2 9–12] Steatosis, inflammation (portal and lobular), hepatocyte ballooning and fibrosis were scored using the NASH Clinical Research Network criteria.[4] Steatosis was graded as 0 = involving <5%; 1 = involving up to 33%; 2 = involving 33–66%; and 3 = involving >66% of hepatocytes. Lobular inflammation was graded as 0 = no foci; 1 = fewer than 2 foci per ×200 field; 2 = 2–4 foci per ×200 field; and 3 = more than 4 foci per ×200 field. Hepatocyte ballooning was graded as 0 = none; 1 = few balloon cells; and 2 = many/prominent balloon cells. Fibrosis was graded as: 0 = no fibrosis; 1 = perisinusoidal or periportal; 2 = perisinusoidal and portal/periportal; 3 = bridging; and 4 = cirrhosis. Portal tract inflammation was graded as 0 = none; 1 = mild; 2 = moderate; and 3 = severe. Features of steatosis, lobular inflammation, and hepatocyte ballooning were

Table 2 Frequency of the metabolic syndrome and its components in the 197 children with non-alcoholic fatty liver disease (NAFLD)

	n (%)
Large waist	166 (84.26)
Low HDL-cholesterol	99 (50.25)
Hyper-triglyceridaemia	25 (12.69)
Hypertension	26 (13.20)
Impaired fasting glucose or diabetes	10 (5.08)
⩾ 3 of the above (metabolic syndrome)	20 (10.15)

HDL, high-density lipoprotein.

combined to obtain the NAFLD activity score (NAS). Cases with NAS ≥5 were diagnosed as NASH, cases with NAS ≤ 2 as simple steatosis, and cases between these values as indeterminate.[4]

Statistical analysis

Continuous variables are given as median, interquartile range (IQR) and minimum and maximum values because of skewed distributions. IQR was calculated as the difference between the 75th and 25th percentiles. Between-group comparisons of continuous variables were performed with the Wilcoxon–Mann–Whitney test. Correlation analysis was performed using Spearman's rho. Three pre-specified multivariable logistic regression models were used to examine the relationship between liver fibrosis and metabolic syndrome components. The outcome variable of the models was liver fibrosis of any degree (1 = yes; 0 = no). The predictors of model 1 were age (continuous), gender (1 = male; 0 = female), overweight or obesity (1 = yes; 0 = no) and the metabolic syndrome components (large waist, low HDL-cholesterol, hyper-triglyceridaemia, hypertension and impaired fasting glucose or diabetes) coded as dichotomous (1 = yes; 0 = no).[18 21] Model 2 avoided dichotomisation of all predictors that could be evaluated as continuous.[22] In model 2, age was modelled as a 1 year increase, BMI as a 1 kg/m^2 increase, waist as a 5 cm increase, HDL-cholesterol and triglycerides as a 10 mg/dl increase, systolic and diastolic blood pressure as a 10 mm Hg increase and glucose as a 10 mg/dl increase. Multivariable fractional polynomials were used to test whether model fit could be improved by transformation of continuous predictors.[23] Because there was no substantial gain in model fit, the predictors were left untransformed in the final model. Lastly, model 3 added per cent body fat (continuous and modelled as a 10% increase) to the predictors of model 2 to test whether body composition modified the relationship between liver fibrosis and metabolic syndrome. Model fit was checked using standard diagnostic plots and the Hosmer–Lemeshow statistic.[24] Statistical significance was set to a p-value <0.05. All statistical tests are two-tailed. Statistical analysis was performed using STATA 10.0 (StataCorp, College Station, TX, USA).

RESULTS

One hundred and ninety-seven Caucasian children with NAFLD were studied. Table 1 gives their measurements stratified by gender. Males (n = 136) and females (n = 61) had similar measurements with the exception of gamma-glutamyl transferase (GGT), which was higher in males (p = 0.003).

Fifty-four children (27%) were overweight and 128 (65%) were obese. Table 2 gives the frequency of metabolic syndrome and its components. Eighty-four per cent of children had a large waist, 50% had low HDL-cholesterol, 13% had hyper-triglyceridaemia, 13% had hypertension and 5% had impaired fasting glucose or diabetes. Metabolic syndrome, defined as three or more of the above, was present in 10% of the children. Insulin resistance, as detected by a value of HOMA ≥3, was present in 75 (38%) children.

Table 3 gives the features of liver biopsies. Steatosis was mild to moderate and inflammation mild in most cases; ballooning was present in about one in every two children; lastly, 67% of patients had fibrosis, which was mild in most cases. Sixty children (30%) had NASH.

Table 4 gives the three multivariable models that were used to examine the relationship between gender, age, BMI, metabolic syndrome components and the odds of liver fibrosis (see the section 'Statistical analysis' for details). In model 1, all predictors besides age are dichotomous, reflecting the operational definition of the metabolic syndrome.[18 21] According to model 1, the only significant risk factor for liver fibrosis is a large waist (OR = 2.40; 95% CI, 1.04 to 5.54). The precision of this estimate is low, however, because of the dichotomisation of the predictors.[22] Model 2 employs all variables besides gender as continuous and shows that age (OR = 0.70, 95% CI, 0.55 to 0.89 for a 1 year increase) is (inversely) associated with the outcome together with waist (OR = 2.07; 95% CI, 1.43 to 2.98 for a 5 cm increase). Expectedly,[16 25] age and waist were positively and strongly correlated (Spearman's rho = 0.79, p<0.0001). As can be seen from the trivial changes of the ORs of model 3, which added body fat to the predictors of model 2, body composition did not confound the relationship between liver fibrosis and metabolic syndrome.

DISCUSSION

In children and adolescents with NAFLD, metabolic syndrome might confer a greater risk of serious liver disease.[2] The present study, which examined the association between liver fibrosis and metabolic syndrome, shows that waist circumference is the only component to be independently associated with liver fibrosis in children with NAFLD.

The prevalence of obesity and its associated complications is dramatically increasing in childhood, assuming almost epidemic proportions.[26] The observed association with NAFLD makes it essential for health care providers to pay attention to preventing, diagnosing and treating fatty liver disease at an early age.[1] Similarly to adults, the assessment of abdominal fat may represent a valuable tool for identifying those children with NAFLD who have liver fibrosis. We have recently observed that higher BMI and older age both increase the risk of developing liver fibrosis.[10] BMI is a well-established measure of total fatness and cardiometabolic risk which requires only simple measurements of weight and height. The rationale for using waist circumference in clinical practice is that it is a surrogate measure of abdominal fat and, most important, a predictor of early and late cardiometabolic complications of childhood obesity.[25 27]

We assume that the prevalence of NAFLD in children and adolescents is increasing in parallel with the escalation of central obesity as detected by the progressive increase of waist circumference.[15] Abdominal obesity contributes to the reduction of hepatic and systemic insulin sensitivity,[1] and, for that reason,

Table 3 Features of the liver biopsies of the 197 children with non-alcoholic fatty liver disease (NAFLD)

	0		1		2		3	
	n	%	n	%	n	%	n	%
Steatosis	0	0.00	62	31.47	78	39.59	57	28.93
Inflammation	23	11.68	146	74.11	26	13.20	2	1.02
Ballooning	106	53.81	51	25.89	40	20.30	–	–
Fibrosis	64	32.49	114	57.87	7	3.55	12	6.09

Table 4 Multivariable analysis of risk factors for liver fibrosis in the 197 children with non-alcoholic fatty liver disease (NAFLD)

	Model 1		Model 2		Model 3	
Characteristic	**OR (95% CI)**	**p Value (Wald)**	**OR (95% CI)**	**p Value (Wald)**	**OR (95% CI)**	**p Value (Wald)**
Male gender	0.73 (0.36 to 1.50)	0.394	0.70 (0.33 to 1.51)	0.369	0.71 (0.33 to 1.51)	0.370
Age (years)*	1.11 (0.99 to 1.24)	0.072	0.70 (0.55 to 0.89)	0.003	0.70 (0.55 to 0.90)	0.005
Overweight or obese	2.30 (0.72 to 7.37)	0.161	–	–	–	–
Large waist	2.40 (1.04 to 5.54)	0.040	–	–	–	–
Low HDL-cholesterol	0.62 (0.32 to 1.22)	0.167	–	–	–	–
Hypertriglyceridaemia	3.20 (0.85 to 12.04)	0.086	–	–	–	–
Hypertension	2.37 (0.74 to 7.57)	0.145	–	–	–	–
IFG or diabetes	0.50 (0.12 to 2.09)	0.343	–	–	–	–
BMI (kg/m^2)*	–	–	1.01 (0.92 to 1.10)	0.886	1.00 (0.88 to 1.14)	0.958
Waist (cm)†	–	–	2.07 (1.43 to 2.98)	<0.0001	2.06 (1.43 to 2.98)	<0.0001
HDL (mg/dl)‡	–	–	1.23 (0.92 to 1.65)	0.162	1.23 (0.92 to 1.65)	0.162
Triglycerides (mg/dl)‡	–	–	1.07 (0.99 to 1.15)	0.089	1.07 (0.99 to 1.15)	0.090
Systolic BP (mm Hg)‡	–	–	1.20 (0.91 to 1.59)	0.198	1.20 (0.91 to 1.59)	0.198
Diastolic BP (mm Hg)‡	–	–	0.85 (0.52 to 1.39)	0.520	0.85 (0.52 to 1.39)	0.525
Glucose (mg/dl)‡	–	–	0.91 (0.67 to 1.22)	0.520	0.91 (0.67 to 1.22)	0.519
Per cent body fat‡	–	–	–	–	1.02 (0.49 to 2.14)	0.950
p Value model (LR-test)	0.003		<0.0001		<0.0001	
p Value HL statistic	0.2790		0.7214		0.6315	

Model 1 employs dichotomous predictors (besides age); model 2 employs continuous predictors (besides gender); and model 3 adds per cent body fat (continuous) to the predictors of model 2.
*Continuous and modelled as a 1 unit increase.
†Continuous and modelled as a 5 unit increase.
‡Continuous and modelled as a 10 unit increase.
BMI, body mass index; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; HL statistic, Hosmer–Lemeshow statistic; IFG, impaired fasting glucose; LR, likelihood ratio; OR, odds ratio.

it is very likely to play a major role in the pathogenesis of NAFLD.[8] In the presence of central obesity, the increased amount of visceral adipose tissue is more resistant to insulin, exhibits a greater lipolysis, and produces more free fatty acids than adipose tissue does in other sites.[28] The increased availability of substrate for lipogenesis and the relative hyperinsulinaemia due to insulin resistance enhance hepatic lipogenesis leading to a vicious cycle mechanism.[29]

The present study is the first to investigate the relationship between abdominal adiposity and liver fibrosis in a large series of children and adolescents with NAFLD. In a similar study performed in adults,[30] the distribution of fat, both at the abdominal and dorso-cervical level, was significantly associated with inflammation and fibrosis. Fat distribution at the dorso-cervical level was indeed the single most significant contributor to the severity of histological diagnosis. This contribution was enhanced by the addition of BMI and waist circumference to dorso-cervical adiposity in the predictive model. In our series, waist circumference but not BMI explained this variability at multivariable analysis. Worthy of note is that we did not detect fat deposition at the dorso-cervical level, likely because the so-called ''buffalo hump'' may develop later in the natural history of the disease in adults in whom a secondary dysfunction of the hypopituitary–adrenal axis occurs.

A ''large waist'' is an integral part of the definition of paediatric and adult metabolic syndrome.[18 21] In this study, we defined a large waist as one $\geq 90^{th}$ percentile for age and gender.[16 18 21] When dichotomised at this value, waist circumference was the only independent predictor of liver fibrosis. That this was not an effect of the dichotomisation is shown by the fact that waist was even a more precise predictor of liver fibrosis when employed as continuous variable. Expectedly, age entered in the latter model because waist and age are strongly and positively associated.[16] Unfortunately, waist circumference is often measured at different sites and a standardisation of its measurement has yet to be reached.[31–33] Because waist circumference is a predictor of liver fibrosis in children with NAFLD, it is extremely important that its measurement be standardised for future studies.

None of the metabolic syndrome components besides waist was associated with liver fibrosis in the present study. This is not attributable to the dichotomisation of the components employed by the definition of metabolic syndrome because the lack of association persisted when continuous predictors (even if the precision of the estimate was much higher in the latter case) were used. This finding reinforces the importance of separately evaluating the contribution of metabolic syndrome components to the risk of liver disease.[34]

In conclusion, abdominal rather than generalised obesity contributes to liver fibrosis in children with NAFLD. Therefore, the presence of abdominal obesity, as estimated by waist circumference, should be considered an additional criterion for the selection of children and adolescents who should undergo extensive investigation, including liver biopsy.

Competing interests: None.

Ethics approval: The study protocol conformed to the Declaration of Helsinki and the recommendations of the Ethics Committee at the ''Bambino Gesù'' Hospital.

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Editor's quiz: GI snapshot

ANSWER

From the question on page 1261

Figures 2 and 3 show a voluminous hiatal hernia with entrapment of stomach, colon, mesenteric fat and the entire pancreas. Furthermore, upon endoscopic examination, the stomach showed an additional secondary organo-axial volvulus with anterior rotation and obstruction of the pylorus without ischaemia. A nasogastric tube was left in place in an attempt to reduce the volvulus endoscopically. Finally, surgical repair of the defect was obtained with subsequent clinical and biochemical recovery.

Intrathoracic herniation of the pancreas represents a rare cause of pancreatitis and may result from a combination of parenchymal ischaemia caused by abnormal traction on the vascular pedicle, direct trauma to the parenchyma upon repetitive passage through the diaphragm and/or intermittent folding of the main pancreatic duct.[1 2] This entity should be taken into consideration when confronted with large hiatal hernias and biochemical suggestion of biliary pancreatitis.

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