Ultrasound Diagnosis of Hepatic Steatosis as a Surrogate for Atherosclerosis

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Abstract
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Introduction: Ultrasonography has become available to most physicians in primary care. Increasingly hepatic steatosis becomes a chance finding, which has been shown to be associated with cardiovascular risk factors, surrogates of vascular disease, and vascular events. This study tries to answer the question whether it is justified to recommend a cardiovascular workup in response to the incidental finding of hepatic steatosis in asymptomatic healthy individuals.

Methods: The data of 259 healthy women and 561 men aged 19–93 years, who consecutively underwent a primary preventive check-up, were retrospectively analyzed. Ultrasonography for diagnosis of hepatic steatosis, determination of the maximal intima media thickness (IMT) and plaques of the carotid arteries was performed by a single certified physician according to conventional criteria.

Results: Hepatic steatosis was found in 28.3% men and 7.7% women. In 88% the steatosis was judged to be mild. These individuals differed from those without hepatic steatosis in body mass index, ALAT, GGT, HbA1c, fasting glucose, triglycerides, HDL and lipoprotein(a). The IMT was higher and plaques were more prevalent. In logistic regression analysis hepatic steatosis was a highly significant predictor of the presence of an IMT > 0.8 mm or carotid plaques besides age and sex. This was also the case in analyses including BMI, or multiple risk factors, which added only lipoprotein(a) as a predictor.

Conclusion: The incidental diagnosis of hepatic steatosis is a strong indicator for the presence of cardiovascular risk factors and even signs of developing atherosclerosis. Thus, the recommendation of further cardiovascular workups seems appropriate.

Introduction
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Ultrasonography has become a widespread diagnostic tool available to most general practitioners and internists. Whether used for a specific diagnostic or a preventive workup, it may yield information that goes beyond the specific question asked. One example of great impact is the chance finding of atherosclerosis which may be a sign of developing cardiovascular disease. In recent years an increasing prevalence of hepatic steatosis has been noticed. It is well established that hepatic steatosis is associated with risk factors for atherosclerosis, particularly type 2 diabetes and the components of the metabolic syndrome [1,2]. In several studies and various populations an association between non-alcoholic fatty liver disease (NAFLD) and surrogates of cardiovascular disease has been observed [3].

In this context a strong correlation between hepatic steatosis diagnosed by ultrasonography or liver histology and intima media thickness has been documented [4,5]. Targher et al. found a significantly increased intima media thickness in patients with type 2 diabetes with a sonographically diagnosed non-alcoholic fatty liver as compared to diabetic patients with a normal liver [6]. Also, Ramilli et al. [4] demonstrated a correlation between hepatic steatosis detected by ultrasound with increased body mass index, arterial hypertension, and elevated intima media thickness and the presence of carotid plaques in Italian outpatients referred for an abdominal ultrasound for any reason. In Korea Choi et al. [7] found a strong association of hepatic steatosis with carotid plaques by ultrasound in randomly consecutive patients, even after adjustment for age, sex, BMI, and the individual factors of a

metabolic syndrome. Targher et al. went even one step further and showed an increased risk for future cardiovascular events in patients with hepatic steatosis [5,8].

This study intends to investigate into the potential of abdominal ultrasound to predict the prevalence of atherosclerosis in primarily healthy subjects. This may add to the question of whether it is justified and advisable to recommend a cardiovascular workup to patients with hepatic steatosis, despite no cardiovascular problems. For this purpose, the data of 820 primarily healthy individuals presenting with no acute symptoms in a preventive medical check-up setting were retrospectively analysed, and the association of hepatic steatosis diagnosed by ultrasonography with risk factors for atherosclerosis and increased carotid intima media thickness or plaques was evaluated.

Materials and Methods
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The Center for Preventive Medicine Hamburg at the University Hospital Hamburg-Eppendorf offers medical check-ups for preventive medical advice, but no workups of acute diseases. Thus, primarily individuals in a healthy state are seen who may have long-standing medication for stable chronic diseases, though. Between March 2006 and July 2007 consecutively 259 women and 561 men aged 19–93 years free of acute symptoms or diseases were included in this retrospective explorative analysis.

The check-up included a physical examination, measurements of blood pressure and body mass index (BMI), and routine laboratory values determined by standard procedures including total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and lipoprotein(a), fasting glucose, HbA1c, and liver enzymes (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and gammaglutamyl transferase (GGT)). Hypertension was defined by a systolic blood pressure ≥ 140 mmHg or diastolic of ≥ 90 mmHg or being on antihypertensive therapy.

Ultrasonographic investigations were performed by a single experienced and certified internist certified by the German association of ultrasound in medicine (DEGUM) level III using a high end device (Siemens Acuson Antares premium edition, Siemens, Erlangen, Germany) with a curved 2–6 MHz array for the abdominal organs and a linear 5–9 MHz array for the examination of the extracranial vessels and taking the maximum intima media thickness of the distal wall of one of the common carotid arteries.

The diagnosis of hepatic steatosis by ultrasound was graded according to the criteria established by Joseph et al. 1991 [9]: "mild steatosis": slightly hyperechoic, but homogenous echo structure; "moderate steatosis": hyperechoic structure, dorsal diminishing of echo signal and beginning rarefication of hepatic vessels; "severe steatosis": hyperechoic and irregular parenchym structure, suspected fibrocirrhotic change, irregular margin and reduced elasticity.

An abnormal intima media thickening refers to a maximal intima media thickness of > 0.8 mm of the far wall of the common carotid artery [10–12]. Plaques were defined as atheromatous, calcified or mixed circumscribed wall thickenings, and stenoses were defined as wall irregularities taking more than 60 % of the vessel lumen graded according to Hennerici et al. [13] and Touboul et al. 2012 [14].

Statistical analyses were performed using the XLSTAT software 2012 (Addinsoft Germany). For comparing the prevalence of characteristics of individuals with (cases) or without (controls)

a fatty liver, the Mann-Whitney test was applied for continuous parameters and the Chi-square test for discontinuous data. Multivariate analyses were performed by logistic regression. P-values of < 0.05 were regarded significant.

Results
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Data of 820 patients were analysed. The basic characteristics of 561 men and 259 women with (cases) or without (controls) hepatic steatosis as diagnosed by abdominal ultrasound are given in ▫ Table 1. In 154 men (28.3 %) and 20 women (7.7 %) hepatic steatosis was diagnosed by abdominal ultrasound. 88 % of these patients had mild steatosis [9]. Only 2 women and 18 men were judged to have moderate steatosis, and 1 man with severe hepatic steatosis was suspected to have fibrocirrhosis.

Cases and controls were of comparable age (▫ Table 1). In line with the higher ultrasonographic classification of hepatic steatosis in cases, ALAT and GGT were also on average higher in both male and female cases than in controls (▫ Table 1). Correspondingly, the percentage of those with ALAT or GGT above the upper limit of normal was higher in cases of both genders.

Male and female cases also differed significantly from controls in their BMI, fasting blood sugar, HbA1c, triglycerides and HDL cholesterol, while LDL cholesterol was not significantly different in both sexes (▫ Table 1). The mean BMI was 2.5 and 5.9 kg/m^2 higher in male and female cases, respectively, compared to that of controls. 55.8 % of male cases were overweight (BMI ≥ 25 kg/m^2) and 26.0 % obese (BMI ≥ 30 kg/m^2) in contrast to 42.2 % and 12.6 % of controls, respectively. Of female cases 52.6 % were overweight and 36.8 % obese, compared to 22.1 % and 4.4 % controls, respectively. The 2 women with moderately fatty liver were obese, as were 13 of the 20 men with moderately to severe fatty liver. Only 2 men with moderately fatty liver were of normal weight according to the conventional BMI classification.

In line with differences in weight, cases were characterized more often by components of the metabolic syndrome as defined by the International Diabetes Federation [15], i.e., elevated triglycerides > 150 mg/dl, and HDL cholesterol < 50 or 40 mg/dl for women and men, respectively (▫ Table 2). Fasting glucose ≥ 100 mg/dl and hypertension were more prevalent in cases, though only in women the differences reached significance.

An IMT of > 0.8 mm or plaques in the common carotid arteries were more prevalent in male cases (36.4 %) than in controls (29.0 %) (p = 0.092), yet the difference between cases (40.0 %) and controls (16.7 %) reached only significance in women (p = 0.001). Also, plaques in the common carotid arteries or bulbi were numerically more frequent in male cases (31.2 %) than in controls (24.1 %) (p = 0.088), and in female cases (40.0 %) and controls (16.7 %) (p = 0.438), which, however, did not reach significance in both genders. Even though elevated IMT has often been associated with fatty liver especially in men, it frequently occurred also in individuals without a fatty liver as well. Still, the logistic regression analysis revealed male sex and hepatic steatosis besides age as highly significant predictors of an IMT > 0.8 mm or the manifestation of carotid plaques detected by ultrasound. Excluding BMI from the analysis did not materially alter the results. In a multivariate analysis including major cardiovascular risk factors, besides age only hepatic steatosis and elevated lipoprotein(a) proved to be statistically significant predictors of the presence of elevated IMT or carotid plaques in both genders despite multiple adjustments (▫ Table 3).

Table 1 Characteristics of individuals with and without hepatic steatosis diagnosed by ultrasonography and the significance of differences of the means.

Men n = 561	Controls n = 407			Cases with hepatic steatosis n = 154			Significance
	Mean	Median	1 SD	Mean	Median	1 SD	p-value
Age [years]	56.6	57.0	12.0	55.7	55.5	10.1	n.s.
BMI [kg/m²]	25.5	25.2	2.8	28.0	27.3	3.6	**<0.0001**
Fasting blood sugar [mg/dl]	89.1	87.0	15.2	94.4	91.5	19.5	**0.0004**
Hemoglobin A1c [%]	5.5	5.5	0.5	5.7	5.6	0.6	**0.004**
Total cholesterol [mg/dl]	206.3	203.0	37.6	207.0	208.0	37.7	n.s.
LDL-cholesterol [mg/dl]	122.2	118.5	34.1	124.3	124.0	35.4	n.s.
HDL-cholesterol [mg/dl]	63.4	61.0	16.3	54.8	53.0	14.1	**<0.0001**
Triglycerides [mg/dl]	104.1	86.0	63.1	152.5	129.0	77.0	**<0.0001**
ASAT (GOT) [IU/l]	27.9	27.0	7.0	33.8	30.0	13.3	**<0.0001**
ALAT (GPT) [IU/l]	27.8	25.0	11.3	43.7	37.0	26.5	**<0.0001**
GGT [IU/l]	33.4	25.0	28.2	47.1	37.5	34.8	**<0.0001**

Women n = 259	Controls n = 239			Cases with hepatic steatosis n = 20			Significance
	Mean	Median	1 SD	Mean	Median	1 SD	p-value
Age [years]	57.0	57.0	12.3	61.0	60.0	5.1	n.s.
BMI [kg/m²]	23.2	23.0	3.5	29.2	29.5	3.1	**<0.0001**
Fasting glucose [mg/dl]	84.6	84.0	11.5	100.1	97.0	15.2	**<0.0001**
Hemoglobin A1c [%]	5.5	5.5	0.4	5.7	5.7	0.4	**0.005**
Total cholesterol [mg/dl]	217.5	216.0	36.3	228.1	233.0	35.4	n.s.
LDL-cholesterol [mg/dl]	115.5	112.0	34.6	128.1	137.0	43.2	n.s.
HDL-cholesterol [mg/dl]	84.5	83.0	20.9	67.1	61.0	25.9	**<0.0001**
Triglycerides [mg/dl]	84.4	76.0	36.3	164.6	143.0	83.0	**<0.0001**
ASAT (GOT) [IU/l]	25.5	24.0	8.2	27.7	24.0	7.6	n.s.
ALAT (GPT) [IU/l]	21.2	19.0	9.3	34.1	28.0	16.9	**<0.0001**
GGT [IU/l]	24.8	18.0	23.5	36.0	31.0	39.7	**0.018**

Table 2 Frequency of pathological clinical and ultrasonographic parameters and the significance of their differences in individuals with and without hepatic steatosis diagnosed by ultrasonography.

Men	Controls [%]	Cases with hepatic steatosis [%]	Significance p-value
BMI ≥ 25 [kg/m²]	54.9	81.8	**<0.0001**
Hypertension [%]	35.0	42.2	0.113
Fasting glucose ≥ 100 mg/dl]	19.0	26.3	0.06
LDL-cholesterol ≥ 130 mg/dl	39.1	41.1	0.673
HDL-cholesterol < 50 mg/dl	20.8	36.8	**0.0001**
HDL-cholesterol < 40 mg/dl	2.3	11.8	**<0.0001**
Triglycerides > 150 mg/dl	16.5	38.6	**<0.0001**
ALAT (GPT) > 45 IU/l	7.6	30.3	**<0.0001**
GGT > 55 IU/l	10.4	22.4	**0.00025**
IMT > 0.8 mm	29.0	36.4	0.092
Carotid plaque	24.1	31.2	0.088
IMT > 0.8 mm or carotid plaque	33.7	41.6	0.082
Women	**[%]**	**[%]**	**p-value**
BMI ≥ 25 [kg/m²]	10.5	26.4	**<0.0001**
Hypertension [%]	31.6	68.4	**0.001**
Fasting blood sugar ≥ 100 mg/dl]	7.8	42.1	**<0.0001**
LDL-cholesterol ≥ 130 mg/dl	16.8	52.6	**0.0002**
HDL-cholesterol < 50 mg/dl	3.4	21.1	**0.001**
HDL-cholesterol < 40 mg/dl	0.4	0.0	0.774
Triglycerides > 150 mg/dl	6.5	47.4	**<0.0001**
ALAT (GPT) > 34 IU/l	7.8	42.1	**<0.0001**
GGT > 38 IU/l	13.8	21.1	0.385
IMT > 0.8 mm	16.7	40.0	**0.01**
Carotid plaque	18.0	25.0	0.438
IMT > 0.8 mm or carotid plaque	23.0	55.0	**0.004**

Logistic regression	Parameter	p-value	Odds ratio	lower (95%)	upper (95%)
IMT >0.8 mm	Age [years]	<0.0001	1.080	1.062	1.099
	Male sex	0.001	1.995	1.326	3.001
	BMI [kg/m^2]	0.197	1.034	0.983	1.088
	Steatosis	0.031	1.583	1.042	2.403
Carotid plaque	Age [years]	<0.0001	1.108	1.087	1.131
	Male sex	0.018	1.669	1.091	2.554
	BMI [kg/m^2]	0.907	1.003	0.950	1.059
	Steatosis	0.019	1.714	1.094	2.684
IMT >0.8 mm or plaque	Age [years]	<0.0001	1.087	1.069	1.105
	Male sex	0.009	1.659	0.134	2.427
	BMI [kg/m^2]	0.502	1.017	0.968	1.069
	Steatosis	0.009	1.730	1.149	2.605
IMT >0.8 mm or plaque	Age [years]	<0.0001	1.089	1.068	1.111
	Male sex	0.369	1.252	0.766	2.046
	BMI [kg/m^2]	0.177	0.951	0.883	1.023
	BZ [mg/dl]	0.150	1.011	0.996	1.025
	HbA1c [%]	0.759	0.929	0.582	1.484
	TG [mg/dl]	0.113	1.003	0.999	1.006
	HDL-C [mg/dl]	0.192	0.992	0.981	1.004
	LDL-C [mg/dl]	0.061	1.005	1.000	1.011
	Lipoprotein(a) [mg/dl]	0.009	1.007	1.002	1.012
	Hypertension	0.573	1.144	0.717	1.826
	Steatosis	0.021	1.773	1.092	2.880

Table 3 Logistic regression of clinical parameters as to prediction of an intima media thickness >0.8 mm in the common carotid arteries or plaques in the common carotid arteries or bulbi.

Discussion

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The results of this study clearly indicate that hepatic steatosis as diagnosed by abdominal ultrasonography is a valid marker of developing atherosclerosis in otherwise healthy people in a preventive check-up setup: to our knowledge, this is the first study demonstrating this correlation in an outpatient population of otherwise healthy individuals. The multivariate analysis even implies that hepatic steatosis adds to the effects of the major cardiovascular risk factors. It has been suggested that cardiovascular disease is the most important factor of outcome in patients with non alcoholic fatty liver disease and determinates the life expectancy much more than the progression of liver disease itself. Not only intima media thickness is increased, but there is also an impairment of flow-mediated vasodilation [16].

It has been shown that the presence of non-alcoholic fatty liver disease diagnosed by ultrasound is independently associated with an increased prevalence of ischemic heart disease [17,18]. The SHIP study, a large population based study in Northern Germany, showed in a 5- and 10-year follow-up that patients with a fatty liver had a significant higher morbidity and mortality than patients without this condition [19,20].

Certainly, the cohort under investigation is not a representative population. However, this has been judged not to be necessary to answer the very practical question, whether it is sensible to recommend cardiovascular diagnostics based on the finding of hepatic steatosis in a thus far healthy population. Also, the accuracy of ultrasound for the detection of steatosis is not crucial in this respect, although it has been found reasonably specific [9,21,22]. The strength of this study is the retrospective design, since no study objective could have possibly prejudiced the results of the ultrasonographic investigation and examination bias is omitted. Furthermore, the scheduling in the center does not allow sharing knowledge with the investigator regarding results of laboratory values, cardiac echo or ECG at the time of the abdominal ultrasound.

In our study, hepatic steatosis diagnosed by abdominal ultrasound turned out to be stronger than any individual major cardiovascular risk factor, but for lipoprotein(a) to predict subclinical atherosclerosis of the carotid arteries. This is probably due to the fact that ectopic fat is a major causal factor for the components of the metabolic syndrome; thus, hepatic steatosis subsumes the effects of these factors similar to the definition of the metabolic syndrome [1,2].

Moreover, ultrasound demonstrates the risk pattern to the patient in real time, not only by visualizing the fatty liver, but also displaying the developing atherosclerosis of abdominal vessels.

Ultrasound is also very well-suited for follow-up exams to monitor the therapeutic success. Weight loss and physical exercise may induce normalization of liver tissue [23]. This is visually more impressive than the reduction of intima media thickness by 0.1 mm. So, based on this study and previous experience [24], we think abdominal ultrasound to be appropriate in medical prevention, not only to evaluate the abdominal organs, but also to assess patients who are at a higher risk for cardiovascular diseases.

In summary, detecting hepatic steatosis has a diagnostic impact on the choice of therapeutic measures for the prevention of cardiovascular disease by itself, though it seems appropriate to take hepatic steatosis as a call for further classification of the induced risk factors and the impact on the arterial wall. In conclusion, this study demonstrates that the incidental finding of hepatic steatosis is an appropriate indication for further cardiovascular work-ups in times of individualized medicine and prevention, especially in men.

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