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Acute effect of weight loss on levels of total bilirubin in obese, cardiovascular high-risk patients: an analysis from the lead-in period of the Sibutramine Cardiovascular Outcome trial

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Abstract

Low levels of bilirubin are associated with an increased risk of cardiovascular adverse events. Weight reduction is known to reduce several cardiovascular risk factors, but effects on bilirubin levels have not been reported. We studied the response of weight loss therapy with sibutramine and lifestyle change on levels of total bilirubin in an overweight or obese, cardiovascular high-risk population. Data from the first 4 weeks of the lead-in period of the Sibutramine Cardiovascular Outcome study were analyzed. A total of 10 198 patients provided body weight measurements before and after 4 weeks of sibutramine treatment (10 mg daily), of whom 1059 (10.4%) gained weight, 1467 (13.7%) lost greater than 0% to 1%, 2492 (23.2%) lost greater than 1% to 2%, 2280 (21.2%) lost greater than 2% to 3%, 1498 (13.9%) lost greater than 3% to 4%, and 1402 (13.1%) lost greater than 4% of their initial weight, respectively. At screening, bilirubin concentrations were similar between weight loss groups (around 11 μmol/L, $P = .7$) and increased linearly as a function of weight loss. The effect was significantly more pronounced in men compared with women (P for interaction = .003). Adjusted for multiple variables, each 1% increase in weight loss was associated with 0.21-μmol/L (± standard error 0.027) increase in men ($P < .0001$) and 0.11-μmol/L (±0.024) increase in women ($P < .0001$). Short-term weight loss during administration of sibutramine in combination with diet and exercise advice is effective in increasing bilirubin levels within the reference range, with bilirubin increasing as a linear function of weight change. The effect is greater in men than in women.

1. Introduction

Serum bilirubin concentrations are inversely related to risk of myocardial infarction, coronary artery disease death, peripheral vascular disease, and stroke [1,2]. The strength of association is similar to that of smoking, elevated systolic blood pressure, and high-density lipoprotein (HDL) cholesterol [3,4]. A recent meta-analysis of bilirubin levels in men

Conflicts of interest: WC, AMS, LVG, NF, WPTJ, IDC, and CTP are members of the SCOUT Executive Steering Committee. RAR is working for Abbott Laboratories.

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showed that a concentration less than 10.0 μmol/L is associated with increased cardiovascular risk [5]; and for each 1.0-μmol/L increase in bilirubin concentration, risk of cardiovascular disease (CVD) was decreased by 6.5% [5].

Bilirubin is known to have both antioxidative [6,7] and anti-inflammatory properties [8,9] and has been suggested as a future possible target of intervention [10,11]. It is also important to emphasize that these concentrations of bilirubin are at levels within the normal reference interval and, hence, significantly lower than levels seen in pathologic liver conditions.

Weight reduction is known to reduce several cardiovascular risk factors; and as bilirubin concentration has also been shown to be closely related to the cardiovascular risk, it can be hypothesized that levels of bilirubin should increase with weight loss. However, to our knowledge, the response of bilirubin to weight loss has never been reported. Therefore, we investigated this topic in the large population of overweight or obese, cardiovascular high-risk patients who received sibutramine during the 6-week lead-in period of the Sibutramine Cardiovascular OUTcome (SCOUT) study.

2. Methods

The SCOUT study is an ongoing randomized, double-blind, multicenter, clinical study assessing the cardiovascular outcomes in overweight and obese patients at increased risk of cardiovascular adverse events [12]. This article is based on analyses from the first 4 weeks of the single-blind lead-in period (from screening to week-2 visits; these time points were chosen because of the availability of weight and bilirubin data). During this period, all patients received a daily dose of 10 mg of sibutramine together with diet and exercise advice. Patients 55 years or older with either a body mass index (BMI) from 27 to 45 kg/m^2 or a BMI from 25 to 27 kg/m^2 plus a waist circumference of at least 102 cm in men and at least 88 cm in women were included in the study. All patients had either a history of coronary artery disease, peripheral arterial occlusive disease, or stroke, or documented type 2 diabetes mellitus (DM) with at least 1 well-defined risk factor (ie, hypertension, dyslipidemia, current smoker, or diabetic nephropathy with evidence of microalbuminuria). As a result of the low event rate, inclusion criteria were changed 15 months after the start of enrolment, so that subsequent patients were required to have both CVD and type 2 DM [12]. Patients were screened during a 2-week period before sibutramine administration. At the screening visit and after 4 weeks of sibutramine administration, samples were obtained for assessment of blood biochemistry and hematology; and a physical examination was performed (including measurements of weight, blood pressure, etc). Some of the patients had a second hematology or blood biochemistry sample taken either in relation to the screening visit or in relation to the 4-week visit. For the present analysis, these secondary blood samples were used only if values from the first measurement were missing. All blood biochemistry samples were taken while fasting, but not at a standardized time of the day. Measurements of bilirubin were total bilirubin concentrations measured in micromoles per liter. The reference range for total bilirubin was defined as 0 to 22 μmol/L.

For the present study, patients were divided into 5 groups according to the percentage weight change during the first 4 weeks of sibutramine administration. Weight records were not available for 544 patients during this time interval.

The SCOUT trial is registered at ClinicalTrials.gov (NCT00234832).

2.1. Ethics

The study was performed in conformity with the Declaration of Helsinki and was approved by all relevant ethical committees. All patients gave their written informed consent before participating.

3. Statistics

Primary analyses were performed with parametric methods (t test and analysis of variance for continuous variables and χ^2 test for discrete variables), and sensitivity analyses were repeated with nonparametric methods (rank sum test for continuous variables and Mantel-Haenszel χ^2 for discrete variables). Unless otherwise specified, results from parametric methods have been reported.

Linear regression models were used to examine the effect of multiple parameters on changes in total bilirubin concentrations. All variables with possible a priori effects on bilirubin concentration were included. Unless otherwise mentioned, tests for relevant interactions were found to be nonsignificant ($P > .05$).

Data available by September 2006 were used in all analyses. All calculations were made using SAS version 9.1 (SAS Institute, Cary, NC). A P value less than .05 was regarded as statistically significant. No statistical adjustment was made for the number of comparisons performed.

4. Results

A total of 10 742 patients were enrolled and received 10-mg/d doses of sibutramine, plus exercise and diet advice. Of these, 10 198 had body weight measurements available before and 4 weeks after initiation of sibutramine administration, including 1059 (10.4%) patients who gained weight, 1467 (13.7%) who lost greater than 0% to 1%, 2492 (23.2%) who lost greater than 1% to 2%, 2280 (21.2%) who lost greater than 2% to 3%, 1498 (13.9%) who lost greater than 3% to 4%, and 1402 (13.1%) who lost greater than 4% of their initial weight, respectively. In

patients in the "gained weight" group, the median increase in weight was 0.3% (fifth and 95th percentiles: 0.0% and 2.2%) over the 4 weeks. Characteristics of the different weight-change groups are presented in Table 1. Bilirubin concentrations at screening did not differ between the groups.

Overall, mean bilirubin concentrations were increased by 0.17 μmol/L over the 4 weeks (95% confidence interval [CI], 0.11-0.24; $P < .0001$). An increasing linear trend was observed between changes in total bilirubin concentrations and amount of weight loss (Fig. 1). Patients who gained weight experienced significantly decreased mean bilirubin levels, whereas patients who lost greater than 2% of weight experienced significant increases in mean bilirubin levels. In total, 49 patients experienced increases in bilirubin concentrations of more than 10 μmol/L; and of these, 8 increased more than 15 μmol/L, with 1 patient who had an increase of more than 20 μmol/L. Overall, 265 patients (2.6% of the total), estimated to be evenly distributed in all weight-change groups, reached a concentration greater than 22 μmol/L (upper reference limit). Mean concentration in these patients was 27.3 μmol/L (±SD 5.2 μmol/L). Mean changes in bilirubin concentrations were similar in patients with and without a diagnosis of liver disease (most cases were steatosis) ($P > .9$). An elevated concentration of alanine aminotransferase (ALT) (>48 U/L) at screening had no influence on the change in bilirubin concentrations ($P = .7$).

In multivariable regression analysis, weight loss was shown to have a strong influence on the increase in bilirubin levels (Table 2).

4.1. Sex differences

The impact of weight loss on total bilirubin levels differed in men and women (P value for interaction = .003); and therefore, analyses were stratified for sex (Table 2). In men,

Table 1
Baseline characteristics according to 4-week percentage change in weight

	Gained weight (n = 1059, 10.4%)	Lost 0%-1% (n = 1467, 14.4%)	Lost >1%-2% (n = 2492, 24.4%)	Lost >2%-3% (n = 2280, 22.4%)	Lost >3%-4% (n = 1498, 14.7%)	Lost >4% (n = 1402, 13.7%)
Sex, male (%)	64%	62%	60%	55%	55%	51%
Age (y)	63.8 (±6.4)	63.5 (±6.0)	63.8 (±6.1)	63.8 (±6.1)	64.0 (±6.3)	63.2 (±6.0)
BMI (kg/m^2)	33.9 (±4.6)	34.5 (±4.6)	34.3 (±4.5)	34.5 (±4.6)	34.6 (±4.5)	34.6 (±4.5)
History of coronary artery disease (%)	67%	64%	67%	66%	65%	67%
History of hypertension, medical treated (%)	89%	87%	88%	87%	87%	90%
History of dyslipidemia (%)	80%	80%	82%	83%	80%	79%
Heart failure (%)	9%	7%	9%	8%	8%	9%
Type 2 DM (%)	87%	86%	85%	83%	81%	81%
History of cholecystitis (%)	3%	2%	2%	3%	3%	3%
History of cholelithiasis (%)	12%	10%	11%	12%	12%	13%
History of hepatitis (%)	4%	3%	3%	3%	2%	3%
History of liver disease (%)[a]	5%	5%	5%	4%	4%	5%
Blood pressure, systolic (mm Hg)	138 (±13)	138 (±13)	138 (±13)	138 (±13)	139 (±13)	139 (±13)
Blood pressure, diastolic (mm Hg)	78 (±9)	78 (±8)	78 (±8)	78 (±8)	78 (±9)	78 (±8)
Use of alcohol (%)	55%	58%	56%	55%	53%	52%
Smokers (%)	12%	12%	10%	9%	9%	9%
Total bilirubin (μmol/L)[b]	11.0 (±4.5)	11.0 (±4.7)	11.0 (±4.5)	10.9 (±4.5)	11.0 (±4.4)	11.1 (±4.6)
Blood glucose (mmol/L)	8.9 (±3.4)	8.6 (±3.3)	8.6 (±3.3)	8.4 (±3.1)	8.3 (±3.0)	8.2 (±2.9)
Triglycerides (g/L)	2.31 (±1.40)	2.30 (±1.38)	2.27 (±1.39)	2.27 (±1.44)	2.22 (1.47)	2.22 (±1.37)
Total cholesterol (mmol/L)	5.01 (±1.17)	5.03 (±1.15)	4.99 (±1.13)	5.05 (±1.13)	5.02 (±1.13)	5.11 (±1.18)
HDL cholesterol (mmol/L)	1.19 (±0.29)	1.18 (±0.29)	1.20 (±0.29)	1.20 (±0.30)	1.20 (±0.29)	1.20 (±0.29)
ALT concentration (U/L)[b]	24.9 (±13.5)	26.7 (±16.1)	26.6 (±15.3)	26.4 (±15.4)	26.2 (±15.3)	27 (±16.0)
AST concentration (U/L)[b]	22.2 (±10.3)	23.2 (±11.2)	23.3 (±10.8)	23.4 (±11.5)	22.9 (±10.1)	23.8 (±11.5)
ALP concentration (U/L)[b]	73.8 (±24.8)	72.3 (±23.1)	72.1 (±23.9)	72.7 (±24.8)	71.8 (±26.4)	73.9 (±22.9)
Waist circumference, men (cm)	113 (±10)	115 (±11)	115 (±11)	114 (±11)	114 (±10)	115 (±11)
Waist circumference, women (cm)	110 (±12)	110 (±13)	110 (±11)	109 (±12)	109 (±11)	108 (±11)
Use of oral antidiabetics, all sorts (%)	46%	48%	47%	48%	51%	50%
Use of insulin (%)	31%	27%	27%	23%	19%	16%
History of peripheral occlusive arterial disease (%)	13%	12%	12%	11%	8%	9%
Previous stroke (%)	9%	8%	8%	8%	7%	9%

Continuous variables are presented as means (±SD). Blood samples were obtained during screening visit, as were medical histories. Body mass index, waist circumference, pulse, and blood pressure are values from the first day of sibutramine administration.

[a] Most cases were diagnosed as steatosis.

[b] Reference ranges of bilirubin: 0 to 22 μmol/L; ALT: 0 to 48 U/L; AST: 0 to 42 U/L; and ALP: 20 to 125 U/L.

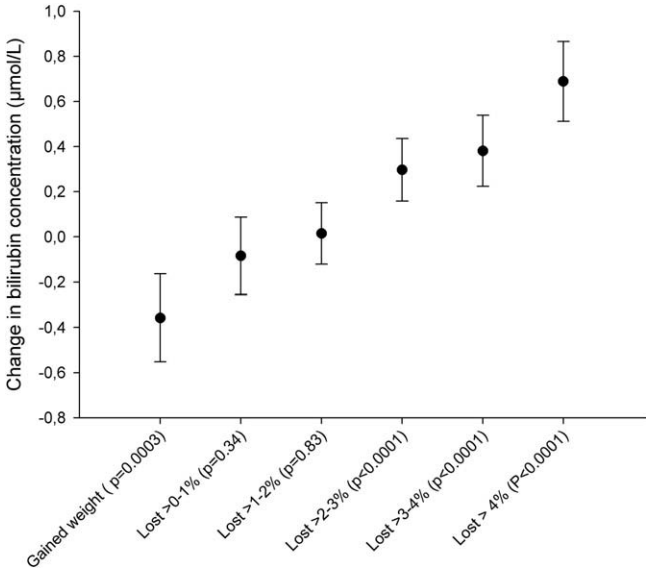

Fig. 1. Mean change in levels of total bilirubin, according to weight change. Error bars illustrate 95% CIs.

for each 1% increase in weight loss, total bilirubin levels were found to increase by 0.21 (±SE 0.027) μmol/L. Correspondingly, women experienced increases in bilirubin levels of 0.11 (±0.024) μmol/L for each 1% increase in weight loss.

Screening concentrations of bilirubin were significantly higher in men compared with women, with mean concentrations of 11.9 (±SD 4.8) μmol/L in men and 9.9 (±3.8) μmol/L in women ($P < .0001$). Screening characteristics of both sexes were similar, but differed in the prevalence of type 2 DM and CVD. Women had a higher prevalence of diabetes (87% compared with 81% in men, $P < .0001$), whereas men had a higher prevalence of CVDs (84% compared with 65% in women, $P < .0001$). Furthermore, BMI was significantly higher among women compared with men (35.5 [±SD 4.8] and 33.6 [±4.1] kg/m^2, respectively; $P < .0001$).

Using a "reduced" model, including factors for sex and weight loss and stratifying by inclusion criteria group, each 1% increase in weight loss was associated with bilirubin increases in men (n = 1148, 0.31 ± 0.063, $P < .0001$) and women (n = 600, 0.11 ± 0.062, $P = .07$) in the CVD group (P for difference between sexes = .05), in men (n = 4076, 0.19 ± 0.033, $P < .0001$) and women (n = 2321, 0.098 ± 0.037, $P = .008$) in the CVD + DM group (P for difference between sexes = .08), and in men (n = 987, 0.24 ± 0.071, $P = .0008$) and women (n = 1597, 0.11 ± 0.038, $P = .005$) in the DM-only group (P for difference between sexes = .06). The prevalence of CVD and/or DM was not found to modify the sex differences in the 4-week change of total bilirubin (P for interactions between CVD

Table 2
Estimated influences on change in bilirubin concentration for the whole population and according to sex

	Both sexes		Women		Men	
	Estimated change in bilirubin concentration (±SE)	P value	Estimated change in bilirubin concentration (±SE)	P value	Estimated change in bilirubin concentration (±SE)	P value
Sex, male	0.65 (±0.071)	<.0001	–	–	–	–
Bilirubin concentration at screening (for 1-μmol/L increment)	−0.27 (±0.0073)	<.0001	−0.31 (±0.011)	<.0001	−0.25 (±0.0097)	<.0001
Change in HDL cholesterol (for 1-mmol/L increase)	1.07 (±0.21)	<.0001	0.99 (±0.26)	.0002	1.03 (±0.33)	.0015
Change in triglycerides (for 1-g/L decrease)	0.26 (±0.052)	<.0001	0.39 (±0.074)	<.0001	0.14 (±0.072)	.04
Weight loss (for 1% decrease)	0.17 (±0.019)	<.0001	0.11 (±0.024)	<.0001	0.21 (±0.027)	<.0001
Use of insulin	−0.34 (±0.077)	<.0001	−0.27 (±0.10)	.007	−0.40 (±0.12)	.0006
Change in AST (for 1-IU/L increase)	0.044 (±0.003)	<.0001	0.050 (±0.0082)	<.0001	0.046 (±0.0094)	<.0001
Change in white cell count (for 1-GI/L decrease)	−0.096 (±0.023)	<.0001	−0.032 (±0.028)	.3	−0.16 (±0.036)	<.0001
Change in LDL cholesterol (for 1-mmol/L decrease)	−0.16 (±0.047)	.0005	−0.19 (±0.058)	.0008	−0.14 (±0.073)	.05
Type 2 DM	−0.30 (±0.092)	.001	−0.32 (±0.13)	.02	−0.30 (±0.13)	.02
Smoke	−0.38 (±0.11)	.0006	−0.32 (±0.16)	.04	−0.42 (±0.15)	.0006
Change in glucose (for 1-mmol/L decrease)	−0.022 (±0.014)	.1	−0.040 (±0.018)	.03	−0.0049 (±0.021)	.8

Variables are presented in order of statistical significance for the analysis including both sexes, with the most significant values on top. Only variables at a significance level less than .05 are presented. Analysis was also adjusted for age, waist circumference, and BMI at baseline; change in glucose; change in ALP; change in ALT; change in ALP; change in systolic and diastolic blood pressure; and a history of the following conditions: cholelithiasis, dyslipidemia, hepatitis, liver disease (mostly steatosis), hypertension, and CVD (previous peripheral occlusive arterial disease, coronary artery disease, or stroke). In analysis of both sexes, a significant interaction was found between sex and weight loss ($P = .003$). Furthermore, an interaction was found between the white cell count and sex ($P = .01$). No interactions were found between diabetes and weight loss ($P = .1$), or diabetes and white cell count ($P = .1$). LDL indicates low-density lipoprotein.

and sex = .4 in both reduced and full models; P for interactions between DM and sex = 0.6 in reduced and = .8 in full models).

In multivariable analysis, white cell count changes associated with a change in bilirubin levels differed between men and women (P for interaction = .01). In men, each 1×10^9–cells per liter decrease in white cell count was associated with a corresponding decrease in bilirubin levels (-0.16 ± 0.036 μmol/L, $P < .0001$). In women, each 1×10^9–cells per liter decrease in white cell count also was associated with a decrease in bilirubin levels (-0.032 ± 0.028 μmol/L, $P = .3$). The overall 4-week (mean ± SD) changes in white cell count were $-0.016 \pm 1.31 \times 10^9$ cells per liter ($P = .4$) and $-0.098 \pm 1.49 \times 10^9$ cells per liter ($P < .0001$) in men and women, respectively (P for difference = .005).

4.2. Impact of type 2 DM

At screening, patients with diabetes had lower concentrations of bilirubin compared with patients without diabetes (mean concentrations of 10.9 [±4.5] and 11.8 [±4.8] μmol/L in patients with and without diabetes, respectively; $P < .0001$). Because women were shown to have lower screening concentrations of bilirubin and a greater proportion of patients with diabetes were women, we stratified the analyses for both sex and diabetes. Mean screening concentration of bilirubin in women with diabetes was 9.8 (±3.8) μmol/L compared with 10.3 (±3.7) μmol/L ($P = .006$) in women without diabetes. In men, mean screening concentrations were 11.7 (±4.8) μmol/L and 12.6 (±5.1) μmol/L ($P < .0001$) in patients with and without diabetes, respectively.

Fig. 2 illustrates the mean changes for each percentage weight loss stratified for diabetes. In the overall multivariable analysis, there was a tendency toward a difference in impact of weight loss in patients with and without diabetes (P value for interaction = .1). Therefore, we stratified the multivariable analyses for diabetes as well as sex. In men, each 1% increase in weight loss was associated with an increase in bilirubin levels in patients with (0.19 ± 0.030 μmol/L, $P < .0001$) or without (0.29 ± 0.063 μmol/L, $P < .0001$) diabetes (P for difference = .007). In women, each 1% increase in weight loss was associated with an increase in bilirubin levels in patients with (0.094 ± 0.026 μmol/L, $P = .0004$) or without (0.17 ± 0.062 μmol/L, $P = .005$) diabetes (P for difference = .01).

The multivariable analysis further revealed a difference in impact of a change in blood glucose on the change in bilirubin concentration between patients with or without diabetes (P value for interaction = .01). Each 1-mmol/L decrease in blood glucose was associated with a change in bilirubin levels in men with (-0.019 ± 0.021 μmol/L, $P = .4$) or without (0.29 ± 0.15 μmol/L, $P = .008$) diabetes (P for difference = .004). In women, each 1-μmol/L decrease in blood glucose was associated with changes in bilirubin levels for those with (-0.033 ± 0.018 μmol/L, $P = .07$) or without (-0.093 ± 0.15 μmol/L, $P = .2$) diabetes (P for difference = .6).

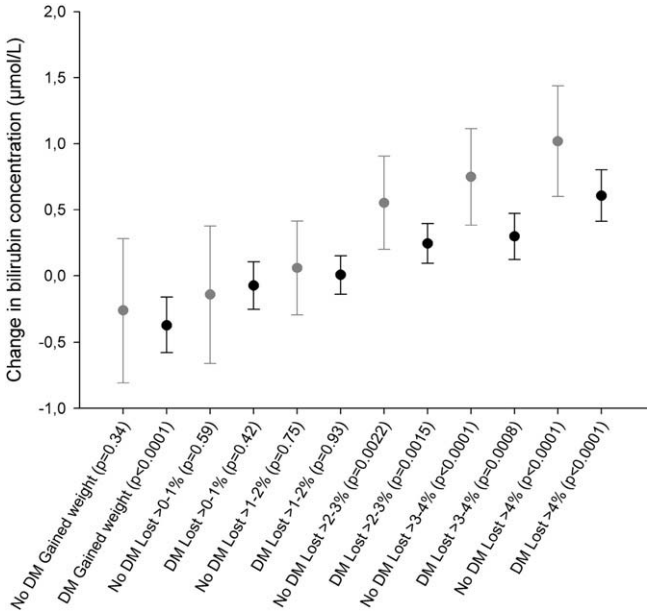

Fig. 2. Mean change in levels of total bilirubin, according to weight change, stratified for diabetes mellitus. Gray plots illustrate mean changes for patients without diabetes, and black plots illustrate mean changes for patients with diabetes. Error bars illustrate 95% CIs.

5. Discussion

Our analysis demonstrated a linear trend between increases in serum bilirubin levels (within or close to the reference range) and the degree of weight change. A weight reduction greater than 2% was associated with significantly increased bilirubin levels, whereas gaining weight was shown to decrease bilirubin levels. The impact was greater in men compared with women. This analysis was based on a large population, which provided sufficient statistical power to detect these changes. The studied population was an older, overweight or obese, cardiovascular high-risk population, which makes the results applicable to many patients seen in clinical practice.

We found a sex difference both in the screening concentrations of bilirubin and in the impact of weight reduction on the increase in bilirubin levels, with both analyses showing higher values/responses in men. This probably reflects a true sex difference and should therefore probably not be interpreted as women having a more severe cardiovascular risk profile and a smaller health benefit from weight reduction.

We further found that patients with diabetes had lower screening concentrations of bilirubin, together with a tendency to smaller effects of weight loss on bilirubin levels. These observations would accord with their recognized increased cardiovascular risk and their recognized lesser

weight responses to lifestyle and sibutramine treatment. It is also possible that the difference reflects a difference in liver metabolism relating to the conjugation of bilirubin or metabolic processes affected by insulin resistance; however, changes in transaminases, as a crude index of hepatic function, were not found to differ in patients with diabetes compared with patients without diabetes (data not shown).

The biological mechanisms beyond the increases in bilirubin levels associated with weight loss are not clear. Bilirubin uptake, conjugation rate changes, and enterohepatic recirculation of bilirubin are all recognized to affect serum levels in different physiopathologic states. Obesity is also associated with a chronic state of low-grade inflammation [13]. Inflammation can drive oxidative stress [14], and a decrease in obesity-associated oxidative stress may in part explain the rise in bilirubin levels. However, a decrease in white cell count, the closest measurement of the inflammatory state available in this study, was found to be associated with a decrease in bilirubin levels. This was opposite to what might be expected; but because this relationship was found to be limited to men and the white cell count did not change significantly over the 4 weeks in men, these findings are assumed to be of minor importance. Possibly, the white cell count as a marker of inflammation is not specific enough for detecting any hypothesized changes in the inflammatory status. Whether the observed increase in bilirubin concentrations reflects a real change in cardiovascular risk must await the long-term randomized outcomes of the study. This 4-week evaluation period was short and had no control group, and it cannot be excluded that the increase seen in bilirubin levels is merely an acute effect of weight loss and/or sibutramine administration and not a marker of CVD risk reduction. It cannot be excluded either that the responses reflect the competition from peripheral metabolite inflow for glucuronidation during the acute phase of weight loss and may not continue to induce higher bilirubins once weight stability occurs.

Gilbert syndrome, which has a population prevalence of 2% to 19% [15,16], could act as a confounder of our findings. However, at least 2 facts suggest otherwise. Firstly, a significant decrease in bilirubin was seen in patients gaining weight. Secondly, Gilbert syndrome is associated with a rather larger increase in bilirubin levels in response to fasting. A study of calorie-restricted patients with Gilbert syndrome reported an increase of 140% in bilirubin levels [17], corresponding to an increase of approximately 14 μmol/L in the present population. The fact that only a total of 49 patients had increases in bilirubin concentrations of more than 10 μmol/L, 7 patients had increases of more than 15 μmol/L, and 1 patient had in increase of more than 20 μmol/L and that the increases were shown to be normally distributed in the studied population would suggest that Gilbert syndrome cannot explain the increases. Furthermore, the prevalence of Gilbert syndrome in the subjects in the SCOUT population, who are known to have a high risk of CVD, might in fact be lower than that in the general population because subjects with Gilbert syndrome have been reported to have a lower prevalence of CVDs [18].

The changes in bilirubin seen in this study cannot readily be ascribed to an effect of sibutramine per se because all patients received sibutramine in this phase of SCOUT; and although sibutramine is metabolized by the liver to generate its 2 active metabolites, this transformation involves the cytochrome P450 enzyme system and not the pathways involved in bilirubin conjugation and excretion.

Although this population may have an increased prevalence of nonalcoholic fatty liver disease, which in the early stages of weight loss can cause an increase in liver enzymes, the overall normality of liver enzymes in our population would also argue that the changes in bilirubin seen were not due to nonalcoholic fatty liver disease. In multivariable analysis, changes in ALT and alkaline phosphatase (ALP) were not significantly associated with a change in bilirubin concentration. A change in aspartate aminotransferase (AST) concentration was one of the parameters with the strongest association to change in bilirubin concentration, but AST concentrations did not change significantly over the 4 weeks (data not shown).

In relation to the observed sex differences, concentrations of bilirubin in cardiovascular patients have been reported previously to be lower in women compared with men [19]. This suggests that female hormones influence the concentration of bilirubin, and oral contraceptives and postmenopausal estrogen use are known to reduce bilirubin levels [20] by mechanisms that remain unclear. Furthermore, the relationship between CVD and bilirubin levels seems more uncertain in women. In the Framingham Offspring Study, an inverse relationship between serum bilirubin levels and any cardiovascular event was found in men; but the relationship was only suggestive in women [1]. Using data from the National Health and Nutrition Examination Survey, Perlstein et al [21] recently confirmed these sex differences. The relationship between increasing levels of bilirubin and decreasing odds of developing peripheral occlusive arterial disease was shown for men, but was not as clear in women [21]. This could mean that the cardiovascular benefits of higher serum bilirubin concentrations are minimized by female sex hormones.

In summary, our findings indicate that a short period of weight loss therapy with sibutramine in cardiovascular high-risk patients induces a rapid increase in total bilirubin levels. The question is whether the long-term results from the SCOUT trial will show a reduction in cardiovascular adverse events with increasing weight loss and whether these effects can be ascribed to decreases in well-known risk factors such as hypertension and insulin resistance or whether changes in bilirubin may also play a role.

5.1. Limitations of the study

The first blood samples on bilirubin were taken during the first (screening) visit; however, changes in weight were

calculated from the first day of sibutramine administration, which in some individuals might have been as much as 2 weeks after the first visit. Because bilirubin concentration seems to be sensitive to small changes in weight and patients might have experienced a change in weight between the first visit and the first day of sibutramine administration, it is possible that our study underestimated the real effects of weight loss on bilirubin levels. Another limitation is the lack of data on hormone status in the women, thought to explain at least some of the difference in bilirubin concentrations between women and men. Furthermore, the present study had no control group; so it was not possible to discount a possible but unlikely role of sibutramine on bilirubin levels. All patients were cardiovascular high-risk patients, and it is not known if patients at lower cardiovascular risk have as good a response in bilirubin concentration to weight loss. However, because patients with only diabetes may have a less adverse risk profile compared with patients with a history of cardiovascular adverse events [22], this could mean that the population having only diabetes (those enrolled within the first 15 months) posed a less severe cardiovascular risk compared with patients with diabetes and CVD (those enrolled after 15 months). We performed a study stratified for these 2 groups and found no significant difference in response to weight loss (data not presented).

A further limitation was the lack of more specific inflammatory markers such as C-reactive protein or γ-glutamyl transferase, which may be associated with bilirubin levels and changes.

6. Conclusion

Short-term weight loss during use of sibutramine is associated with increases in total bilirubin levels. Men have a greater increase in bilirubin levels. Considering the cardiovascular protective effects of bilirubin, a small amount of weight loss seems potentially effective in reducing the risk of cardiovascular adverse events. However, the outcome of this trial and additional analyses will be needed to establish if there are selective cardiovascular benefits of higher circulating bilirubin levels.

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