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Short Report

Abdominal fat distribution measured by ultrasound and aerobic fitness in young Danish men born with low and normal birth weight

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ABSTRACT

Abdominal subcutaneous and visceral adipose tissue thickness was examined by ultrasound in 17 men with low birth weight (LBW) and 26 with normal BW control individuals to determine if abdominal obesity in LBW individuals is due to increased visceral or subcutaneous fat mass/thickness, or both. Men born with LBW had an increased waist-to-hip ratio (P = 0.04), greater abdominal fat thickness (P = 0.05) and increased visceral (VAT) and subcutaneous adipose tissue (SAT) thickness compared with controls, however the latter not statistically significant (P = 0.08, P = 0.10). A significant difference between birth weight groups in both SAT (P = 0.04) and VAT (P = 0.03) was found after adjustment for weight, whereas no significant difference in either SAT (P = 0.93) or VAT (P = 0.30) was found after adjustment for BMI. Increased waist-to-hip ratio in LBW individuals is due to increased total abdominal fat including both subcutaneous and visceral fat.

Introduction

Impaired growth in utero, resulting in low birth weight (LBW), is associated with obesity, insulin resistance and type 2 diabetes (T2D). We have shown that individuals born with LBW exhibit hepatic and adipose tissue insulin resistance in early adulthood, and develop whole-body insulin resistance when exposed to metabolic challenges as overfeeding and physical inactivity [1,2].

The distribution of fat in various fat depots and organs including the liver play a key role in the development of metabolic disease including T2D. The body mass index (BMI) does not necessarily reflect body composition, and the waist-to-hip ratio (WHR) is a non-optimal surrogate marker of fat distribution. Importantly, the WHR does not discriminate between intraabdominal (visceral) (VAT) or subcutaneous abdominal fat (SAT), respectively. A low physical activity level is related to accumulation of VAT, and increased VAT is associated with insulin resistance [3]. Previous studies have documented an inverse association between LBW and increased abdominal obesity [4,5] as recently confirmed by the Great Chinese Famine study, showing that early life exposure to famine increased the risk of abdominal obesity [6]. Furthermore, the relative weight gain in early life from birth is equally important in the development of abdominal adiposity [7].

We have shown that individuals born with a LBW have a significantly higher proportion of abdominal fat but less lower body fat relative to total fat mass, despite of similar weight and BMI compared to individuals with a normal birth weight (NBW) [1,8]. Furthermore, we found that men with a LBW have a relatively more immature fat cell type reflected by reduction in differentiation markers, suggesting that an adverse intrauterine environment influence adipocyte functions, potentially linking LBW with increased risk of developing T2D [9].

To our knowledge, no previous studies have provided data to conclusively document that an increased WHR in LBW individuals is due to increased abdominal adipose tissue. Furthermore, we are unaware of any studies that have studied the distribution of SAT and VAT, in healthy young adults born with and without LBW. We therefore aimed to determine if LBW is associated with an increased amount of VAT determined by ultrasound in young, healthy and

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lean men whom previously had participated in other studies where multiple metabolic defects including insulin resistance had been shown [1,2]. Secondly, we aimed to determine if men with LBW exhibit decreased aerobic fitness as compared to controls.

Methods

A total of 89 healthy young males born at term (39–41 weeks), originally recruited from the Danish Medical Birth Registry, were invited to participate [1,2,8]. Seventeen LBW men (BW < 10^{th} percentile), and 26 NBW men (BW ≥ 50^{th}–<90^{th} percentile) were enrolled. Study participants with diabetes or with family members with known diabetes were excluded. Furthermore, a BMI > 30 kg/m^2, >10 h exercise/week and an intake of medication known to affect glucose and lipid metabolism did also exclude individuals from participation. The protocol was approved by the local Ethics Committee (J.nr. Nr KA-03129-gm) and by The Danish Data protection Agency (J.nr. 2003-41-3553). Written informed consent was obtained and procedures were conducted in accordance with ethical principles embodied in the Declaration of Helsinki.

Examinations

Weight, height and WHR were measured after an overnight fast and subjects were instructed to abstain from strenuous physical activity and alcohol for 48 h before the examination.

Abdominal fat distribution was determined by ultrasound (Brüel & Kjær, Diagnostic Ultrasound System 3535) using a revised protocol according to Stolk et al. [10]. Examination was performed by two non-radiologist operators trained in the use of the ultrasound system and blinded to the birth weight of the subjects. The transducer was placed horizontally on the abdomen, and a sagittal scan was performed at the abdominal middle at the midpoint between the lateral iliac crest and lowest rib. SAT thickness was measured by an 8 MHz linear transducer and depth of penetration was 4–6 cm with electronic callipers positioned at the skin-fat interface to the fat-muscle interface (linea alba) without compression. VAT thickness was measured without compression, using a 3.5–5 MHz convex transducer, as the distance from the internal face of linea alba, beneath the muscle fashia to the anterior wall of aorta [11,12]. The depth of penetration was 8–11 cm depending on amount of abdominal fat. Measurements of SAT and VAT thickness were repeated three times by each of the two operators with an inter-operator coefficient of variation of 1.96% for SAT and 4.36% for VAT.

Size and shape of the liver was evaluated by ultrasound [13,14]. Two images were taken during breath-hold; one of the left liver lope and edge and a second of the liver and left kidney. Liver images were evaluated independently by the two operators and classified as either (1) normal, (2) mild where enlargement is modest, borders moderately rounded and parenchyma mildly increased reflectivity or (3) severe cases where the liver is severely enlarged, markedly rounded borders and a dense and bright parenchyma [13,14].

Physical activity was determined by an international physical activity questionnaire (IPAQ), and the total metabolic equivalent (MET) in min/week was calculated. The VO_{2max} was determined by an incremental ergometer bicycle test (ER 800, Jaeger, Germany). After a warm-up (100 W), the workload was increased stepwise by 25 W/min and continued until physical exhaustion [15,16].

Statistics

Normal distributed outcomes are presented by mean and SD and differences between the groups were examined by Student's t-test. Median and interquartile range are used for skewed variables where differences between the groups are examined by Mann–Whitney *U* test. Regression analyses were made to adjust the differences in VAT and SAT for BMI, weight and height. Statistical analyses were performed using R-studio, Boston, and P ≤ 0.05 was considered statistically significant and borderline significant if 0.05 < P < 0.10.

Table 1
Characteristics of the study participants.

	Low birth weight (n = 17)	Normal birth weight (n = 26)	*P-value*
Birth weight (g)	2720 ± 188	3900 ± 195	*<0.001*
Age (years)	25.8 ± 1.6	25.6 ± 0.8	0.61
Weight (kg)	77.0 (12.2)	80.1 (10.2)	0.82
Height (cm)	179.1 ± 4.9	185.6 ± 7.0	*0.0008*
BMI (kg/m^2)	25.2 (3.6)	22.5 (2.9)	0.06
WHR	0.86 (0.06)	0.83 (0.05)	*0.04*
Total abdominal fat (cm)	6.02 (2.60)	5.30 (1.76)	*0.05*
Subcutaneous fat (cm)	1.82 (1.22)	1.52 (0.83)	0.10
Visceral fat (cm)	4.44 ± 1.13	3.86 ± 0.91	0.08
Visceral/subcutaneous	2.10 (1.07)	1.64 (2.69)	0.44
MET-minutes/week	3222 (4020)	3766 (3420)	0.50
VO_{2max} (ml/min/kg)	40.7 (14.9)	45.8 (8.4)	0.20
VO_{2max} (ml/min)	3513 ± 722	3661 ± 496	0.47

Values are mean ± SD and median (IQR). WHR: waist-hip ratio; Total abdominal fat: VAT + SAT; MET: metabolic equivalent. Differences between LBW and NBW individuals are analysed by Student's t test for normally distributed data and by Mann–Whitney U test for skewed variables.

Results

The LBW individuals had a lower height (P < 0.0008), higher WHR (P = 0.04) and tended to have higher BMI (P = 0.06). Total abdominal fat thickness (SAT + VAT) was elevated in LBW men (P = 0.05) (Table 1). There was a trend towards higher visceral fat thickness in LBW compared with NBW participants (P = 0.08), whereas there was no difference in subcutaneous fat thickness (P = 0.10) (Fig. 1). After adjustment for weight, a significant difference in both SAT (β: −0.43 (−0.84; −0.01), P = 0.04) and VAT (β: −0.62 (−1.18; −0.06), P = 0.03) between LBW and NBW was found, whereas after adjustment for height no significant impact of birth weight on SAT β: −0.37 (−0.99;0.26), P = 0.25) or VAT β: −0.63 (−1.36;0.09), P = 0.09) was observed. Furthermore, after adjustment for BMI, no significant impact of birth weight on either SAT (β: −0.02 (−0.37; 0.33), P = 0.93) or VAT (β: −0.29 (−0.85; 0.27), P = 0.30) was found.

There was no difference in VAT:SAT ratio between the groups (P = 0.44) nor in MET-minutes/week (P = 0.50) or VO_{2max} (P = 0.20) (Table 1). Liver images showed that 3 LBW (17.6%) versus 1 NBW participant (3.8%) had mild cases of fatty liver. None were classified with severe fatty liver.

Discussion

In this study, we documented that an increased WHR in men born with LBW is associated with, and most likely due to increased abdominal fat content assessed by ultrasound compared to control individuals. The LBW men had relatively more VAT and SAT than NBW men. Neither VAT nor SAT differences between groups reached statistical significance. However, the differences became significant after adjustment for weight. Furthermore, no differences in aerobic fitness or physical activity were found.

The current findings are in accordance with previous findings using DXA-scanning, showing that young LBW individuals deposit more fat in the abdomen compared to NBW controls despite of comparable weight and BMI [1,8]. In this study, where the LBW individuals tended to have increased BMI, no differences in VAT and SAT between the groups were found after adjusting for BMI.

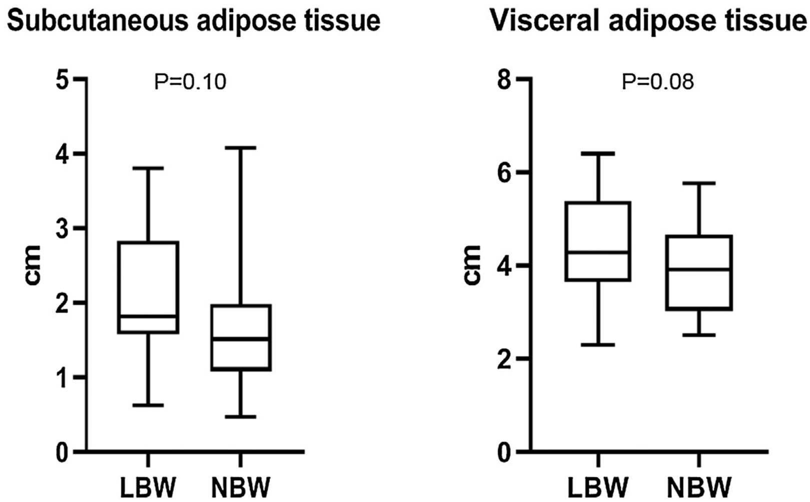

Fig. 1. Subcutaneous and visceral adipose tissue thickness determined by ultrasound in young men with LBW and NBW. Data are medians and IQR.

However, we have not observed increased BMI of men with LBW in our previous cohorts. In theory, this finding could be a result of increased accumulation of VAT and SAT with age in the LBW men since the previous studies were performed, so a higher BMI among the LBW group now become apparent. The current finding of increased BMI among the LBW men may also be related to lack of power. However, after adjustment for weight, the difference between LBW and NBW in both VAT and SAT became significant, indicating that LBW individuals have relatively more VAT and SAT as compared to NBW control.

Distribution of fat is an important determinant of metabolic disease, and VAT and ectopic fat are thought to be more detrimental with respect to the development of insulin resistance and T2D [17]. The higher abdominal fat mass in LBW individuals is in accordance with our a priori hypothesis of fetal undernutrition being associated with a more dysmetabolic phenotype [1,2]. Interestingly, previous studies have suggested that the inverse association between BW and abdominal fat is specific to VAT [18,19], and that both low and high BW is associated with visceral but not subcutaneous adiposity [20]. However, in our study VAT was not significantly increased in LBW subjects, and in fact SAT was non-significantly increased in LBW subjects to the same extent as the increased VAT level. Thus, more studies and data are needed to understand the relative contribution of increased VAT and SAT in LBW subjects, and their respective role(s) in development of insulin resistance. Of note, despite increased VAT in general is thought to be associated with increased risk of metabolic disease, studies have suggested that increased SAT also is a risk factor [21]. Furthermore, children born small for gestational age (SGA) tend to have more VAT than those born appropriate for gestational age (AGA), even when not overweight [22], supporting the importance of measuring adipose tissue distribution, and not just weight, to provide a more complete understanding of metabolic risk.

The finding of mild fatty liver in 17.6% of the LBW individuals compared to 3.8% of NBW controls, support our hypothesis, and suggests a greater tendency to ectopic fat storage among the LBW individuals. This is further supported by a study where nonalcoholic fatty liver disease (NAFLD) was observed in 34.8% of SGA children whereas none of the children born AGA had any sign of fatty liver disease [23].

We have previously shown impaired adipose tissue development, including reduced expression of the differentiation markers fatty acid binding protein 4 (*FABP4*), peroxisome proliferator–activated receptor γ (PPARG), and the glucose transporter type 4 (*GLUT4*) in LBW individuals possibly influencing adipocyte functions [9]. This combined with our current findings of more abdominal and potentially more visceral and ectopic fat in young LBW men, agree with the adipose tissue expandability hypothesis, suggesting that functional impairment of SAT results in increased visceral and ectopic fat storage. The previous findings of increased lipolysis and hepatic insulin resistance and development of peripheral insulin resistance during overfeeding in LBW men, including participants from the current study, may be explained by increased visceral and ectopic fat storage. However further studies are needed to validate our findings in a larger cohort ensuring adequate power and possibly using more sophisticated methods such as magnetic resonance (MR) or computerized tomography (CT) scans. Finally, it would be interesting to compare VAT and SAT to measurements of peripheral insulin sensitivity.

Conclusion

In conclusion, we have shown that LBW is associated with significant changes in abdominal body fat content in early adulthood also reflected by an increased WHR. The use of ultrasound allowed us to discriminate between SAT and VAT, and we found a tendency towards more VAT and ectopic liver fat storage in the LBW men.

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Declarations of interest

None.

Author contributions

LGG, AV and CB designed the study, wrote the manuscript, contributed to the interpretation of data and discussion as well as reviewed and edited the manuscript. AQL and KKL performed the study, analyzed data, reviewed and edited the manuscript. RTJ and NSH analyzed data, reviewed and edited the manuscript. ACA and AA contributed to the discussion as well as reviewed and edited the manuscript. All authors have approved the final version of the manuscript.

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