Author's response to reviews

Title: The relationship between various measures of obesity and arterial stiffness in morbidly obese patients

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Version: 2 Date: 22 October 2010

Author's response to reviews: see over
Dear Editor-in-Chief

Please find enclosed our revised manuscript entitled: “The relationship between various measures of obesity and arterial stiffness in morbidly obese patients.”

The authors are Njord Nordstrand (corresponding author), Espen Gjevestad, Dinh Khiem, Dag Hofsø, Erling Saltvedt, Ingrid Os and Jøran Hjelmesæth.

We are thankful for the opportunity to revise our manuscript. All the referees’ constructive comments have been addressed in a point-to-point reply. The referees highlighted several important issues and we feel that taking these considerations into account have improved the manuscript.

We hope that the revised manuscript is now acceptable for publication in BMC Cardiovascular Disorders.

All authors have contributed to the work and agree to it being submitted to BMC Cardiovascular Disorders. The manuscript has not been published previously and is not under review in any other journal. The manuscript has been proofread by an English native speaker.

We thank the reviewers for both their thorough and thoughtful evaluation of the manuscript as well as their critical yet constructive comments. The point-by-point response to the concerns of referee 1 and 2 follows below.

Sincerely,

Njord Nordstrand
Reviewers report
Title: The relationship between various measures of obesity and arterial stiffness in morbidly obese patients
Version: 1 Date: 1 September 2010
Reviewer: Tracy Baynard

Reviewers report:
The relationship between various measures of obesity and arterial stiffness in morbidly obese patients

Nordstrand, et al.
The authors conducted study investigating the relationship between morbid obesity using several anthropometric measures and pulse wave velocity (PWV) as a marker of arterial stiffness. The authors noted sex differences for prevalence rates of comorbidities and PWV. Further, sex differences were observed for several relationships between some anthropometric measures and PWV, with women demonstrating stronger negative associations.

Major Compulsory Revisions:

Introduction:
1. 1st paragraph—I suggest re-working this paragraph. Much of this is known and the authors provide only 2 country-specific epidemiology points (US and Norway). I would try to make my point more quickly…and perhaps offer a Northern European/Scandinavian statistic etc. …

Answer: We acknowledge the reviewers suggestions. Accordingly, changes have been made in the 1st paragraph in order to present a more logical approach to our hypothesis.

2. Overall, the introduction is a bit choppy and not focused well enough. The 2nd paragraph offers little justification for studying abdominal fat and overall obesity in relation to cardiovascular disease (CVD) risk in morbidly obese individuals. What reason is there to think the relationship in this group of individuals would differ from Class I & II obese individuals? It is not sufficient enough to state “no previous study has explored”…. The authors need to work on the “So what” aspect of their rationale.

Answer: The reviewer makes a valid point regarding justification and the second paragraph has been removed from the paper. We have presented justifications for our study based on results from articles that demonstrate differences in anthropometric measures and cardiovascular risk factors between morbidly obese and less obese subjects. We also would like to address the importance of further research regarding early risk markers given the latency time for development of cardiovascular disorders in obese and morbidly obese subjects. It is important to investigate whether or not the predictive power of anthropometric measures differs with regards to arterial stiffness in morbidly obese patients.

3. The paragraph on PWV also reads a bit choppy. I would suggest presenting some evidence on obesity and PWV, rather than just stating the obvious that PWV is associated with negative CVD risk. Secondly, the inclusion of augmentation index is rather awkward and comes off as a second thought.

Answer: We have removed the first sentence from the paragraph and added evidence regarding the effect of obesity on PWV. We acknowledge that the implementation of augmentation index may disturb rather than strengthen the paper. The augmentation index and PWV are connected, but PWV is a direct measure of arterial stiffness and is considered
to be the gold standard. Augmentation index is an indirect measure that needs careful interpretation. This manuscript presents an analysis of cross-sectional baseline data from a non-randomized clinical trial (ClinicalTrials.gov Identifier NCT00626964). The usage of the augmentation index was included in the protocol and is not a "second thought". Nevertheless, after thorough discussions we have decided to remove the analyses of augmentation index from the revised manuscript.

4. Lastly, it is quite surprising that sex differences are not once mentioned in the introduction, given the actual analyses performed, results provided and discussion generated. This creates a large disjointed effect between the rationale for the study and what was actually presented. This needs to be addressed.

Answer: We agree strongly with the reviewer. Men and women differ substantially in terms of body composition. For a given BMI men have higher lean mass and greater visceral and hepatic adipose tissue, whereas women have elevated general adiposity. These differences in fat distribution may contribute to a more insulin-sensitive environment in women. Estrogen plays a role in gender differences (premenopausal women) because it has an effect on insulin and glucose homeostasis, adipose tissue distribution and proinflammatory markers. All of these factors are likely to have either a direct or indirect effect on arterial stiffness.

Methods:
1. What dictated assignment to the groups?, as this was not a randomized study.

Answer: All participants were recruited from our tertiary care centre and had to reside within 100 km of either the hospital for rehabilitation or our clinic. The patients in the intensive lifestyle intervention group were all selected from patients that had signed up for participation in a standardized health promoting and weight reductive program at the hospital for rehabilitation. Participants in the surgery group were selected from patients preparing for bariatric surgery in our hospital. The decision regarding type of intervention was made prior to the inclusion to our study and was not a part of our protocol. The inclusion period started February 2008 and ended February 2010. Initially, 148 patients accepted our invitation to participate in the study, 15 patients withdrew before the study started, leaving a total of 133 patients in the present analysis.

2. How many subjects were morbidly obese based on BMI alone vs. having Class I or II obesity with a comorbidity?

Answer: A total of 106 patients (59 women) had a BMI ≥ 40 kg/m². Of these patients, thirty-one patients (24 women) were morbidly obese based on BMI alone (no comorbidity and BMI ≥ 40 kg/m²), whilst 27 (18 women), had a BMI between 35 and 40 kg/m². This has been added in the first paragraph under Results.

3. Were all patients able to have their 12th rib and iliac crest accurately palpated, considering their level of obesity? What ‘back-up’ markers were used if this was not feasible? Reliability of waist circumference measures?? Error of these measures is significantly elevated in an obese population—even for circumference measures. Many body comp labs perform circumference measures at least twice.

Answer: All of our patients were able to have their 12th rib and iliac crest accurately palpated. A trained nurse working at the morbid obesity centre performed these measures in all the
patients involved in this study. We agree with the reviewer that waist circumference measure errors increase in an obese population. However, Norhamn et al. showed an intra-observer variation of only 1.4% regarding waist circumference in patients with BMI ranging from 26 to 45 kg/m^2. “Reliability of anthropometric measurements in overweight and lean subjects: consequences for correlations between anthropometric and other variables.” International Journal of Obesity (2000) 24; 652-657.

4. Reliability data for PWV and Alx? This is important considering the difficulty in obtaining these measures in this population. Were attempts made at measuring peripheral PWV? If so, why is that data not included in this manuscript?

Answer: Augmentation index is removed from this paper and will not be further discussed here. (See under “discussion” point 3.)

The “Expert consensus document on arterial stiffness; methodological issues and clinical applications” states on pg.4 that “the measurement of PWV is generally accepted as the most simple, non-invasive, robust and reproducible method to determine arterial stiffness. Carotid-femoral PWV is a direct measurement and corresponds to the widely accepted propagative model of the arterial system.” We sampled three separate sets of data and calculated the mean PWV for usage in our results. This is in accordance with the guidelines in the consensus document. We have not been able to find any data on reliability of PWV measurements in a population of morbidly obese subjects.

5. The authors state in their limitations that the distance measured for the PWV between the carotid and femoral artery may introduce some level of artifact, given they appeared to lay the tape measure directly on the subject for these measures. Did the authors not also take measurements in a horizontal plane, by placing the tape measure directly above their “spots” and getting a true liner measure that way? This is commonly done in this population.

Answer: We appreciate the opportunity to elaborate on this important issue. Yes, the measurements were performed with each patient in a horizontal plane. The locations of the sternal notch, carotid pulse and femoral pulse were located. We placed the tape directly above the spots. As the reviewer states, this method is commonly done in this population. However, we can not exclude the possibility that the measured distance might have been overestimated in patients with large amounts of abdominal fat deposition. The implication of this could be that the actual velocity of the pulse wave is lower than the measured velocity, and thus the association between anthropometric measures of central adiposity and PWV is strengthened. In order to avoid misunderstandings regarding our method we have removed this from the “limitations” section.

6. Validity of bioelectrical impedance using the Inbody Analyzer in this type of population? Granted, DEXA is out of the question as is MRI due to their weight. Has anybody validated against hydrostatic weighing in this population?

Answer 6 a:

Das et al. validated BIA against a three compartment model using body density by air displacement plethysmography and total body water by H\textsubscript{2}\textsuperscript{18}O dilution. In this study they also validated hydrostatic weighing against their reference method in 11 selected extremely obese subjects and reported that hydrostatic weighing overestimated the percentage of fat mass by 0.6%. Conversely, BIA underestimated the percentage of fat mass (1.1 to 5.7% depending on the algorithm used) in morbid obese individuals, but the investigators concluded that the BIA method was comparable to the reference method for determining changes over time. They did not use the advanced BIA techniques involving multi-frequency and four compartments view that is used in the Inbody 720 to enhance its efficacy. The Inbody 720
has been validated against DEXA in obese patients. In this group the Inbody 720 provided up to 6\% lower values of percentage fat mass in women. The numbers were slightly better in men. However, the Inbody 720 has not been validated against hydrostatic weighing in morbidly obese patients.

Answer 6 b: Heath E et al. published “Bioelectric impedance and hydrostatic weighing with and without head submersion in persons who are morbidly obese” in the Journal of the American Dietetic Association; Aug 1998. They reported that BIA under-predicted percentage body fat by a mean of 5.7\% in men and 9.1\% in women when compared with the traditional hydrostatic weighing method. When they performed hydrostatic weighing without head submersion they observed only minor differences for men (0.1\% improvement), but in women the BIA under-predicted fat by 6.3\%, an improvement of 2.8\%.

In conclusion, BIA probably underestimates the body fat percentage by up to 10\%. It is difficult to get a precise picture of fat distribution in morbidly obese subjects. Bioelectrical impedance analysis is not a perfect method but it has acceptable accuracy, is easy accessible and probably the only method applicable to the majority of morbidly obese subjects.

7. Were medications controlled for—at least statistically?

Answer: Antihypertensive medications were controlled for in the regression analysis.

8. Which data were skewed and log transformed?

Answer: As described under the paragraph “Statistical methods,” HOMA-IR, S-f-glucose, S-f-insulin and S-triglycerides were skewed and log transformed.

Results:

1. Performing correlation analyses between BMI and in particular the WHtR would seem to violate issues of colinearity—please address/justify.

Answer: Spearman’s rank correlation was used to assess the bivariate association between the outcome (PWV) and each of exposure variables (various measures of body composition). However, we did not analyse correlations between the various anthropometric measures. In addition, the multiple linear regression analyses included each (one) of the various measures of body composition. Thus, we believe that the possible collinearity between anthropometric measures should not be a problem in our analyses.

Discussion

1. Limitations & Strengths section—the authors state that they excluded non-white participants. This is not made clear in the methods section. Justify why non-whites were excluded and approximately how many were excluded for this reason?

Answer: We did not exclude any non-white participants. This mistake has been corrected in the revised manuscript. Only one participant from all the patients recruited to our study was a non-white Caucasian.

2. Similar to the introduction, the discussion is lacking in the depth presented. The discussion for the most part is an extended “limitations” section and needs some expansion/deletion in areas. For instance, are there any physiological explanations for the sex differences? This would help provide a more sound
Answer: The reviewer addresses very important issues in this point. The possibility that physiological factors can explain the gender differences has been added to the discussion in the revised manuscript. Both differences in body composition and hormonal factors have been considered. The protective effect of estrogen is important when assessing cardiovascular risk in this group. Also, the fact that our males were slightly older and suffered more from comorbidities when compared with the females must be recognized. We did expect gender differences, but we did not expect the apparent lack of association between the different measures of body composition and PWV in males. It is not unlikely that the high level of comorbidities and many years of exposure to cardiovascular risk factors will hit harder in the male group. These factors and differences have been added to the discussion in the revised manuscript.

Minor Essential Revisions:

1. Background—2nd paragraph, last sentence. Please change “effect” to association.

Answer: The sentence referred to has been removed.

2. Background—3rd paragraph—CAD does not need to be spelled out again here, it was already abbreviated in the 1st paragraph.

Answer: We agree with the reviewer.

3. How long was the overnight fast? 10-12 h?

Answer: The overnight fast started at 12 PM and lasted till the pulse wave velocity was measured after the blood sampling had been performed. The minimum time for the overnight fast was 10 hours. The recommendations for standardization of subject conditions when performing non-invasive determination of arterial stiffness published in the “Expert consensus document on arterial stiffness: methodological issues and clinical applications” were followed. This has been addressed in the revised manuscript.

4. Statistical software package?

Answer: The statistical analysis was performed using SPSS 16.0 (SPSS Inc., Chicago, IL).

5. Delete the word “significantly” from your results section (text). Your p-values should denote the level of significance. If p-values are not there, insert them in the appropriate places.

Answer: We acknowledge that the term “significantly” might be redundant in some sentences, and accordingly these have been removed. However, to avoid repeating the exact p-values from the tables, the term significant(ly) still might be appropriate in some sentences.

6. Discussion—2nd paragraph—change “Afro” to “African”.

Answer: The term Afro-american has been changed to African American.
Reviewer's report

**Title:** The relationship between various measures of obesity and arterial stiffness in morbidly obese patients

**Version:** 1  **Date:** 11 August 2010

**Reviewer:** Francesco Natale

**Reviewer's report:**

Major Compulsory Revisions

1) I would be interested in knowing how many patients had BMI < 40. Please also elucidate correlation between measures of obesity and arterial stiffness in this subgroup

*Answer:* A total of 27 (18 women) patients had a BMI between 35 and 40 kg/m^2_. In this subgroup both WHtR (r=0.461, p=0.023) and WHR (r=0.587, p=0.003) were correlated to PWV. This association remained significant after adjustment for age, hypertension and type 2 diabetes mellitus. However, it is difficult to draw any conclusions due to small sample size.

2) Could you clarify in discussion: correlation between visceral fat area as calculated in your study (data from bioelectrical impedance analysis (BIA)) and RMN of visceral fat and/or echocardiographic epicardial fat if there.

*Answer:* The data requested by the reviewer were unfortunately not sampled in this study.