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The Effects of Cystatin C and Alkaline Phosphatase Changes on Cognitive Function 12-Months: After Bariatric Surgery

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Abstract

Background—The mechanisms for improved cognitive function post-bariatric surgery are not well understood. Markers of kidney and liver function (i.e., cystatin C and alkaline phosphatase (ALP)) are elevated in obese individuals and associated with poor neurocognitive outcomes in other samples. Bariatric surgery can improve cystatin C and ALP levels, but no study has examined whether such changes correspond to post-operative cognitive benefits.

Methods—78 bariatric surgery patients completed a computerized cognitive test battery prior to and 12-months after surgery. All participants underwent an eight-hour fasting blood draw to quantify cystatin C and ALP concentrations.

Results—Cognitive function improved after surgery. Cystatin C levels decreased at the 12-month follow-up; however, no changes were found in ALP concentrations. At baseline, higher cystatin C levels predicted worse attention/executive function, but no such effects emerged for ALP. Regression analyses controlling for possible medical and demographic confounds and baseline factors revealed that decreased ALP levels following surgery predicted better attention/executive function and memory abilities. Post-surgery changes in cystatin C did not correspond to cognitive improvements.

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Conclusions—Decreased ALP levels predicted better cognition following bariatric surgery, suggesting improved liver function as a possible mechanism of post-operative cognitive benefits. Future studies with neuroimaging and longer follow-up periods are needed to determine whether bariatric surgery can decrease risk for adverse brain changes and dementia in severely obese persons via improved metabolic function.

Keywords

Obesity; bariatric surgery; cognitive function; cystatin C; alkaline phosphatase; metabolic function

1. Introduction

Obesity affects nearly 80 million American adults and is expected to account for up to 18% of United States healthcare costs by the year 2030 (Go et al., 2013). These rising costs may at least partially be attributed to the negative effects of obesity on the brain. As an example, obesity is a recognized risk factor for Alzheimer's disease, vascular dementia, and accelerated brain atrophy (Xu et al., 2011; Gunstad et al., 2008). Obesity also plays an independent role in the development of cognitive impairment, with obese persons of all ages exhibiting deficits in attention/executive function and memory (Stanek et al., 2013; Lokken et al., 2009; Gunstad et al., 2011).

Reduced neurocognitive function in obese persons does not appear to represent a permanent state and may be partially reversible via weight loss. For instance, bariatric surgery, an effective treatment option for weight loss in severely obese individuals, has been shown to yield short- and long-term improvements in cognitive function (Alosco et al., 2014a; Miller et al., 2013; Alosco et al., 2014b). The mechanisms for these post-operative cognitive improvements are unclear, as recent work reveals largely non-contributory effects from comorbid medical condition resolution and substantial weight loss (Alosco et al., 2014a).

Although not previously examined, routinely screened for markers of metabolic function may serve as more sensitive predictors of post-bariatric surgery cognitive function. Specifically, kidney and liver biomarkers (i.e., cystatin C and alkaline phosphatase (ALP)) are elevated in obese persons and strong predictors of poor health outcomes, including greater risk for mortality and cardiovascular events in older adults (Shlipak et al., 2005; Wannamethee et al., 2013; Golik et al., 19991; Muntner et al., 2008). Poor kidney and liver function may also contribute to obesity associated cognitive deficits. For example, both cystatin C and ALP are inversely correlated with cognitive function, implicated in the pathogenesis of Alzheimer's disease, and theorized to play a role in brain functions (Kellet et al., 2011; Rajagopalan et al., 2013; Yaffe et al., 2008; Deng et al., 2001; Fonta et al., 2004).

Past work shows that bariatric surgery can improve cystatin C and ALP concentrations (Toolabi et al., 2011; Fenske et al., 2013), though no study has examined whether this pattern of metabolic improvements is also associated with post-bariatric surgery cognitive benefits. The current study examined whether changes in cystatin C and ALP correspond to improved cognitive function following bariatric surgery. We hypothesized that bariatric surgery would result in improved cystatin C and ALP serum levels and such changes would result in postoperative cognitive improvements at a one-year follow-up.

2. Materials and Methods

2.1 Participants

A total of 78 participants were recruited into a multi-site NIH prospective study examining the effects of bariatric surgery on cognitive function. All patients were enrolled in the Longitudinal Assessment of Bariatric Surgery (LABS) parent project and recruited from existing LABS sites (Columbia, Cornell, and Neuropsychiatric Research Institute) (Belle et al., 2007). Inclusion criteria included enrollment in LABS, between 20-70 years of age, and English-speaking. Patients were excluded for history of neurological disorder or injury (e.g., dementia, seizures), moderate or severe head injury (defined as >10 minutes loss of consciousness), past or current history of severe psychiatric illness (e.g. schizophrenia, bipolar disorder), past or current history of alcohol or drug abuse (defined by DSM-IV criteria), history of a learning disorder or developmental disability (defined by DSM-IV criteria), or impaired sensory function. All but one patient underwent Roux-en-Y gastric bypass and thus no comparisons for type of surgery were conducted. The present sample represents all individuals that had complete baseline and 12-month clinical data, blood work, and cognitive testing. Refer to Table 1 for demographic and clinical characteristics of the sample.

2.2 Measures

2.2.1 Cognitive Function—The IntegNeuro cognitive test battery assessed cognitive function in multiple domains. The IntegNeuro is a computerized battery that can be completed in 45-60 minutes and demonstrates excellent psychometric properties (Paul et al., 2005; Williams et al., 2005). Alternate forms of the IntegNeuro are also used to help limit practice effects from repeated assessments with this instrument. The cognitive domain and specific tests included:

Attention/Executive Function

Switching of Attention: This task is a computerized adaptation of the Trail Making Test A and B (Reitan, 1958). Participants are first asked to touch a series of 25 numbers in ascending order as quickly as possible. This is followed by the presentation of 13 numbers (1-13) and 12 letters (A-L) that participants alternately touch in ascending order. These tests assess attention and psychomotor speed as well as executive function. Time to completion served as the outcome measure in the current study.

Maze Task: This task is a computerized adaptation of the Austin Maze (Walsh, 1985) and assesses executive function. Participants are presented with a grid (8×8 matrix) of circles and asked to identify the hidden path through the grid. Distinct auditory and visual cues are presented for correct and incorrect responses. The trial ends when the subject completed the maze twice without error or after 10 minutes has elapsed.

Memory

Verbal List-learning: Participants are read a list of 12 words a total of 4 times and asked to recall as many words as possible after each trial. Following presentation and recall of a distraction list, participants are then asked to recall words from the original list. After a 20-

minute filled delay, participants are asked to freely recall the learned list and perform a recognition trial comprised of target words and non-target words. Total long and short delayed free recall of these verbal list items assessed memory in the current study.

Language

Letter Fluency: Participants are asked to generate words beginning with a given letter of the alphabet for 60 seconds. A different letter is used for each of the three trials. Total number of correct words generated across the three trials served as the dependent variable.

Animal Fluency: In this task, participants generate as many animal names as possible in 60 seconds. Total correct served as the dependent variable.

2.3 Procedures

The Institutional Review Board approved all procedures and participants provided written informed consent prior to study involvement. All bariatric surgery patients underwent a blood draw after fasting for eight hours, and blood assays were analyzed at the LABS Central Laboratory. Participants also completed a computerized cognitive test battery within 30 days prior to surgery. These same procedures were performed 12-months following surgery. Participant's height and weight were measured at each time point and used to calculate body mass index (BMI). Medical and demographic characteristics were ascertained via self-report and corroborated by a medical record review performed by trained research staff.

2.4 Statistical Analysis

Raw scores from neuropsychological measures were converted to T-scores using normative data adjusting for age, gender, and estimated intelligence. A T-score of 35 (i.e., 1.5 SD below the mean of normative standards) was deemed to reflect meaningful cognitive impairment. Composite scores for attention/executive function, memory, and language domains were computed at each time point that consisted of the mean of T-scores of the cognitive tasks that comprise each domain. Baseline to 12-month difference scores were computed for the following variables: BMI, total cholesterol, cystatin C, and ALP. BMI and total cholesterol change served as covariates in the current analyses. Difference scores for cystatin C and ALP represented the primary predictor variables of interest.

Descriptive analyses were performed to characterize the sample in terms of medical and demographic variables. Bivariate correlations examined the association among cystatin C and ALP with medical and demographic characteristics. Repeated measures analyses of variance (ANOVA) then examined changes in BMI, cognitive function in each domain, as well as changes in cystatin C and ALP from baseline to 12-months following surgery.

Regression analyses controlling for age, baseline BMI, total baseline cholesterol levels, and pre-operative status of hypertension, type 2 diabetes mellitus (T2DM), and sleep apnea (1 = positive; 0 = negative) were conducted to examine the baseline effects of cystatin C and ALP on test performance in attention/executive, memory, and language domains. Separate hierarchical regression analyses then investigated the effects of post-operative changes in

cystatin C and ALP levels on each cognitive domain at the 12-month follow-up. Specifically, performance in attention/executive function, memory, and language at 12-months were entered as the dependent variable resulting in a total of three hierarchical regression models for both cystatin C and ALP. For models examining the predictive validity of cystatin C, age, BMI and total cholesterol difference scores, 12-month diagnostic status of hypertension, T2DM, and sleep apnea, and baseline performance of the respective domain were entered in block 1. Pre- to post-operative change in cystatin C was then entered in block 2 to determine its incremental predictive validity on 12-month cognitive function. These same procedures were repeated for models examining the post-operative effects of ALP on cognitive function. Sample size for these change analyses was reduced to 73 due to missing 12-month data on medical covariates.

3. Results

Sample Characteristics

On average, the sample fell in the very severely obese category at baseline with an average BMI of 46.63 (SD = 5.28). The sample exhibited an average BMI of 30.51 (SD = 5.39) 12-months following surgery, placing them in the obese classification and representing a significant decline ($F(1,77) = 1173.09, p < 0.001$). At baseline, total cholesterol levels were also elevated and hypertension, T2DM, and sleep apnea were all prevalent, though participants generally demonstrated improvements in medical comorbidities at 12-months after surgery. Average pre-operative levels of cystatin C and ALP fell within the upper-end of the normative range. As a whole, cystatin C levels declined 12-months post-surgery ($F(1,77) = 6.47, p = 0.01$) and ALP levels remained stable ($F(1,77) = 1.29, p = 0.26$). However, on the individual level, 41.0% of the sample exhibited some type of post-operative improvements (i.e., decline) in ALP levels. Interestingly, independent samples *t*-tests and chi-square analyses showed that the subset of participants that exhibited post-surgery ALP improvements had a trend for higher, but still in the normative range, baseline ALP levels ($t(51.98) = 1.95, p = 0.06$; mean (SD) = 82.63 (25.64) versus 72.29 (18.12)), but did not differ from the remaining sample on baseline demographic (e.g., age), clinical (e.g., BMI), or medical characteristics (e.g., hypertension, T2DM, sleep apnea, cholesterol, cystatin C; $p > 0.05$ for all).

Cystatin C, ALP, and Medical/Demographic Characteristics

Bivariate correlations and independent samples *t*-tests examined the association among baseline cystatin C and ALP levels and sample characteristics. Higher baseline cystatin C levels were associated with older age ($r(76) = 0.29, p < 0.01$), increased BMI ($r(76) = 0.22, p = 0.05$), and greater likelihood of having hypertension ($t(76) = 2.20, p = 0.03$). No such pattern emerged for other demographic (e.g., sex) or medical variables ($p > 0.05$). Females had higher levels of ALP relative to males ($t(76) = -2.03, p = 0.05$), but ALP was not associated with any other demographic or medical variables at baseline ($p > 0.05$ for all). There were no significant associations between 12-month cystatin C and ALP concentrations and 12-month medical comorbidities ($p > 0.05$).

Baseline and 12-Month Cognitive Test Performance

Table 2 presents cognitive test performance in the sample at baseline and 12-months after surgery. The most common baseline cognitive impairments (i.e., T-score < 35) were found on tasks of memory and language, including long and short delayed free recall and the letter fluency task. Attention/executive function impairments were less common (e.g., <10%).

Relative to baseline, impairments on cognitive testing were less prevalent 12-months following surgery on many measures of attention/executive function, memory, and language. As a whole, repeated measures ANOVA revealed significant improvements in attention/executive function ($F(1,77) = 70.16, p < .001$) and memory ($F(1,77) = 28.85, p < .001$) 12-months post-operatively. There were no significant pre- to post-operative changes in language abilities ($F(1,77) = 0.68, p = 0.41$).

Baseline Cystatin C, ALP, and Cognitive Function

See Table 3 for a full summary of regression analyses examining the baseline association among cystatin C, ALP, and cognitive function. After accounting for age, baseline BMI, total baseline cholesterol levels, and pre-operative diagnostic status of hypertension, T2DM, and sleep apnea, higher baseline cystatin C serum concentration was associated with reduced attention/executive function ($\beta = -0.33, p = 0.01$). This pattern did not emerge for memory or language ($p > 0.05$ for each). Baseline ALP levels did not demonstrate a significant association with baseline cognitive function in any domains ($p > 0.05$ for all).

Predictive Validity of Post-Surgery Changes in Cystatin C and ALP on Cognitive Function

Regression analyses showed that decreases in ALP corresponded to improved attention/executive function ($\beta = -0.18, p = 0.02$) and memory abilities ($\beta = -0.23, p = 0.04$) 12-months post-surgery, even after controlling for age, BMI change, 12-month medical comorbidities, and baseline factors. Post-surgery changes in ALP did not predict language abilities ($p > 0.05$). See Table 4. Unexpectedly, pre- to post-operative changes in cystatin C concentrations did not correspond to cognitive function in any domain ($p > 0.05$ for all).

4. Discussion

The current study shows that cognitive function improves following bariatric surgery. These findings continue to support the notion that obesity-associated cognitive dysfunction may be partially reversible via bariatric surgery. However, past work has provided little insight into possible mechanisms for these cognitive improvements. The current study extends the literature by showing that improved liver function (i.e. ALP) is independently related to the cognitive improvements found after bariatric surgery. Several aspects of these findings warrant discussion.

We found that post-surgery decreases in serum ALP concentrations independently predicted better attention/executive function and memory abilities at the 12-month follow-up. ALP is a sensitive marker of liver function and levels are often elevated in obese individuals (Golik et al., 1991). This is concerning, as higher ALP concentrations are seen in Alzheimer's disease patients and correlated with the neurotoxic effects of tau protein (Vardy et al., 2012; Diaz-

Hernandez et al., 2010). Fortunately, ALP concentrations have been shown to improve following bariatric surgery (Toolabi et al., 2011). Yet, the literature is not entirely consistent on this matter, as extant evidence also shows no changes in ALP concentrations after bariatric surgery (De Abreu et al., 2007). The current sample as a whole demonstrated no change in ALP levels from pre- to post-surgery, but there were many participants that exhibited declines over time (i.e., 41.0%) and this subgroup of participants appears to account for the improvements in cognitive function. For example, this subset had higher baseline ALP levels and thus may have experienced the most post-operative metabolic and overall health benefits relative to the remaining sample. There are also several possible explanations uniquely linked with ALP that may also help explain the association between ALP and cognitive improvements. Improved ALP may enhance cortical functions via its interaction with neurotransmitters as well as possibly promote endothelial, neuronal, and synaptic functions (Fonta et al., 2004; Langer et al., 2007). ALP may also be a marker of inflammation levels (van Hoof & De Broe, 1994) and postoperative cognitive benefits associated with reduced ALP might be moderated through decreased inflammatory processes. More broadly, the association between ALP levels and better neurocognitive function may simply be a surrogate of the effects of improved liver function. Indeed, past work demonstrates cognitive impairments are prevalent and persisting in patients with non-alcoholic fatty liver disease (Elliot et al., 2013). Future studies with extended follow-ups (e.g., 5 years) should examine whether continued improvements in liver function after bariatric surgery translates to reduced risk of adverse brain changes and dementia in severely obese persons.

Counter to expectations, no baseline association emerged between ALP concentrations and cognitive function. These findings may be largely attributed to the relatively normal levels of ALP in the overall sample (mean = 72.39), including in the subset of participants that exhibited significant changes in ALP over time (mean = 82.63). ALP concentrations may have not reached threshold at the pre-operative time point to negatively impact cognition. However, this is likely not the only explanation, as ALP levels have been inversely correlated with cognitive function in other patient samples (e.g., Alzheimer's disease) that exhibit clinically normal ALP levels (Kellet et al., 2011). Nevertheless, our findings suggest that even fluctuations of ALP levels within the normative range may impact cognitive function in obese individuals. Future studies that utilize healthy obese and normal weight controls are much needed to clarify the effects of ALP on cognitive function.

Higher cystatin C levels were associated with poorer attention/executive function at baseline. These findings are consistent with the extant evidence that demonstrates the negative effects of cystatin C on cognitive dysfunction and increased risk for Alzheimer's disease in older adults (Ghidoni et al., 2010; Yaffe et al., 2008). Mechanisms for these effects are believed to involve the close association between chronic kidney disease and cardiovascular disease and inflammation (Yaffe et al., 2008). Higher cystatin C has also been correlated with subclinical brain infarcts in the elderly (Seliger et al., 2005) and colocalizes with beta amyloid in the hippocampus and entorhinal cortex of patients with Alzheimer's disease (Deng et al., 2001). This is unfortunate, as cystatin C levels are elevated in obese individuals and may exacerbate risk for Alzheimer's disease in this population (Xu et al., 2011). Nonetheless, such elevations can be attenuated through weight loss (Muntner et al.,

2008; Fenske et al., 2013). While we found significant declines in cystatin C post-operatively, these changes did not predict improved cognitive function. Post-surgery declines in cystatin C in the whole sample and at the individual level may not have exceeded threshold to produce cognitive benefits. Future studies should examine whether a longer follow-up period would increase the sensitivity of cystatin C changes to post-operative cognitive function.

The current study is not without limitations. First, practice effects are always a possible limitation in the examination of neuropsychological performance at repeated time points. However, this concern is at least partially attenuated by the use of alternate versions of the IntegNeuro and past work that shows minimal practice effects on computerized cognitive test batteries (Falsetti et al., 2006). Moreover, recent work that utilizes obese controls also confirms post-bariatric surgery cognitive improvements (Gunstad et al., 2011). Nevertheless, future studies that employ healthy and patient comparison groups are needed to elucidate the effects of cystatin C and ALP on cognitive function in bariatric surgery and other samples of obese persons. Likewise, past work suggests that cystatin C and ALP are associated with brain structure and function and case-controlled studies should implement neuroimaging to determine the pre- and post-surgery effects of these markers on the brain. Randomized control trials with extended follow-ups are also needed to confirm the directionality of our findings. For instance, it is possible that neuronal injury stemming from the effects of severe obesity (Bolzenius et al., 2013) may actually drive the subclinical increases in ALP (Kellett et al., 2011). The assessment of serum levels of cystatin C and ALP in the current study may have lacked sensitivity to neurocognitive outcomes, possibly offering another possible explanation for the lack of effects of post-surgery cystatin C and baseline ALP on cognitive function. Indeed, plasma levels of these biomarkers (i.e., ALP) are sensitive to neurocognitive outcomes in other patient samples and future studies should explore the current aims using cerebrospinal fluid measured cystatin C and ALP. Lastly, past work shows that behavioral weight loss interventions (e.g., exercise) also promote cognitive function in obese individuals (Siervo et al., 2011). Thus, future work is needed to examine the nature and extent of exercise-related metabolic and cognitive benefits in severely obese persons, particularly as it compares to the effectiveness of bariatric surgery on these variables.

5. Conclusions

The mechanisms for improved cognitive function post-bariatric surgery are poorly understood. The current study suggests that improved metabolic function (e.g., decreased ALP levels) following bariatric may be one post-operative contributor to cognitive improvements. Future studies that employ controls and extended follow-ups are needed to clarify mechanisms for the current findings and whether bariatric surgery can reduce risk of dementia in severely obese persons via improved metabolic function.

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Highlights

- Bariatric surgery is associated with cognitive improvements
- Improved liver function may contribute to post-surgery cognitive benefits
- Bariatric surgery may reduce dementia risk in obesity via better metabolic function

Table 1
Demographic and Medical Characteristics

Medical/Demographic Characteristics	Baseline	12-Months	F/Chi-Square
Age	43.50 (10.59)	--	--
Female (%)	82.1	--	--
Body Mass Index, mean (SD) kg/m ²	46.63 (5.28)	30.51 (5.39)	1173.09**
Hypertension (% yes)	44.9	38.5	3.23 (p = 0.07)
Type 2 diabetes (% yes)	24.4	17.9	0.91
Sleep Apnea (% yes)	35.9	16.7	1.93
Total Cholesterol, mean (SD), mg/dL	177.10 (38.66)	158.58 (26.95)	20.59**
Cystatin C, mean (SD) mg/L	0.86 (0.28)	0.81 (0.34)	6.47*
ALP, mean (SD) U/L	76.59 (21.96)	79.08 (25.83)	1.29

Note. Sample size varies for diagnostic status of hypertension, type 2 diabetes, and sleep apnea; statistics for differences in these variables is based on complete data for each time point.

*
p < 0.05

**
p < 0.001

Table 2
Neuropsychological Test Performance (T-score mean (SD)) among the Bariatric Surgery Patients

	Baseline M(SD)	12-months M(SD)	Baseline % T-score < 35	12-Months % T-score < 35
<i>Attention/Executive Function</i>				
SOA-A	55.50 (13.72)	63.78 (12.55)	9.0	2.6
SOA-B	53.21 (15.25)	60.42 (12.09)	7.7	6.4
Maze Task	50.25 (11.88)	54.76 (10.02)	9.0	5.1
<i>Memory</i>				
LDFR	46.78 (10.85)	53.91 (9.48)	14.1	2.6
SDFR	47.04 (10.47)	53.14 (9.82)	11.5	1.3
<i>Language</i>				
Verbal Fluency	46.74 (11.44)	47.30 (10.50)	17.9	11.5
Animals	50.59 (10.78)	51.32 (10.79)	5.1	5.1

Note. SOA = Switching of Attention; LDFR = Long Delayed Free Recall; SDFR = Short Delayed Free Recall

Table 3
Baseline Associations among Cystatin C, ALP, and Cognitive Function

	Attention/Executive Function		Memory		Language	
	β	SE b	β	SE b	β	SE b
Block 1						
Age	-.08	.15	-.01	.14	.23	.14
Baseline BMI	-.05	.25	.16	.23	.02	.23
Total Cholesterol	.15	.03	.09	.03	.04	.03
Hypertension	-.05	3.04	-.14	2.83	-.27	2.80
T2DM	-.05	3.46	-.08	3.23	.02	3.19
Sleep Apnea	-.13	2.76	-.06	2.57	-.14	2.54
R ²	.08		.08		.07	
F	0.98		1.03		.90	
Block 2 Model 1						
Baseline Cystatin C	-.33*	4.67	.05	4.57	-.12	4.49
R ²	.16		.08		.08	
F for R ²	7.26*		.16		.85	
Block 2 Model 2						
Baseline ALP	.02	.06	-.07	.05	.05	.05
R ²	.08		.09		.07	
F for R ²	.02		.39		.17	

Note.

* $p < 0.05$; BMI = body mass index; T2DM = type 2 diabetes mellitus

Table 4
Predictive Validity of Post-Surgery ALP Changes on Cognitive Function

	Attention/Executive Function		Memory		Language	
	β	SE b	β	SE b	β	SE b
<i>Block 1</i>						
Age	.10	.07	-.18	.10	.02	.07
BMI Change	-.03	.20	-.21	.28	.04	.20
Total Cholesterol Change	-.23**	.02	.06	.03	-.15	.02
12-Month HTN	.15	1.46	-.01	2.04	-.04	1.45
12-Month Sleep Apnea	.01	1.84	.14	2.66	.01	1.85
12-Month T2DM	.00	1.82	-.14	2.57	.02	1.83
Baseline of DV***	.74**	.07	.32**	.10	.75**	.07
R ²	.65		.25		.60	
F	17.31**		3.11**		14.09**	
<i>Block 2</i>						
ALP Change	-.18*	.04	-.23*	.05	-.05	.04
R ²	.68		.30		.61	
F for R ²	5.83*		4.20*		.40	

Note.
* $p < 0.05$;
** $p < 0.01$;
*** Baseline test performance of the 12-month dependent variable was entered as a covariate;

BMI = body mass index; HTN = hypertension; T2DM = Type 2 Diabetes Mellitus; sample size = 73 due to missing 12-month data on medical covariates